Type 2 diabetes in adults: management (update)

Consultation on draft guideline - Stakeholder comments table
01/09/2021 – 14/10/2021

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Action on Smoking and Health (ASH)	Guideline	General	General	The guideline should more explicitly recommend smoking cessation as routine component of diabetic care. People with diabetes who smoke have an increased risk of premature death and an increased risk of cardiovascular disease in comparison to non-smokers with diabetes.[i] [ii]Regardless of the type of diabetes, smoking makes it more difficult to treat and manage. Evidence suggests that active and passive smoking are associated with significantly increased risk of diabetes.[iii] [iv] According to a 2015 systematic review and meta-analysis, current smokers have a 37% increased risk of diabetes than non-smokers.[iii] Smoking is a well-known independent risk factor for hypertension which is a major risk factor for diabetes. Smoking is also associated and responsible for other major diabetes-related health complications[v] [vi] [vii]such as: • Kidney disease • Poor blood flow in the legs and feet that can lead to infections, ulcers, and possible amputation (removal of a body part by surgery, such as toes or feet) • Retinopathy (an eye disease that can cause blindness) • Peripheral neuropathy (damaged nerves to the arms and legs that cause numbness, pain, weakness, and poor coordination). Quitting smoking has been shown to reduce or delay the risk of cardiovascular morbidity and mortality in people with diabetes.[i] [viii] A study of US Nurses found that women with Type 2 diabetes who had stopped smoking for 10 or more years had a mortality relative risk of 1.11 compared with diabetic women who had never smoked.[ix] In light of evidence demonstrating that smoking is an independent risk factor for diabetes as well as an aggravating factor for diabetes complications, smoking cessation treatment should be a routine component of diabetic care.[x] However, survey evidence suggests that many smokers with diabetes are not receiving this advice. As part of a regular survey of its	Thank you for your comment. The committee agree that continued smoking places the individual with type 2 diabetes at higher risk of additional complications and that it is important to recommend smoking cessation as a part of diabetic lifestyle advice. NICE has a number of guidelines aimed at reducing smoking including stop smoking interventions and services, Smoking: harm reduction, and Smoking: acute, maternity and mental health services and a guideline on Tobacco: preventing uptake, promoting quitting and treating dependence which is due to publish in November 2021. There are existing recommendations that cross refer to the published guidelines from within the section on dietary advice and bariatric surgery. This section of the guideline was not prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest existing recommendations needed amending.

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				members in 2014, Diabetes UK found that just over half of smokers had not received support or advice to quit, although the sample size was very small.[xi] Similarly, a 2014 survey of NHS diabetes service users found that 17% of the 714 respondents reported not being asked about their smoking status or provided with stop smoking advice in the last 12 months.[xii] However, there is some evidence to show that smoking cessation is associated with altered glycaemic control and weight gain amongst smokers with diabetes.[xiii] [xiv] Concerns about weight gain should be addressed by health care providers whilst emphasising the fact that the health benefits of smoking cessation far outweigh post-cessation weight gain, even in people who are focused on weight management.[xv] [xvi]	
Association of British Clinical Diabetologists (ABCD)	General	General	General	ABCD amalgamated feedback: NG 28 a. My first comment is on the patient education section 1.2, currently it says, 'offered structured education to people with type 2 diabetes and their family members or carers at the time of diagnosis'. I am unsure as to why the committee has suggested they only limit this to the time of diagnosis and why not offer education annually that is tailored to the needs of the person with diabetes. b. Section 1.71 the committee says that if two drugs in the same class are appropriate to choose the option with the lowest acquisition cost. I would strongly disagree with this, the example here is Lixisenatide and Semaglutide. If the cheaper option has no cardiovascular benefit and has no benefit compared to placebo then I would prefer to give a medication which is slightly more expensive and has proven cardiovascular benefit.	Thank you for your comments. a. The section of the guideline covering patient education was not within the scope of this update. The current committee did not review any evidence on this topic and we are unable to comment on why the previous committee made this recommendation. b. The committee reviewed the recommendation on choosing drug treatment, in relation to the bullet point on lowest acquisition cost following stakeholder comments. They agreed that once the clinical circumstances and needs of the person with type 2 diabetes, including their need for CV protection, have been taken into account, if 2 drugs in the same class are suitable for that individual then the prescriber is still expected to choose the option with the lowest acquisition cost to help use NHS resources wisely. However, they also reviewed the wording around the recommendations for SGLT2s as a class and have slightly amended the wording of the draft recommendations for people at high cardiovascular (CV) risk who can (and cannot take metformin to refer to SGLT2i with proven CV benefit. They made this change to take into account that there was a greater degree of uncertainty around the CV benefit

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				c. Section 1.7.5 whilst I appreciate that the committee have suggested there is no cost effectiveness data on GLP-1 analogue treatment, I feel that their omission of this is an error because of the strength of data available. My primary concern as a diabetes Doctor is to prevent premature cardiovascular mortality and if there are agents which are available that do that i.e. SGLT2 inhibitors and GLP-1 analogues then why use a medication which only affects the surrogate marker of HbA1c and does not affect premature cardiovascular mortality?	associated with ertugliflozin because, depending on the choice of model used in the NMA, it did not consistently show a clinically meaningful reduction in hospitalisation for heart failure compared to placebo, unlike empagliflozin, canagliflozin and dapagliflozin. It was also not statistically significantly better than placebo for the 3-point MACE outcome unlike canagliflozin and empagliflozin. However, in the NMAs ertugliflozin could not be differentiated from the other SGLT2i for hospitalisation for heart failure, non-fatal stroke, non-fatal myocardial infarction, or the 3 point MACE (see the evidence review and rationale in the updated guideline for more details). The committee recommended SGLT2i with proven CV benefit because this wording would enable the prescribers to select a particular drug from within the SGLT2i class if they thought this was clinically justified based on the individual characteristics of their patient, whilst future proofing the recommendation should additional evidence or new SGLT2i be made available. Taken together these recommendations should ensure that the individual receives treatment tailored to their CV needs. GLP-1s were not cost-effective options and were therefor not recommended (see response to c for more details). c. and f. The committee did review data on the cost-effectiveness of GLP-1 analogues using the economic model, which took into account their cardiovascular benefits from the cardiovascular outcome trials. The evidence showed that SGLT2 inhibitors as a class were most likely to be cost-effective treatments for people with established cardiovascular disease (CVD) or at high risk of developing

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					CVD and so the committee recommended them for these groups of people. In contrast, GLP-1 analogues were not cost effective in any of the analyses carried out as part of the economic modelling work. Injectable semaglutide was the only GLP1 to have an ICER below £30,000 in the base case results. However, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce there level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confident in those findings, compared again to the findings for SGLT2 inhibitors. The committee were therefore unable

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				d. The discrepancy between the NICE guidance and the EASD/ADA guidance is stark and will cause confusion amongst non-specialists. e. Section 1.7.11 where Repaglinide is recommended it is likely to make the committee look behind the times; I am not aware of anybody prescribing Repaglinide for any reason for several years and therefore whilst it is recommended, the data are quite sparse and therefore nobody does this. f. In the visual summary 2, first line treatment once again I think the omission of GLP-1 analogue from high cardiovascular disease risk or established cardiovascular disease is an error. These comments also arise from page 21 of 60 in the treatment options, if further interventions are needed why GLP-1s are not added whereas DPP4s which are	to recommend this class of drugs. Therefore, based on the recommendations people with established CVD or at high risk of developing CVD will have the option to take SGLT2s for their cardiovascular benefit. NICE has a responsibility to take cost-effectiveness into account when making recommendations to ensure that the recommendations made represent the best use of NHS resources (in particular, the opportunity costs of spending additional resources), this is also required by the legislation that originally established NICE (the Health and Social Care Act 2012). d. The committee were aware of the ADA guidance, but their decisions were made according to the NICE guideline manual and took into account the evidence relevant to our review question. Although the NICE guidance may differ to the guidance provided by ADA, the committee were confident that their recommendations reflected the evidence they reviewed and their clinical judgement. It is of particular importance to note that the NICE guideline used an original economic model as the basis to recommend the most clinically and cost-effective options while the ADA guidance did not systematically take cost-effectiveness into account. e. The recommendation for the use of repaglinide was retained from the 2015 version of the guideline but was the subject of a question aimed at stakeholders during consultation. Based on stakeholder feedback the committee agreed to stand down this recommendation on repaglinide because stakeholders advised that it is not commonly used in current practice. f- see response to c above

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				effectively just HbA1c lowering agents and cardiovascular protective agents are not recommended. g. I therefore strongly disagree with recommendation 1.7.21. h. Section 1.7.27, the committee suggest using Detemir or insulin glargine however the committee will be aware that neither of these agents are 24 hour duration insulin, even the more concentrated forms of insulin glargine. Therefore, if there are economic data to suggest that, for example the District Nurses have to go into administer once daily insulin at variable times of day because they cannot see the same people at the same time every day then insulin Degludec may be an important option which has not been mentioned here. Insulin Degludec allows people to remain in their own homes rather than have to be potentially rehoused if the District Nurses cannot visit them and manage their insulin appropriately. 1. Educational resources: I agree that first line F2F structured education is the gold standard but should there not be an acknowledgment that digital education resources may provide an acceptable option 2. I could not see anything about potential referral to diabetes remission services 3. Self-monitoring section: should SMGB be offered as part of a structured education course irrespective of treatment. There is evidence this is where is can be helpful	g. The committee have agreed to remove the recommendation on not using GLP-1 RA solely for cardiovascular benefit following the stakeholder consultation. Upon reviewing the recommendation, the committee agreed that it was inappropriate to make a decision about treatment choice based solely on a single factor (cardiovascular risk) and that, as detailed in recommendation on choosing drug treatments, multiple factors should be taken into account instead. h. Consulattaion recommendation 1.7.27 covers the choice of insulin types and regimens. This section of the guideline was not included in the scope of the current update. The committee did not review any evidence on this topic and were therefore unable to make the requested changes. Similarly: 1. Patient education 2. Referral to remission services and 3. self-monitoring were also not part of the scope the pharmacological treatment review. There is another piece of work being carried out to look at blood glucose monitoring in people with type 2 diabetes and this will be published by March 31st 2022. 4. The committee were aware that the aim of very-low carbohydrate and ketogenic diets is to replace dietary carbohydrate with fat with the specific intention of inducing a ketotic state. In people with type 2 diabetes taking an SGLT2 inhibitor (SGLT2i) this may increase the risk of diabetic ketoacidosis (DKA). DKA is a rare, but serious, complication in type 2 diabetes. The committee highlighted this risk because the SGLT2 inhibitors are comparatively new drugs and, in the committees' view, clinical experience with them is low in primary care in some areas, but the new

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				4. Is there any evidence that those on a ketogenic diet have increased risk of DKA with an SGLT-2. I thought this was an idiopathic and unpredictable. 5. GLP-1s - CV evidence does not seem to have been considered or at least it does not come through. 1. There should be a distinction between atherosclerotic cardiovascular disease (ASCVD) i.e. a patient who is at risk or have had an MI/stroke, from a patient with heart failure (HF). In the former case the recommendation should be to use a GLP1-RA as second-line or first-line in case of metformin intolerance. In case of HF the second line should be a SGLT2i or first-line in case of metformin intolerance.	recommendations are expected to greatly increase their use in this setting. Additionally, the summary of product characteristics (SmPC) for SGLT2i advise caution in people with restricted food intake in relation to ketosis. However, taking stakeholder comments into account, the committee have revised the wording to better reflect the need to check whether the individual would be at an increased risk of DKA if they take an SGLT2i rather than causative effect of such diets. They also included mention of several risk factors for DKA as examples, including the use of very-low carbohydrate and ketogenic diets. The list is not meant to be exhaustive but to highlight some risk factors that the committee thought were particularly important for prescribers to be aware of. The committee made an additional recommendation to highlight to the clinician that they should try to address any modifiable risk factors before starting SGLT2i treatment. 5. Please note that evidence for newer GLP-1 mimetics was included in this review. Cardiovascular outcome trial evidence for every currently licensed GLP-1 mimetic with a licensed indication for type 2 diabetes in the UK was included in both the evidence review and economic model. Please see the Evidence review for full details. 1. Although there were a number of stakeholder comments asking for clarification of the treatment options for people with type 2 diabetes in whom SGLT2 inhibitors (SGLT2i) were contraindicated or not tolerated, there were no cardiovascular outcome trial style clinical trials identified that looked at the effectiveness of treatments for people at high cardiovascular (CV) risk in this population. The committee therefore used the evidence for effectiveness and cost effectiveness for other interventions from the same economic modelling scenarios as those looking at the cost-effectiveness of SGLT2i. Based on the evidence from the

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					included cardiovascular outcome trials the committee has made recommendations for people with established atherosclerotic cardiovascular disease and/or heart disease as a single group. This was based on the inclusion criteria in the trials and that when the SGLT2 inhibitors were cost effective when these were modelled as a single group. No separate modelling was undertaken for people with or at risk of MI/stroke and therefore no separate recommendations were made for this population. Although there were a number of stakeholder comments asking for clarification of the treatment options for people with type 2 diabetes in whom SGLT2 inhibitors (SGLT2i) were contraindicated or not tolerated, there were no cardiovascular outcome trial style clinical trials identified that looked at the effectiveness of treatments for people at high cardiovascular (CV) risk in this population. The committee therefore used the evidence for effectiveness and cost effectiveness for other interventions from the same economic modelling scenarios as those looking at the cost- effectiveness of SGLT2i. The committee reviewed the stakeholder comments regarding the use of GLP-1 mimetics and examined the updated economic evidence relating to GLP-1 mimetic treatment for people with type 2 diabetes and high cardiovascular risk. Please see details covered in point c (above). The committee therefore agreed that they were unable to recommend injectable semaglutide for people with type 2 diabetes and high cardiovascular risk who were unable to take and SGLT2i. As a result, the committee noted that people with high CV risk who could not take metformin with an SGLT2i would be offered metformin alone at treatment initiation. If they were also unable to take metformin then the clinician would select another treatment from the remaining options, namely sulfonylureas, DPP-4s or pioglitazone,

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				2. To consider removing repaglinide as second-line completely (1.7.11) as there is no CVD or renal benefits with it and we should move away from a purely glucocentric strategy for T2D management. 3. VD risk status to be better elaborated – what is deemed as high risk, low risk etc. it should not be based on QRISK 2.	depending on the individual's clinical circumstances and preferences. The committee decided against listing the options for people with type 2 diabetes who were at high CV risk and could not take an SGLT2i because they thought that this was an unnecessary level of detail given that they could not recommend a GLP-1 mimetic in place of the SGLT2i, that the treatment options were therefore the same for these people as for the rest of the type 2 diabetes population and because apart from for metformin, the guideline does not include details of which drug to take if a particular drug is contraindicated or not tolerated but rather expects the prescriber to use their clinical judgment. 2. Please see the response to point e. (above) 3. The committee deliberated over the definition of high risk of developing CV risk disease (high risk of future major adverse cardiovascular event such as an MI or stroke) to capture this population. They agreed that a QRISK2 score of >10% would be appropriate because this score takes into account most of the factors that were used to define this population in the economic model (and factors such as age, gender and ethnicity. They noted that QRISK2 is recommended for the assessment of CV risk in people with the 2 diabetes in the NICE guideline on NICE guideline on Cardiovascular disease: risk assessment and reduction, including lipid modification and is widely used and accepted in current general practice. Although other algorithms for assessing CVD risk exist, such as QRISK3, they are not in widespread use currently. Since a review of the evidence about the accuracy of such algorithms in comparison to each other and QRISK2 was not within the scope of this work, the

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				(Visual summary 2) a. CVD risk and status should be separated into ASCVD and heart failure which could be present together or not.	committee agreed that QRISK2 was a pragmatic choice for assessing CV risk in people with type 2 diabetes a. Thank you for your comment, We have now changed this to chronic heart failure or ASCVD. 4. GLP-1 mimetics are not first line treatment options and are therefore not included in the first line treatment visual summary. 5. We have changed this to GLP-1 mimetics in line with the guideline. 6.a. See the response to c above concerning the lack of cost-effectiveness of the GLP-1s in the current analyses. The committee therefore were unable to recommend GLP-1s specifically for people with established cardiovascular disease or those at high risk of cardiovascular disease. However, the existing recommendations for people with type 2 diabetes concerning GLP-1s at the end of the treatment pathway were unaffected by the current review and thus retained, but the committee were unable to edit them. 6.b. Thank you for your comment. It is unclear what is meant by your comment as the guideline does not recommend a GLP-1 mimetic in place of insulin routinely. It is an option for people in whom insulin therapy would have a significant occupational implication. However, this does not mean that the factors set out in the recommendation on choosing drug treatments are not relevant to choosing drug treatments. Refusal of any medication having been informed of the risks and benefits is a patient right. The responsibility for prescribing an appropriate drug is that of the prescriber. 6.c. The section of the guideline covering

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				4. There is no mention of GLP-1RA in visual summary 2. Importantly, the availability of an oral GLP-1 RA means that it should be used in preference to a DPP-IVi . The latter group does not provide protection from ASCVD or HF. 5. Visual summary 4 – GLP-1 should be written as GLP-1RA 6. 1.7.19 to 1.7.24 needs revision and is confusing. a. GLP-1RA - liraglutide especially has shown to reduce MACE and should be considered as second-line or third-line. The BMI cut-off of 35Kg/m^2 is less importance and CVD protection has been seen in patients with lower BMI. b. Using GLP-1RA as an alternative to insulin is fraught with danger; it may get prescribed to patients instead of insulin in those who refuse insulin but are having osmotic symptoms. Further, if these patients are also on a SGLT2i they are likely to end up with DKA. c. 1.7.24 implies that all patients on a GLP-1 RA and insulin will need to be followed up long term in secondary care ("continuing support") 7. There should be some mention of using caution when using a sulphonylureas in combination with a SGLT2i because of the risk of hypoglycaemia	Insulin-based treatments was not within the scope of this update. The committee did not review any evidence on this topic and were therefore unable to make any changes. 7. While the committee agree that caution around the risk of hypoglycaemia should be used when any combination of blood glucose lowering drugs are prescribed, the committee agreed that this is a general consideration which should be part of the prescribing process and they therefore declined to add this to the recommendations. The recommendation on choosing drug treatments recommends that healthcare professionals should take the safety of drugs into account when prescribing, this includes risks from taking more than 1 glucose lowering drug. 8. As requested by stakeholders, the committee have amended the recommendation on choosing drug treatments to include renal, as well as cardiovascular, protection. 9. The committee reviewed the stakeholder comments and have decided to continue treating SGLT2 inhibitors (SGLT2i) as a class. However, they recognised that there was a greater degree of uncertainty around the CV benefit associated with ertugliflozin because, depending on the choice of model used in the NMA, it did not consistently show a clinically meaningful reduction in hospitalisation for heart failure compared to placebo, unlike empagliflozin, canagliflozin and dapagliflozin. It was also not statistically significantly better than placebo for the 3-point MACE outcome unlike canagliflozin and empagliflozin. The committee therefore recommended SGLT2i with proven CV benefit because this wording would enable the prescribers to select a particular drug from within the SGLT2 class if they thought this was clinically justified based on the individual characteristics of their patient, whilst future proofing the recommendation should additional evidence or new SGLT2s

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					be made available. As per the recommendation on choosing drug treatment, once the clinical circumstances and needs of the person with type 2 diabetes, including their need for CV protection, have been taken into account, if 2 drugs in the same class are suitable for that individual then the prescriber is still expected to choose the option with the lowest acquisition cost to help use NHS resources wisely. 9b Please see response above.
				8. 1.7.1 Discuss with adults with type 2 diabetes the benefits and risks of 2 drug treatment and the options available. Base the choice of drug 3 treatments on: 4 • the person's individual clinical circumstances, for example, 5 comorbidities, contraindications and risks from polypharmacy 6 • the person's individual preferences and needs 7 • the effectiveness of the drug treatments in terms of metabolic 8 response and cardiovascular protection 9 • safety (see MHRA guidance) and tolerability of the drug 10 treatment 11 • monitoring requirements 12 • the licensed indications or combinations available 13 • cost (if 2 drugs in the same class are appropriate, choose the 14 option with the lowest acquisition cost). [2015, amended 2021 The above paragraph does not include renal protection (please consider adding)	10. Thank you for your comment about the amended [2021] recommendation 1.7.10. The recommendation could not be amended as requested because no evidence for these suggestions was searched for or included in the update. Additionally, the committee agreed that this would be too much information to contain in a single recommendation affecting its readability. The visual summary (table 4) document summarises such key information.
				9. 2 1.7.5 Based on the person's cardiovascular risk assessment: 8 • If they have congestive heart failure or established 9 atherosclerotic cardiovascular disease, offer an SGLT2 inhibitor 10 in addition to metformin. 11 • If they are at high risk of developing cardiovascular disease, 12 consider an SGLT2 inhibitor in addition to metformin. [2021]	

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				Not all SGLT2 inhibitors have shown cardiovascular protection Suggest use SGLT2 inhibitor with evidence for protection from or prevention of ASCVD .Ertugliflozin does not have strong evidence. 9b For first-line drug treatment in adults with type 2 diabetes, if 23 metformin is contraindicated or not tolerated: 24 • If they have congestive heart failure or established 25 atherosclerotic cardiovascular disease, offer an SGLT2 inhibitor 26 alone. 27 • If they are at high risk of developing cardiovascular disease, 28 consider an SGLT2 inhibitor alone. [2021] Please see the comment above 10. 4 1.7.10 For first-line drug treatment in adults with type 2 diabetes, if 2 metformin is contraindicated or not tolerated and if they are not in 3 either of the groups in recommendation 1.7.9, consider: 4 • a DPP-4 inhibitor or 5 • pioglitazone or 6 • a sulfonylurea or 7 • an SGLT2 inhibitor for people	11. Given that the economic model was primarily the focused on looking at treatments reducing all CV risks, the current economic model looks at the cost-effectiveness of these treatments in both the total diabetic population, and across three other subgroups which have varying levels of high cardio vascular risk (the definitions of which are listed in section 3.1 in the economic reposrt). Sturucturing a cost-effectiveness analysis that models looking at just one particular CV outcome such as stroke was thought to be inappropriate, as it would result in a significant underestimation of adverse events, especially since the risk facors contributing towards stroke in a high risk subgroup will likely contribute towards other CV events as well. The committee were therefore unable to make separate recommendations for people at risk of stroke. 12. While the committee were obviously aware the issues raised by the current COVID-19 pandemic, treatment of type 2 diabetes concurrent with or during the pandemic was out-of-scope for this guideline update. These issues were not taken into account as part of the economic analysis because the impact of COVID on the type 2 diabetes drug treatment

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				who meet the criteria in NICE 8 technology appraisal guidance 390, or TA572 [2015, amended 9 2021 Suggest the following wording DPP4 inhibitors if risk of hypoglycaemia is high Pioglitazone if weight gain, macular oedema, ankle oedema and fractures are not an issue Sulphonylurea if rapid glucose reduction is needed and the risk of hypoglycaemia is low and weight gain not a major concern SGLT2 inhibitors for ……. 11. 5 Consider adding Consider GLP1 agonist therapy with proven evidence as a second line or third line treatment in people at risk of stroke SGLT-2 inhibitors do not reduce stroke but GLP-1 agonists with evidence do 12. In addition to this specific feedback, ABCD would request that NICE is mindful of the detrimental repercussions of the Covid 19 pandemic , resulting in escalation in HbA1c in many of those with pre-existing type 2 diabetes, increase in people passing from pre-diabetes to overt type 2, and the exacerbation of glycaemic control that infection with covid 19 and dexamethasone treatment has had. This should be taken into the cost analysis too. We are fully supportive of all recommendations from CaReMe group	pathway was not part of the scope of this work and we therefore didn't search for evidence on this. It is expected that if more people moved from pre-diabetes to overt type 2 that this would not affect the cost-effectiveness of the treatments in the model but rather that there would be more people entering the model for initial treatment. It might affect the resource impact of the recommendations when they are put into practice. NICE is undertaking a resource impact assessment of the draft recommendations in preparation for finalisation of the guideline update. This includes consideration of the sizes of the populations that would be covered by the SGLT2 inhibitor recommendations for people with established cardiovascular disease (CVD) and high risk of CVD. The committee will have access to this document but do not take it into account when finalising their recommendations because their role here is to determine the most clinically and cost-effective treatment options for people with type 2 diabetes and high CV risk. Considerations around the resource implications associated with the implementation of these recommendations do not fall within their remit. The resource impact document will be made available on the guideline webpage and can be used by commissioners and other people to model the resource impact of these recommendations with varying population sizes.

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AstraZeneca	Guideline	013, 028, 029		**Concern** The current draft guideline refers users to "always check the British National Formulary (BNF) and Summary of Product Characteristics (SPC) for any drug being prescribed". However, AstraZeneca would like to note that the BNF entry, in particular for dapagliflozin, has not been recently updated and does not reflect the change in eGFR cut-offs since the SPC has been updated to include HFrEF and CKD indications. Given that the current BNF entry contains inaccurate prescribing information, AstraZeneca believe that this could lead to significant barriers to prescribing at a local level and issues with implementing the updated NICE guideline. **Rationale** Regarding safety information on SGLT2 inhibitors, the draft guideline recommends that users refer to the BNF or SPC for any drug being prescribed. The BNF entry for dapagliflozin currently includes the following recommendations on use of dapagliflozin in cases of renal impairment: • avoid initiation if eGFR less than 60 mL/min/1.73 m^2 (reduced efficacy) • avoid if eGFR persistently less than 45 mL/min/1.73 m^2 (reduced efficacy) • If eGFR less than 60 mL/min/1.73 m^2 monitor renal function at least 2–4 times per year. However, these recommendations are now out of date, as dapagliflozin has been approved for use for the treatment of symptomatic chronic HFrEF and for the treatment of CKD. The SPC contains updated guidance for cases of renal impairment, reflecting the fact that dapagliflozin has shown strong renal efficacy in clinical trials and therefore can be used in patients with lower eGFR levels than currently recommended in the BNF entry: • It is not recommended to initiate treatment with dapagliflozin in patients with an eGFR <15 mL/min/1.73m^2. • In patients with diabetes mellitus, the glucose lowering efficacy of dapagliflozin is reduced when eGFR is <45 mL/min/1.73m^2, and	Thank you for your comment. As requested, we have contacted the BNF to ask them to update this entry.

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				is likely absent in patients with severe renal impairment. Therefore, if eGFR falls below 45 mL/min/1.73m^2, additional glucose lowering treatment should be considered in patients with diabetes mellitus. AstraZeneca have been engaging with the BNF across several months in order to update this entry, but the BNF entry for dapagliflozin remains out of date. AstraZeneca are concerned that the BNF may prevent the delivery of quality care aligned with the recommendations published in the updated NICE NG28 guideline in the event that the entry remains outdated at the time of publication. **AstraZeneca requests that NICE engages with the BNF to update this entry.**	
AstraZeneca	Guideline	014	007 - 008	**Concern** Recommendation 1.7.1 refers to basing the choice of drug treatment on "cardiovascular protection", among other factors. SGLT2 inhibitors have been shown through multiple clinical trials to have positive renal benefits in patients with T2DM and CKD.[3, 14, 24, 38] As NICE have committed to including recommendations around CKD in this guideline (based on the separate consultation on Type 2 diabetes in adults: management - SGLT2 inhibitors for chronic kidney disease (update) [GID-NG10246]), AstraZeneca feel this recommendation should be updated to include "cardiovascular and renal protection". **AstraZeneca requests that the Committee update recommendation 1.7.1 to reflect that drug choice should also consider renal benefits (proposed changes in red):** • the effectiveness of the drug treatments in terms of metabolic response and cardiovascular and renal protection	Thank you for your comment. Following committee discussion of stakeholder comments the recommendation on choosing drug treatments has been amended to include consideration of cardiovascular and renal protection (third bullet). As you note, the renal benefits of using SGLT2 inhibitors in people with type 2 diabetes and CKD have been assessed in a separate piece of work that has recently been out for stakeholder consultation and was published in November 2021. The final recommendations on renal and cardiovascular benefits will be brought together in a single updated guideline document when this current work on cardiovascular benefits is published in 2022.
AstraZeneca	Guideline	014	012	**Concern** Recommendation 1.7.1 refers to basing the choice of drug treatment on "licensed indications", among other factors. AstraZeneca agree that this is an important consideration, however, this has not been reflected at other key points within the guideline.	Thank you for your comment. The recommendation on choosing drug treatments, including the bullet on licensed indications, has now been included in the visual summary in full. Prescribers should consult the SPCs before prescribing, therefore we did not feel it was necessary to detail all of the licensed indications in the visual summary.

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				Rationale This recommendation is currently missing from visual summary 1 (prescribing guidance) and so should be included in the list of considerations for choosing treatments here. Furthermore, there is currently little information in the guideline on the licensed indications for the available treatments, which is a key omission given the variation in licensed indications across treatments. AstraZeneca suggest that, to provide clarity for prescribers and support evidence-based prescribing, it would be helpful to include the licensed indications in the treatment algorithm and/or in a dedicated table clearly showing the licensed indications for each treatment within each drug class. **AstraZeneca requests that visual summary 1 (prescribing guidance) is updated to include "licensed indications" in the list of considerations for choosing treatments, and that further information on the licensed indications is provided in the guidance (in the treatment algorithm and/or as a dedicated table).**	
AstraZeneca	Guideline	014	013	**Concern** Recommendation 1.7.1, regarding choice of drug treatment and options available, states "if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition costs". AstraZeneca believes this statement to be inappropriate for SGLT2 inhibitors given that the current class-level recommendations for SGLT2 inhibitors imply all drugs within the class are appropriate in all patient populations and do not accurately reflect the differences in the available clinical and cost-effectiveness evidence for individual SGLT2 inhibitors. The available evidence includes health economic modelling conducted by NICE which demonstrates that SGLT2 inhibitor with the lowest acquisition cost is in fact not the most cost-effective SGLT2 inhibitor. AstraZeneca believes that evidence-based guidelines should consider cost-effectiveness rather than acquisition cost alone, and request that this recommendation is updated to "if 2 drugs in the same class are appropriate based on the strength of the clinical evidence and licenced indications, choose the option which represents the most cost-effective use of NHS resources" to reflect this.	Thank you for your comment. Thank you for your comment. The committee reviewed the stakeholder comments but decided to continue treating SGLT2 inhibitors (SGLT2i) as a class for the following reasons: • There was a degree of uncertainty around whether there were real differences in cardiovascular (CV) benefits between the SGLT2i based on the clinical trial evidence and results from the NMAs. ○ Firstly, for hospitalisation for heart failure, the SGLT2i empagliflozin, canagliflozin, and dapagliflozin produced a clinically meaningful reduction compared with placebo in the random effects NMA model. However, in the sensitivity analyses using a fixed effect model ertugliflozin also showed a clinically meaningful reduction compared to placebo, which reflects the original clinical trial data. The NMA results

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				Rationale Differences in the available clinical evidence between SGLT2 inhibitors As outlined above in comments 4 and 5, AstraZeneca believe that further clarification is needed throughout NG28 to reflect the differences between individual SGLT2 inhibitors in terms of strength of evidence and licenced indications. In brief, there are substantial differences in the strength of clinical evidence for the treatment benefit of individual SGLT2 inhibitors in specific patient populations, including those with T2DM at high risk of developing CVD, patients with HFrEF and patients with CKD. As such, the licenced indications for individual SGLT2 inhibitors vary considerably across the drug class. Differences in the health economic modelling results conducted by NICE for individual SGLT2 inhibitors Importantly, these differences in the available clinical data are reflected in the economic modelling approach taken by NICE to inform this guideline, resulting in clear differences in cost-effectiveness between individual SGLT2 inhibitors. NICE conducted a health economic evaluation on the relative cost and efficacy of SGLT2 inhibitors in the relevant patient populations to inform their update to NG28, which incorporated the drug acquisition costs of each SGLT2 inhibitor. The model generated a wide range of ICERs for the different SGLT2 inhibitors at each treatment line, and concluded that dapagliflozin is more cost-effective than all other SGLT2 inhibitors in each line of treatment and in each subgroup (Table 5), despite ertugliflozin having a lower acquisition cost.[11] It is therefore clear that the SGLT2 inhibitor with the lowest acquisition cost would not necessarily be the most cost-effective option in patients where an SGLT2 inhibitor is considered an appropriate treatment option. The NICE Process and methods guide states that "Guideline recommendations should be based on the balance between the estimated costs of the interventions or services and their expected benefits	could not differentiate between the SGLT2i for this outcome. ○ Secondly, for the 3 point MACE outcome, only canagliflozin and empagliflozin produced a statistically significant reduction compared to placebo but the SGLT2i could not be differentiated from each other in the NMA. ○ Thirdly for all cause and CV mortality empagliflozin showed a clinically meaningful reduction compared to placebo and the other SGLT2i, but the remaining SGLT2i could not be differentiated from each other or placebo in the NMA. ○ Fourthly, for non-fatal MI and non-fatal stroke the NMAs could not differentiate between empagliflozin, canagliflozin, ertugliflozin and placebo. The data for dapagliflozin was reported differently and could not be included in the NMAs. From the clinical trial data dapagliflozin could not be differentiated from placebo for MI and was not meaningfully different from placebo for stroke. ○ Finally, only dapagliflozin showed a clinically meaningful improvement in severe hypoglycaemia compared to placebo but the remaining SGLT2i could not be differentiated from each other and placebo in the NMA. • There was also a degree of uncertainty around the cost-effectiveness of individual SGLT2i in the economic modelling. Although only dapagliflozin was cost-effective at a threshold of £20,000/quality-adjusted life year (QALY) across all model scenarios and CV risk groups it could not be differentiated from the other SGLT2i in the NMA apart from for the all-cause and CV mortality outcomes where it was clinically meaningfully worse than empagliflozin. The ranking of ICERs for the

<table>
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<tr><td></td><td></td><td></td><td></td><td>compared with an alternative (that is, their 'cost effectiveness')".[12] AstraZeneca therefore feel that the cost-effectiveness of the different SGLT2 inhibitors, rather than simply their acquisition cost, should be a consideration in the guidelines and for prescribers

Table 5. Summary of cost-effectiveness for SGLT2 inhibitors
<table>
<tr><th></th><th>All T2D patients</th><th>High CV risk (no prior event)</th><th>Established CVD</th></tr>
<tr><td colspan="4">Initial Therapy – Addition</td></tr>
<tr><td>Dapagliflozin</td><td>£16,145</td><td>£15,376</td><td>£15,695</td></tr>
<tr><td>Canagliflozin</td><td>£31,914</td><td>£24,923</td><td>£25,041</td></tr>
<tr><td>Empagliflozin</td><td>£25,950</td><td>£25,017</td><td>£22,067</td></tr>
<tr><td>Ertugliflozin</td><td>£24,274</td><td>£22,008</td><td>£31,441</td></tr>
<tr><td colspan="4">First intensification – Addition</td></tr>
<tr><td>Dapagliflozin</td><td>£14,756</td><td>£13,814</td><td>£15,415</td></tr>
<tr><td>Canagliflozin</td><td>£34,644</td><td>£27,464</td><td>£29,470</td></tr>
<tr><td>Empagliflozin</td><td>£24,975</td><td>£23,582</td><td>£24,140</td></tr>
<tr><td>Ertugliflozin</td><td>£22,396</td><td>£19,742</td><td>£32,252</td></tr>
<tr><td colspan="4">Second intensification – Addition</td></tr>
<tr><td>Dapagliflozin</td><td>£13,548</td><td>£12,591</td><td>£14,200</td></tr>
<tr><td>Canagliflozin</td><td>£38,727</td><td>£31,780</td><td>£32,899</td></tr>
<tr><td>Empagliflozin</td><td>£24,376</td><td>£23,071</td><td>£23,912</td></tr>
<tr><td>Ertugliflozin</td><td>£21,204</td><td>£18,549</td><td>£29,290</td></tr>
</table>
Source: NICE Evidence Review for NG28, 2021[11]

The clarifications suggested in comments 4 and 5 to outline the strength of evidence available for each SGLT2 inhibitor in the relevant population will enable prescribers to determine the most appropriate SGLT2 inhibitor for a specific patient population and enable evidence-based prescribing, and AstraZeneca also requests the Committee to reflect the full breadth of the clinical and health economic evidence available for individual SGLT2 inhibitors with the following amendments to recommendation 1.7.1 (proposed changes in red):</td><td>other SGLT2i varied across model scenarios and risk groups. The committee agreed that there was sufficient uncertainty in the economic modelling (caused in turn by uncertainty in the underlying clinical data) to mean that they were not sufficiently confident that these different ICERs represented true underlying differences in cost-effectiveness, as opposed to simply random variation in the results between different SGLT2 trials.
• Taking the cost-effectiveness and clinical results into account the committee decided against only recommending dapagliflozin and instead made recommendations for the SGLT2i as a class. However, they recognised that there was a greater degree of uncertainty around the CV benefit associated with ertugliflozin because, depending on the choice of model used in the NMA, it did not consistently show a clinically meaningful reduction in hospitalisation for heart failure compared to placebo, unlike empagliflozin, canagliflozin and dapagliflozin. It was also not statistically significantly better than placebo for the 3-point MACE outcome unlike canagliflozin and empagliflozin. The committee therefore recommended SGLT2i with proven CV benefit because this wording would enable the prescribers to select a particular drug from within the SGLT2 class if they thought this was clinically justified based on the individual characteristics of their patient, whilst future proofing the recommendation should additional evidence or new SGLT2s be made available. As per the recommendation on choosing drug treatment, once the clinical circumstances and needs of the person with type 2 diabetes, including their need for CV protection, have been taken into account, if 2 drugs in the same class are suitable for that individual then the prescriber is still expected to choose the option with the</td></tr>
</table>

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				• cost (if 2 drugs in the same class are appropriate based on the strength of the clinical evidence and licenced indications, choose the option which represents the most cost-effective use of NHS resources).	lowest acquisition cost to help use NHS resources wisely. Please see evidence review A for more a more detailed explanation of the analyses that were carried out and the committee's discussion of the results. The committee discussed your suggested changes to the recommendation about choosing the drug with the lowest acquisition cost if more than one option was appropriate. They agreed that this change was not necessary because the cost-effectiveness of the drugs was taken into account when making the class level recommendation. In addition, as the cost-effectiveness of the drugs varied between treatment stages and population groups this would make the modified recommendation hard to implement in practice. They also noted that as this recommendation applies to all drugs in this section your proposed changes would necessitate the inclusion of a table of cost-effectiveness evidence for all possible drug options making the guideline more complex and harder to follow. They also agreed that given their change to the SGLT2 class level recommendation to cover SGLT2s with proven CV benefit it was not necessary to amend the recommendation about choosing drug treatments to include the text you suggested about the strength of the clinical evidence and that your point about licensed indications was already covered in the same recommendation under 'the licensed indications or combinations available'. The committee agreed that it was still the case that once the clinical circumstances and needs of the person with type 2 diabetes, including their need for CV protection and the proven CV benefit of the drugs if relevant, have been taken into account, if 2 drugs in the same class are suitable for that individual then the prescriber should choose the option with the lowest acquisition cost to help use NHS resources wisely.

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AstraZeneca	Guideline	015	009	**Concern** The definition of "established atherosclerotic cardiovascular disease" is not outlined clearly in the guideline document. **Rationale** AstraZeneca feel that as "established atherosclerotic cardiovascular disease" has been used throughout the guideline as a key eligibility criterion in treatment decision making, defining "established atherosclerotic cardiovascular disease" in this context is important to best inform prescribing decisions and ensure consistency in prescribing across all medical practices. **AstraZeneca requests the Committee include the following definition of "established atherosclerotic cardiovascular disease" used by Primary Care Diabetes Europe in the guideline at first use:** Atherosclerosis leading to coronary artery disease, cerebrovascular disease, or peripheral arterial disease[39]	Thank you for your comment. The committee have now provided a definition of ASCVD in the Terms used in the guideline section. This includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, previous coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease. This differs slightly from your definition, but does cover the same points.
AstraZeneca	Guideline	018	General	In response to question 8 (Do you think the visual summaries could be improved or made more useful? Please explain your response.), AstraZeneca have a number of comments on the visual summaries: **Visual Summary 2 (first-line treatment)** 1. AstraZeneca has received feedback from clinicians experienced in managing patients with T2DM suggests that the layout of the treatment algorithm for first-line treatment (visual summary 2) is unclear and may imply that SGLT2 inhibitors are positioned at second-line therapy following metformin. This is due to the similarity with the format used in other guidelines such as the ADA 2021 Diabetes guidelines which places metformin as first line positioned in a box along the top of the algorithm, similar to the box used here, to detail testing and investigation recommendations.[10] In this algorithm, in the high-risk and established CVD subgroups, metformin and SGLT2 inhibitors should be offered at the same time rather than as first- and	Thank you for your comment. We have added 'Start the SGLT2 inhibitor as soon as metformin tolerability is confirmed' to the recommendation. The technology appraisals apply to people who are not at a high risk of CVD, we have amended the visual summaries to clarify that the TAs have been included for the 'not at high CVD risk' pathway. HbA1c, CV risk and kidney function should all be assessed before initiating treatment and that is why they have been put in the first box before treatment initiation. Definitions of 'high risk' and ASCVD have been added to the visual summaries.

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				second-line options. AstraZeneca therefore suggest that in order to make it visually clearer to users that the recommendation at first-line is for dual therapy with metformin and an SGLT2 inhibitor, additional wording should be included in the established CVD and high-risk subgroup to make this clear. In addition, AstraZeneca suggest 'first-line' should be removed from the purple box at the top of the algorithm and instead added parallel to the first-line recommendation boxes for each subgroup. **AstraZeneca request that the layout of visual summary 2 (first-line treatment) is updated to avoid potential misunderstandings about positioning of SGLT2 inhibitors.** 2. The text box bordered with a dashed line detailing the NICE technology appraisals for SGLT2 inhibitors in visual summary 2 (first-line treatment) lacks clarity. Given the number of available SGLT2 inhibitors and differences in their licensed indications and reimbursement status, this represents an oversimplification of NICE technology appraisals for SGLT2 inhibitors. The most important and relevant statement for understanding this treatment algorithm is the final sentence "this guideline update (2021) recommends SGLT2 inhibitor use in a wider population than the technology appraisals published before August 2021". **AstraZeneca requests the Committee only include the final sentence regarding the updated NICE guideline recommendations for SGLT2 inhibitors in this dashed box and remove the additional text.** **A proposed update to Visual summary 2 which incorporates our comments from points 1 and 2 above is shown in Figure 2 below.** **Figure 2. Proposed changes to Visual Summary 2**	

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				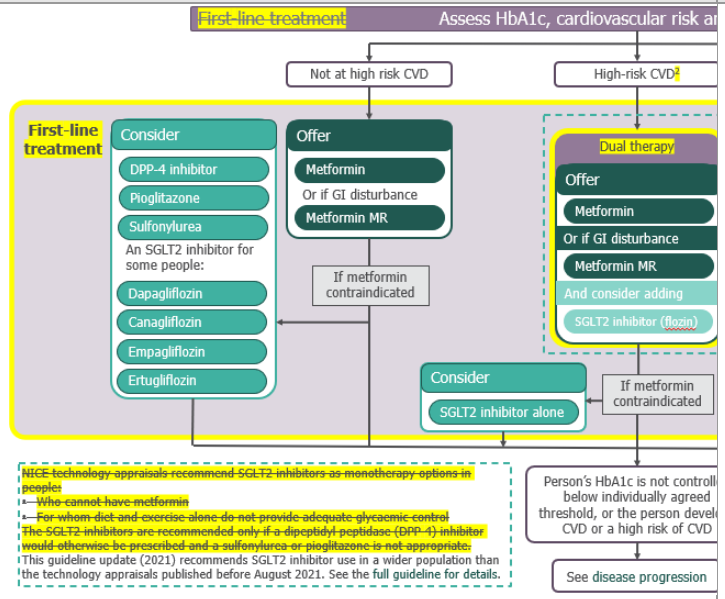 3. The first step of the first-line treatment algorithm (visual summary 2) is to "assess HbA1c, cardiovascular risk and kidney function". It is currently unclear whether these three factors should be assessed together or sequentially to determine the treatment approach. AstraZeneca's understanding is that, due to the comorbid nature of patient population, all three factors (HbA1c, cardiovascular risk, and kidney function) should be considered before making treatment decisions. Therefore, to enable evidence-based prescribing and clarity for prescribers, AstraZeneca suggest that this should be clarified within the treatment algorithm or as a footnote. **AstraZeneca request that further detail is added to visual summary 2 (first-line treatment) to explain whether HbA1c,**	

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				cardiovascular risk and kidney function should be assessed together or sequentially. **Visual Summaries 2 and 3** 1. The definition of "high risk" cardiovascular disease is not outlined in visual summary 2 (first-line treatment) or visual summary 3 (disease progression) in the draft guideline. AstraZeneca feel that defining high-risk CVD in this context within the treatment algorithms, as well as in the full guideline text, is important to best inform prescribing decisions and ensure consistency in prescribing. **AstraZeneca requests the Committee include a definition of "high-risk" cardiovascular disease in the treatment algorithms or include this as a footnote for each diagram. "High risk" CVD should be defined as "***adults with type 2 diabetes who have QRISK2 more than 10% in adults aged 40 and over* ***or*** *clinical judgement of an elevated lifetime risk of cardiovascular disease (defined as the presence of 1 or more cardiovascular risk factor in someone under 40)***", as specified elsewhere in the guideline.**	
AstraZeneca	Guideline	032	027	**Concern** The current draft guideline recommends the use of the QRISK2 tool to assess whether people are at high risk of developing cardiovascular disease (recommendation 1.7.4). AstraZeneca suggest that the updated QRISK3 tool would be more suitable to assess this risk, as further variables (such as CKD stages 3, 4 and 5) are included in the QRISK3 tool providing a more comprehensive assessment of risk. **Rationale** The committee recommended the use of the QRISK2 tool, a validated tool assessing a number of risk factors for CVD, to assess whether people are at high risk of developing CVD because this is the tool recommended in the NICE guideline on "cardiovascular disease: risk assessment and reduction included lipid modification". Additionally, the factors included in	Thank you for your comment. The committee deliberated over the definition of high risk of developing CV risk disease (high risk of future major adverse cardiovascular event such as an MI or stroke) to capture this population. They agreed that a QRISK2 score of >10% would be appropriate because this score takes into account most of the factors that were used to define this population in the economic model (and factors such as age, gender and ethnicity. They noted that QRISK2 is recommended for the assessment of CV risk in people with the 2 diabetes in the NICE guideline on NICE guideline on Cardiovascular disease: risk assessment and reduction, including lipid modification and is widely used and accepted in current general practice. Although other algorithms for assessing CVD risk exist, such as QRISK3,

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				the QRISK2 tool were judged to be similar to those used in the trials and economic model to define this population. Since this guideline was published in 2014, the QRISK3 tool has been developed and validated.[37] QRISK3 includes assessment of further risk factors known to be important for those at risk of developing CVD, including CKD (stages 3, 4 or 5), an important risk factor known to be associated with the development of CVD. AstraZeneca also understand based on communication from NICE that patients with CKD will also be included within this guideline upon final publication. Therefore, AstraZeneca suggest that the QRISK3 tool is recommended to provide a more comprehensive assessment of CV risk. **AstraZeneca requests that the Committee recommend the use of QRISK3 to assess CV risk.**	they are not in widespread use currently. Since a review of the evidence about the accuracy of such algorithms in comparison to each other and QRISK2 was not within the scope of this work, the committee agreed that QRISK2 was a pragmatic choice for assessing CV risk in people with type 2 diabetes.
AstraZeneca	Guideline	General	General	**SUMMARY** AstraZeneca would like to thank NICE for its commitment to advancing clinical care for patients with type 2 diabetes mellitus (T2DM). AstraZeneca also continues to be fully committed to advancing care for patients across the spectrum of cardiovascular (CV), renal and metabolic conditions. With this shared ambition and commitment to improve the lives of patients with these long-term conditions in mind, AstraZeneca welcomes the opportunity to respond to the draft NICE T2DM guidelines (NG28). AstraZeneca agrees with many of the recommendations set out by the committee in NG28, particularly the decision to recommend the use of sodium glucose co-transporter 2 (SGLT2) inhibitors for patients with T2DM who have or develop congestive heart failure or established atherosclerotic cardiovascular disease (ASCVD). However, we strongly feel that there are areas of the draft T2DM guideline update which represent significant missed opportunities to further improve the lives of patients and address areas of inequality of care. The main areas of concern include:	Thank you for your comments and support of the SGLT2 inhibitor class level recommendations for patients with T2DM who have or develop congestive heart failure or established atherosclerotic cardiovascular disease (ASCVD). However, in response to stakeholder comments the committee have slightly amended the wording of the draft recommendations for people at high cardiovascular (CV) risk who can and cannot) take metformin to refer to SGLT2i with proven CV benefit. They made this change to take into account that there was a greater degree of uncertainty around the CV benefit associated with ertugliflozin because it did not show a clinically meaningful reduction in hospitalisation for heart failure, unlike empagliflozin, canagliflozin and dapagliflozin, and was not statistically significantly better than placebo for the 3-point MACE outcome unlike canagliflozin and dapagliflozin. Despite this, in the NMAs ertugliflozin could not be differentiated from the other SGLT2i for hospitalisation for heart failure, non-fatal stroke, non-fatal myocardial infarction, or the 3 point MACE; and for CV and all cause mortality it could only be differentiated from

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				1. This updated guideline for T2DM represents a significant step forward for patients with T2DM. However, given the fundamental changes to T2DM management proposed in this guideline, it is vital that the recommendations are as clear as possible for treating physicians. As such, the guidelines must be explicit in detailing the populations in which they are making recommendations and should avoid generalist terms which lack clarity and may hinder identification of patients who will benefit most. NICE have requested consultee feedback on how to overcome challenges associated with this guideline, and AstraZeneca suggest that clearly calling out specific patient populations throughout the guideline will improve clarity. As such, AstraZeneca request that 'established cardiovascular disease (CVD)' in visual summary 2 is changed to 'established chronic heart failure, atherosclerotic CVD, or chronic kidney disease' to accurately reflect all relevant patient subgroups where SGLT2 inhibitors have demonstrated efficacy, ensure consistency with the written recommendations included in the guideline which specifically mention "congestive heart failure" or "established ASCVD" rather than "established CVD", and provide a clear recommendation to treating physicians 2. The proposed recommendation to "consider" instead of "offer" SGLT2 inhibitors in people with T2DM and at high risk of developing CVD does not reflect the varying strength of evidence of clinical benefit for individual therapies within the SGLT2 inhibitor class, and AstraZeneca suggest that this should be amended to "offer an SGLT2 inhibitor with proven cardiovascular and renal benefits in this patient population" 3. Currently, the draft recommendations across the whole treatment pathway do not reflect the differences in the strength of evidence, and consequently in licenced populations, of the SGLT2 inhibitors in specific patient subgroups such as those with high risk of CVD, those with established heart failure with	empagliflozin, which was clinically meaningfully better than all of the other SGLT2i for these last 2 outcomes. The committee recommended SGLT2 inhibitors with proven CV benefit because this wording would enable the prescribers to select a particular drug from within the SGLT2 class if they thought this was clinically justified based on the individual characteristics of their patient, whilst future proofing the recommendation should additional evidence or new SGLT2s be made available. Please see the responses to your numbered points where you explain these issues in separate detailed comments below. We have not responded here to reduce duplication.

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				reduced ejection fraction (HFrEF), and chronic kidney disease (CKD) 4. The updated guideline currently makes recommendations at a class level for SGTL2 inhibitors, implying that all SGLT2 inhibitors are equally appropriate for patients with T2DM and specific comorbidities despite the significant differences in available clinical and cost-effectiveness evidence for individual SGLT2 inhibitors in specific patient populations. This includes evidence from health economic modelling conducted by NICE which demonstrates that the SGLT2 inhibitor with the lowest acquisition cost is in fact not the most cost-effective. In addition, evidence-based, HTA driven guidelines should not consider acquisition cost over and above cost-effectiveness. AstraZeneca suggest that the proposed recommendation 1.7.1 "if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition costs" should be changed to "if 2 drugs in the same class are appropriate based on the strength of the clinical evidence and licenced indications, choose the option which represents the most cost-effective use of NHS resources". 5. The statement in recommendation 1.7.13 that "SGLT2 inhibitors have an adverse effect on renal function" directly contradicts evidence from Phase III clinical trials demonstrating the renal benefits associated with SGLT2 inhibitors, and the current recommendations disproportionately emphasise the potential side effects associated with SGLT2 inhibitors compared with other medicines currently used to treat T2DM. We consider this statement to be factually inaccurate and clinically misleading. The evidence for these concerns and suggested changes to the recommendations are outlined in detail in the sections below, as well as some additional comments. AstraZeneca respectfully requests the Committee to consider these important additions with a view to improving the speed and quality of care for patients with T2DM in the UK.	
AstraZeneca	Guideline	General	General	**Concern**	Thank you for your comment. The committee discussed the stakeholder comments about the use of the term

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				Throughout the current draft guideline, the terminology "congestive heart failure" is used. AstraZeneca understands that this terminology is not routinely used in clinical practice to refer to patients with heart failure (HF), and also note that the NICE guideline (NG106) for heart failure refers to "chronic heart failure". AstraZeneca therefore requests that "congestive heart failure" is updated to the more widely used term "chronic heart failure" throughout. **AstraZeneca requests that "congestive heart failure" is replaced with "chronic heart failure" throughout the guideline.**	'congestive' heart failure. They agreed that it would be inappropriate to change this to say symptomatic chronic heart failure with reduced ejection fraction because people with heart failure are a larger group of people than those with heart failure with reduced ejection fraction. In addition, the recommendations deliberately cover people with type 2 diabetes and heart failure to match the clinical and economic evidence. Based on stakeholder requests the committee decided to change congestive heart failure to chronic heart failure. This change was made because this term refers to the same population of people with heart failure as congestive heart failure does and it was thought that the wider medical society will understand this term better because it is in wider use currently.
AstraZeneca	Guideline	General	General	**Concern** Given the fundamental changes to T2DM management proposed in this guideline it is vital that the recommendations are as clear as possible for treating physicians, and the populations considered in the guideline are explicitly and clearly defined. As such, the guidelines should avoid the use of generalist terms which lack clarity and may hinder identification of patients who will benefit most. The term "established CVD" in visual summary 2 (first-line treatment) is an example of such a generalist term, and the use of this term is also inconsistent with the written recommendations included in the guideline, which specifically mention congestive heart failure or established ASCVD. In addition, recommendations for patients with T2DM and CKD are not currently included in either the written recommendations or treatment algorithms, despite the known benefits of SGLT2 inhibitors for these patients and a recommendation in the treatment algorithm to assess kidney function to inform treatment options. AstraZeneca request that "established CVD" is replaced with "established chronic heart failure, ASCVD and/or CKD" in visual summary 2, and that CKD is included in addition to established ASCVD or chronic heart failure in recommendations 1.7.4, 1.7.5, 1.7.9 and 1.7.16, to ensure consistency	Thank you for your comment. The visual summary has been changed to heart failure and ASCVD in line with the guideline recommendations. The renal benefits of using SGLT2 inhibitors in people with type 2 diabetes and CKD have been assessed in a separate piece of work that has recently been out for stakeholder consultation and was published in November 2021. The final recommendations on renal and cardiovascular benefits will be brought together in a single updated guideline document when this current work on cardiovascular benefits is published in 2022. The CKD recommendations are situated within the CKD section of the type 2 diabetes guideline and there is a cross reference to them from the drug treatment section. The CKD recommendations are in the section on CKD in the type 2 diabetes guideline with a cross reference from the drug treatment section. We have also linked to this section from the visual summary.

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				throughout the guideline, accurately reflect all relevant patient subgroups where SGLT2 inhibitors have demonstrated efficacy, and ensure that patients with specific co-morbidities that could most benefit from treatment with an SGLT2 inhibitor are explicitly included in these guidelines. The explicit inclusion of patients with CKD within NG28 would also help integrate the recommendations presented here in with those presented in NG203, helping primary care physicians navigate these two closely linked guidelines. **Rationale** Established CVD is an extremely broad term that refers to a variety of conditions affecting the heart or blood vessels. This includes heart and circulatory diseases such as coronary heart disease, angina, heart attack, congenital heart disease, hypertension, stroke and vascular dementia.[1] The evidence supporting the clinical effectiveness of SGLT2 inhibitors primarily originates from studies that were designed to assess efficacy in patients with heart failure, ASCVD and CKD, and do not provide strong evidence for all of these additional conditions (for example stroke or deep vein thrombosis).[2-4] AstraZeneca therefore believe that the use of such broad terminology is inappropriate and does not accurately reflect the available evidence. In addition, the written recommendations throughout the guideline refer to "congestive heart failure or established ASCVD" rather than "established CVD", as does visual summary 3 (disease progression). The use of "established CVD" in visual summary 2 is therefore inconsistent with the rest of the guideline and may lead to confusion as to which patients are likely to benefit from treatment with SGLT2 inhibitors. Importantly, and related to NICE's request for feedback on how to overcome challenges associated with this guideline (question 3 above), the use of "established CVD" could also limit the use of SGLT2 inhibitors for treatment of patients with specific comorbidities (heart failure, ASCVD and CKD) that could most benefit from treatment with an SGLT2 inhibitor. Furthermore, AstraZeneca feel that the inclusion of patients with T2DM and CKD within the NG28 treatment algorithm is critical to ensuring	

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				optimal care for this sizable patient population, in which SGLT2 inhibitors have demonstrated clinical effectiveness. The renal efficacy of SGLT2 inhibitors in patients with T2DM and CKD has been demonstrated in two dedicated renal outcomes trials: DAPA-CKD and CREDENCE. DAPA-CKD enrolled 2,906 (67.6%) patients with T2DM and CKD, and demonstrated that dapagliflozin significantly reduced the risk of the primary composite endpoint of sustained decline in estimated glomerular filtration rate (eGFR) ≥50%, end-stage kidney disease (ESKD) or death from renal or CV causes compared with placebo in this patient subgroup (10.4% versus 15.8%, respectively, hazard ratio [HR] 0.64; 95% CI: 0.52, 0.79; [redacted]).[5, 6] In CREDENCE, which enrolled 4,401 (100%) patients with T2DM and CKD, the relative risk of the primary composite outcome of ESKD, doubling of the serum creatinine level, or death from renal or CV causes was 30% lower in the canagliflozin group compared with the placebo group, with event rates of 43.2 and 61.2 per 1000 patient-years, respectively (HR: 0.70; 95%CI: 0.59, 0.82; p=0.00001).[7] AstraZeneca believes there to be approximately [redacted] patients with CKD and T2DM in England who would benefit substantially from treatment with an SGLT2 inhibitor.[8, 9] Both treatment algorithms included in the current recommendations state that renal function should be assessed when choosing medicines for patients with T2DM, and visual summary 4 states that options and doses of SGLT2 inhibitors may change if eGFR is <60 ml/min/1.73m^2 (i.e. in patients with CKD). As such, inclusion of this important patient population in which SGLT2 inhibitors have proven clinical benefit within the written recommendations and visual summaries of the guideline will help to simplify HCP decision making. This would also align these recommendations with the 2021 American Diabetes Association (ADA) guidelines for the treatment of patients with T2DM, which are widely considered to represent the gold standard approach to risk stratification of the T2DM population and provide separate recommendations for diabetes patients with heart failure, ASCVD and CKD.[10] Finally, AstraZeneca are aware of concern among primary care physicians regarding difficulties in easily identifying optimal treatment for	

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				patients with T2DM and CKD using these recommendations in their current format due to the requirement to refer to multiple guideline documents (NG28 and NG203). Integration of these guidelines through explicit inclusion of patients with CKD and T2DM in NG28 will reduce the risk of misinterpretation and any implementation issues going forwards. [confidential text redacted]	
AstraZeneca	Guideline	General	General	**Concern** The wording of the recommendations in 1.7.5, 1.7.9 and 1.7.16 to "consider" SGLT2 inhibitors in people with T2DM at high risk of developing CVD does not reflect the strength of the clinical evidence available for some SGLT2 inhibitors in this population. Given that a number of SGLT2 inhibitors do have robust clinical evidence to support their use in patients at risk of CVD, AstraZeneca request that the wording used is updated to "offer an SGLT2 inhibitor with proven cardiovascular and renal benefits in this patient population" to reflect the available evidence for dapagliflozin and canagliflozin in this population. The differences in the available evidence for patients at high CV risk are acknowledged by NICE in the evidence summary and model report supporting this guideline, but not in the written recommendations.[11] AstraZeneca believes that the current wording diminishes the strength of the evidence that does exist and may reduce the likelihood of evidence-based, quality care being delivered to patients across the NHS. AstraZeneca therefore firmly believes there is strong evidence to justify the use of "offer" in this context, based on NICE's definitions of how the terms "offer" and "consider" are used in a clinical guideline context.[12] **Rationale** Strength of available clinical evidence for SGLT2 inhibitors in patients with T2DM at high risk of developing CVD There is clear and strong evidence of benefit for dapagliflozin and canagliflozin in this patient population from the DECLARE-TIMI 58 and CANVAS trials, respectively. Both trials enrolled a substantial proportion of patients without established CVD (Table 1), and demonstrated	Thank you for your comment. The committee reviewed the stakeholder comments but decided to continue treating SGLT2 inhibitors (SGLT2i) as a class for the following reasons: • There was a degree of uncertainty around whether there were real differences in cardiovascular (CV) benefits between the SGLT2i based on the clinical trial evidence and results from the NMAs. o Firstly, for hospitalisation for heart failure, the SGLT2i empagliflozin, canagliflozin, and dapagliflozin produced a clinically meaningful reduction compared with placebo in the random effects NMA model. However, in the sensitivity analyses using a fixed effect model ertugliflozin also showed a clinically meaningful reduction compared to placebo, which reflects the original clinical trial data. The NMA results could not differentiate between the SGLT2i for this outcome. o Secondly, for the 3 point MACE outcome, only canagliflozin and empagliflozin produced a statistically significant reduction compared to placebo but the SGLT2i could not be differentiated from each other in the NMA. o Thirdly for all cause and CV mortality empagliflozin showed a clinically meaningful reduction compared to placebo and the other SGLT2i, but the remaining SGLT2i could not

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<tr><td></td><td></td><td></td><td></td><td>significant CV benefits in both the overall population and the subgroup of patients without established CVD but with high-risk of developing CVD. In clinical practice, this group represents a large proportion of patients with T2DM.[13] The lack of a clear recommendation to offer an SGLT2 inhibitor with proven CV and renal benefits in this population could therefore result in missed benefits for this group of patients.

Table 1. Summary of CV outcomes trials for SGLT2 inhibitors
<table>
<tr><th>Trial</th><th>Drug</th><th>Establishe</th></tr>
<tr><td>DECLARE-TIMI 58[2]</td><td>Dapagliflozin</td><td>6,974 (40.6</td></tr>
<tr><td>CANVAS[4]</td><td>Canagliflozin</td><td>6,656 (65.6</td></tr>
<tr><td>EMPA-REG[3]</td><td>Empagliflozin</td><td>6,964 (>99.</td></tr>
<tr><td>VERTIS CV[14]</td><td>Ertugliflozin</td><td>8,236 (>99.</td></tr>
</table>
Footnotes: Definition of eCVD: DECLARE-TIMI 58: Ischaemic heart disease, cerebrovascular disease or peripheral artery disease CANVAS: Documented symptomatic atherosclerotic disease EMPA-REG: History of MI, multivessel CAD, single-vessel CAD not revascularized, unstable angina, history of stroke or PAD VERTIS CV ≥40 years old with T2DM (HbA1c 7.0-10.5%) and established ASCVD of the coronary, cerebral, and/or peripheral arterial systems. Definition of high-risk (i.e. patients with multiple risk factors): DECLARE-TIMI 58: Men aged ≥55 years or women aged ≥60 years with one or more of: hypertension, dyslipidaemia, or use of tobacco CANVAS: Aged ≥50 years with two or more of: diabetes duration ≥10 years, systolic blood pressure >140 mmHg while on antihypertensive treatment, current daily smoking, micro- or macroalbuminuria, or HDL <1mmol/L.
Abbreviations: CVD: cardiovascular disease; SGLT2: sodium-glucose co-transport inhibitor 2.

The DECLARE-TIMI 58 trial had the largest proportion of patients without established CVD (N=10,186 [59.4%]) among the SGLT2 inhibitor CV outcomes trials (CVOTs). Co-primary efficacy endpoints were a composite of major adverse CV events (MACE; defined as CV death, myocardial infarction, or ischemic stroke) and a composite of CV death or hospitalization for heart failure (hHF). Dapagliflozin did not result in a lower rate of MACE in the overall trial population (8.8% in the dapagliflozin</td><td>be differentiated from each other or placebo in the NMA.
○ Fourthly, for non-fatal MI and non-fatal stroke the NMAs could not differentiate between empagliflozin, canagliflozin, ertugliflozin and placebo. The data for dapagliflozin was reported differently and could not be included in the NMAs. From the clinical trial data dapagliflozin could not be differentiated from placebo for MI and was not meaningfully different from placebo for stroke.
○ Finally, only dapagliflozin showed a clinically meaningful improvement in severe hypoglycaemia compared to placebo but the remaining SGLT2i could not be differentiated from each other and placebo in the NMA.
• There was also a degree of uncertainty around the cost-effectiveness of individual SGLT2i in the economic modelling. Although only dapagliflozin was cost-effective at a threshold of £20,000/quality-adjusted life year (QALY) across all model scenarios and CV risk groups it could not be differentiated from the other SGLT2i in the NMA apart from for the all-cause and CV mortality outcomes where it was clinically meaningfully worse than empagliflozin. The ranking of ICERs for the other SGLT2i varied across model scenarios and risk groups. The committee agreed that there was sufficient uncertainty in the economic modelling (caused in turn by uncertainty in the underlying clinical data) to mean that they were not sufficiently confident that these different ICERs represented true underlying differences in cost-effectiveness, as opposed to simply random variation in the results between different SGLT2 trials.
• Taking the cost-effectiveness and clinical results into account the committee decided against only recommending dapagliflozin and instead made</td></tr>
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				group and 9.4% in the placebo group; HR: 0.93; 95%CI, 0.84, 1.03; p=0.17) but did result in a lower rate of CV death or hHF (4.9% vs. 5.8%; HR: 0.83; 95%CI, 0.73, 0.95; p=0.005).[2] A pre-specified subgroup analysis of the co-primary endpoints found that patients with established ASCVD derived a similar treatment benefit of dapagliflozin to patients with multiple risk factors for ASCVD: • Dapagliflozin reduced the risk of the composite of CV death or hHF by 17% (HR 0.83; 95% CI: 0.71, 0.98) in patients with established ASCVD and by 16% (HR 0.84; 95% CI: 0.67, 1.04) in patients with multiple risk factors with no evidence of ASCVD (p-value interaction 0.99)[2] • There was also no statistical difference in the treatment effect of dapagliflozin between patients with established ASCVD (HR 0.90; 95% CI 0.79, 1.02) and patients with multiple risk factors with no evidence of ASCVD (HR 1.01; 95% CI 0.86, 1.20) on the composite MACE outcome (p-value interaction 0.25)[2] In the CANVAS trial, the rate of the primary composite endpoint of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke, was lower with canagliflozin than with placebo and subgroup analysis showed no significant between-group difference compared with placebo for patients with CVD compared to those with multiple risk factors.[15] <u>Strength of available health economic evidence for SGLT2 inhibitors in patients with T2DM at high risk of developing CVD</u> From Section 2.3.2 of the NICE health economic model report AstraZeneca understand that the committee considered the treatment effects of drugs included in CVOTs on hard outcomes (myocardial infarction (MI), heart failure (HF), stroke and ischemic heart disease, weight effects (and associated quality-adjusted life year [QALY] impact) and hypoglycaemia. However, the health economic model report does not provide details related to the consideration of beneficial effects of SGLT2 inhibitors on the progression of renal disease. In cost-effectiveness evaluation, it is mandatory to consider all treatment benefits when full drug acquisition costs are applied. Considering only incremental benefits	recommendations for the SGLT2i as a class. However, they recognised that there was a greater degree of uncertainty around the CV benefit associated with ertugliflozin because, depending on the choice of model used in the NMA, it did not consistently show a clinically meaningful reduction in hospitalisation for heart failure compared to placebo, unlike empagliflozin, canagliflozin and dapagliflozin. It was also not statistically significantly better than placebo for the 3-point MACE outcome unlike canagliflozin and empagliflozin. The committee therefore recommended SGLT2i with proven CV benefit because this wording would enable the prescribers to select a particular drug from within the SGLT2 class if they thought this was clinically justified based on the individual characteristics of their patient, whilst future proofing the recommendation should additional evidence or new SGLT2s be made available. As per the recommendation on choosing drug treatment, once the clinical circumstances and needs of the person with type 2 diabetes, including their need for CV protection, have been taken into account, if 2 drugs in the same class are suitable for that individual then the prescriber is still expected to choose the option with the lowest acquisition cost to help use NHS resources wisely. Please see evidence review A for more a more detailed explanation of the analyses that were carried out and the committee's discussion of the results. You requested that the 'consider' recommendations be increased in strength to 'offer' because of the greater proportion of people at high CV risk in the DECLARE-TIMI 58 and CANVAS trials. During development of the protocol for this piece of work focusing on CV benefit the committee did not identify people with high risk of developing CVD and

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				represents a biased approach that is likely to underestimate cost effectiveness. This is especially relevant since reno-protective effects of SGLT2 inhibitors represent a strong driver in cost effectiveness evaluations due to considerable potential to slow down the progression of CKD and onset of renal failure which largely impacts on life expectancy, QALY and costs. Therefore, the presented outcomes of the economic evaluation for SGLT2 inhibitors across all subgroups can be considered as conservative estimates of the cost effectiveness. The missed value due to the omission of SGLT2 inhibitor-related renal improvements should be acknowledged, especially in the context of the weaker 'consider' recommendation suggested in the high CVD risk group. To illustrate the degree of missed value associated with the omission of renal effects, AstraZeneca have conducted economic evaluations to assess the cost effectiveness of dapagliflozin with and without consideration of reno-protective effects. Details of the economic evaluation are briefly explained below but further information can be found in the summary modelling report that is submitted alongside this consultation response: • The SGLT2 inhibitor model was used. The model was originally developed to evaluate the cost-effectiveness of the SGLT2 inhibitor class versus standard of care (SOC) in T2DM. Details on the model structure and methodology are described by McEwan et al (2020).[16] The model appeared especially suitable since it allows the consideration of surrogate effects as well as effects on hard outcomes (HF, stroke, MI) via hazard ratios, similar to the modelling approach taken by NICE. o In the present analysis, the SGLT2 inhibitor model was applied to assess the cost-effectiveness of dapagliflozin added to SOC vs. SOC alone with and without the consideration of renal effects. Details of the applied modelling exercise are summarised in Table 2.	with established CVD as subgroups of interest. Therefore, we didn't separate data from the included studies based on their types of participants but looked at people in both of these groups as a single high risk population. This approach allows us to compare all of the drug treatments in a single analysis regardless of whether they contained both CV risk populations or only one, which is what the committee wanted us to do. A priori we had no reason to expect that a particular drug in the same class would be less effective if it was not trialled in people at high risk of developing CVD. The economic model included scenarios for high risk of developing CVD, established CVD and these groups combined. As you note, DECLARE-TIMI 58 and CANVAS have 59.4% and 34.4% of participants at high risk of developing CVD. However, as detailed above, the committee took the evidence for all of the SGLT2i into account when making the recommendation for people at high risk of developing CVD at a class level. Because the proportions of people in the high risk of developing CVD category were much lower in the EMPA-REG and VERTIS-CV trials (<1.0% in both cases) the comittee decided that although there was likely to be CV benefit for these people there was greater uncertainty compared to those with ASCVD or heart failure. As you have correctly pointed out, the renal benefits of SGLT2s has not been included in this analysis. This is primarily because this update focuses on evaluating the cardiovascular benefits of these drugs. The renal benefits of using SGLT2 inhibitors in people with type 2 diabetes and CKD have been assessed in a separate piece of work that has recently been out for stakeholder consultation and was published in November 2021. The final recommendations on renal and cardiovascular benefits will be brought together in a single updated guideline document when this current work on cardiovascular benefits is published in 2022.

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				○ A summary of outcomes for projections in a high CV risk (primary prevention) population and the THIN base case population is presented in Table 3. ○ The missed value associated with the non-incorporation of renal effects was quantified as the difference in incremental QALY, incremental costs and net monetary benefit from analyses that included and excluded renal effects. E.g., Missed QALY = $\Delta QALY_{incl.RB}$ - $\Delta QALY_{excl.RB}$ • A comparison of incremental cost-effectiveness outcomes for analyses with and without consideration of renal benefits is presented in Figure 1. [Text and figures identified as confidential have been removed] Based on the demonstrated additional value that can be expected through the consideration of renal effects of SGLT2 inhibitors and the associated increase in cost-effectiveness, we suggest changing the recommendation to "offer" SGLT2i in patients at high risk of developing CVD to reflect the strength of the available clinical and health economic evidence. Alignment of terminology between guidelines As outlined above, there is clear and strong evidence of benefit for dapagliflozin and canagliflozin in patients with T2DM at high risk of developing CVD. AstraZeneca believes the clinical evidence presented would be sufficient to receive a positive recommendation for dapagliflozin or canagliflozin for the treatment of patients with T2DM, with a history of CVD or at high-risk for CVD if this was presented within a NICE Single Technology Appraisal (STA). It is therefore evident that the benefit is highly certain for both dapagliflozin and canagliflozin. As such, according to the NICE Manual for developing guidelines, a recommendation of "offer" is appropriate, as this wording should be used when there is clear and strong evidence of benefit, with "consider" reserved for cases where the benefit is less certain.[12] There is no clinical or economic rationale that	Alignment of terminology between guidelines As you note recommendation 1.6.7 in the NICE guideline on Chronic kidney disease: assessment and management (NG203) uses 'offer' to refer to SGLT2 inhibitors for adults with CKD and type 2 diabetes. However, there is a statement as follows above this recommendation: 'NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. See the guideline update page on our website for more information.' Recommendation 1.6.7 has been superseded by new recommendations based on an additional update that focused on the effectiveness and cost-effectiveness of these drugs in people with type 2 diabetes and CKD. As detailed above, this work was published in November 2021. The approach we take for the use of SGLT2 inhibitors with people with established CVD or high CV risk is broadly in line with that taken in the newly updated CKD recommendations. The committee were aware of the ADA guidance, but their decisions were made according to the NICE guideline manual and took into account the evidence relevant to our review question. Although the NICE guidance may differ to the guidance provided by ADA, the committee were confident that their recommendations reflected the evidence they reviewed and their clinical judgement. It is of particular importance to note that the NICE guideline used an original economic model as the basis to recommend the most clinically and cost-effective options while the ADA guidance did not systematically take cost-effectiveness into account.

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				warrants a "consider" recommendation, which currently serves to diminish the robust clinical evidence that exists and reduce the likelihood of use. This would align the wording used in NG28 with the approach taken in NG203, in which an "offer" recommendation was made for SLGT2 inhibitors in patients with CKD and T2DM with macroalbuminuria despite evidence only being available in that patient population for dapagliflozin and canagliflozin, with additional clarification provided in a footnote that not all SGLT2 inhibitors are licenced for this population. In NG196, a similar approach is also taken where in recommendation 1.6.3 an "offer" recommendation is given for oral anticoagulants, and later in the guidelines the Committee emphasise that when choosing a therapy from the class "treatment should be tailored to the person's clinical needs and preferences".[17] Finally, in the ADA guidelines, which have been widely considered to be the "gold standard" for diabetes treatment, SGLT2 inhibitors "with demonstrated cardiovascular disease benefit" are recommended for patients with T2DM who have established ASCVD or indicators of high risk, established CKD, or heart failure.[10] AstraZeneca therefore requests the recommendation included in the T2DM guidelines for this subgroup is amended in a similar way to reflect the strength of the evidence available for dapagliflozin and canagliflozin in this patient population. **Summary** **AstraZeneca requests the Committee to consider reflecting the full breadth of evidence with the following amendments to recommendations 1.7.5, 1.7.9 and 1.7.16 (proposed changes in red):** 1.7.5 Based on the person's cardiovascular risk assessment: • If they are at high risk of developing cardiovascular disease, ~~consider~~ offer an SGLT2 inhibitor with proven CV and renal benefit in this patient population in addition to metformin. 1.7.9 For first-line drug treatment in adults with type 2 diabetes, if metformin is contraindicated or not tolerated:	

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				• If they are at high risk of developing cardiovascular disease, ~~consider~~ offer an SGLT2 inhibitor with proven CV and renal benefit in this patient population alone. [2021] 1.7.16 For adults with type 2 diabetes already on drug therapy: • If they are or become at high risk of developing cardiovascular disease, ~~consider~~ offer adding an SGLT2 inhibitor with proven CV and renal benefit in this patient population to current treatment or replacing an existing drug with the SGLT2 inhibitor.	
AstraZeneca	Guideline	General	General	**Concern** Currently, the draft recommendations across the whole treatment pathway do not reflect the differences in the available evidence or licenced populations between the available SGLT2 inhibitors. AstraZeneca request that these differences are reflected in the recommendations through additional wording and footnotes where appropriate to enable fully informed prescribing decisions. AstraZeneca wish to flag in particular that, as detailed above, not all CVOTs included patients without established CV disease, and that the strength of the available evidence in patients with HFrEF or CKD should not be considered equivalent across the SGLT2 inhibitor class. Inclusion of patients with CKD within the current guideline update would also reflect the ongoing consultation on the recommendations for SGLT2 inhibitors for chronic kidney disease (NG10246) being developed in parallel with these guidelines, which will partially update the guidelines included here. **Rationale** As summarised above in comment 3, AstraZeneca would like to highlight that not all CVOTs of SGLT2 inhibitors included patients without established CV disease. Further differences in the strength and breadth of the available evidence for each SGLT2 inhibitor are reflected in the licenced population for each drug, which are summarised in Table 4. Importantly, only two of the currently available SGTL2 inhibitors (dapagliflozin and empagliflozin) have sufficient evidence of efficacy and safety in patients with HFrEF to support a marketing authorisation in this population, and only dapagliflozin is currently reimbursed in this population in England. Furthermore, only dapagliflozin is licenced to treat patients with CKD.	Thank you for your comment. For first line treatment we are not recommending off-label use of the SGLT2 inhibitors (SGLT2i) because all currently available SGLT2i have a marketing authorisation for glycaemic control in adults with type 2 diabetes. Some SGLT2i (dapagliflozin and empagliflozin) have a marketing authorisation which includes symptomatic chronic heart failure with reduced ejection fraction alone, but we are not making recommendations for people who have heart failure with reduced ejection fraction who do not have type 2 diabetes. Symptomatic chronic heart failure with reduced ejection fraction is a subgroup of heart failure, which is one of the populations covered by the recommendations for people who also have type 2 diabetes. The committee did not limit the recommendations to adults with type 2 diabetes and symptomatic chronic heart failure with reduced ejection fraction because they intended the recommendation to cover the broader heart failure population, which was defined based on the participants in the cardiovascular outcome trials. In the recommendations for using SGLT2i for initial treatment in addition to metformin or in place of metformin if it is contraindicated / not tolerated, the SGLT2i is being used to provide glycaemic control and cardiovascular benefit. It is only if the use of an SGLT2i is retained despite not providing any glycaemic control that this would potentially be an off-label use. NICE expects that prescribers will use the drugs within the marketing authorisation over off-label use of a

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Table 4. Comparison of current SGLT2 inhibitor licenses in the UK

<table>
<tr><th></th><th>Indicated for T2DM</th><th>Indicated for HFrEF</th><th>I</th></tr>
<tr><td>Canagliflozin[18]</td><td>Yes</td><td>No</td><td></td></tr>
<tr><td>Dapagliflozin[19]</td><td>Yes</td><td>Yes</td><td></td></tr>
<tr><td>Empagliflozin[20]</td><td>Yes</td><td>Yes</td><td></td></tr>
<tr><td>Ertugliflozin[21]</td><td>Yes</td><td>No</td><td></td></tr>
</table>

Footnotes: Canagliflozin can be used for the treatment of diabetic kidney disease as add on to standard of care (e.g. ACE-inhibitors or ARBs).[18]
Abbreviations: CKD: chronic kidney disease; HFrEF: heart failure with reduced ejection fraction; T2DM: type 2 diabetes mellitus.

There is strong evidence for the treatment effect of dapagliflozin in HFrEF from the DAPA-HF trial. DAPA-HF was the first study of an SGLT2 inhibitor in patients with HFrEF, with or without T2DM. It was an event-driven, double-blind RCT with a median follow-up of 18.2 months which enrolled 4,744 patients and compared dapagliflozin (n=2,373) with placebo (n=2,371) for treatment of HFrEF, with patients also receiving current standard care for HFrEF in both arms. Overall, 42% of enrolled patients had T2DM. The results from DAPA-HF are summarised below:

- Dapagliflozin significantly reduced the risk of the primary composite endpoint of CV death, hHF, or an urgent heart failure visit, compared with placebo (16.3% vs 21.2%, respectively, HR 0.74 [95% CI 0.65, 0.85; p<0.001]).[22]
- Dapagliflozin also reduced the risk of each component of the composite endpoint, compared with placebo:
  - hHF – HR 0.70 (95% CI 0.59, 0.83; p<0.001)
  - Urgent heart failure visit – HR 0.43 (95% CI 0.20, 0.90; p=0.0213)
  - CV death – HR 0.82 (95% CI 0.69, 0.98; p=0.0294)
- Dapagliflozin was also superior to placebo for all secondary endpoints, including death from any cause (HR 0.83; 95% CI 0.71, 0.97; nominal p=0.022)

</td><td>licensed medicine where appropriate. Please see additional information on prescribing medicines and off-label or unlicensed use.

As explained in the response to your comment above, the committee decided to continue recommending SGLT2 inhibitors as a class, but they added the provision that they should have 'proven CV benefit'.

The renal benefits of using SGLT2 inhibitors in people with type 2 diabetes and CKD have been assessed in a separate piece of work that has recently been out for stakeholder consultation and was published in November 2021. The final recommendations on renal and cardiovascular benefits will be brought together in a single updated guideline document when this current work on cardiovascular benefits is published in 2022. The CKD recommendations are situated in the section on CKD in the type 2 diabetes guideline with a cross reference from the drug treatment section.</td></tr>
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				There is also evidence for the treatment effect of empagliflozin in HFrEF from the EMPEROR- REDUCED trial (n=3,730; 49.8% of patients had T2DM) in which the risk of the primary composite outcome of CV death or hHF, was significantly reduced with empagliflozin (19.4%) compared to placebo (24.7%) (HR 0.75; 95% CI 0.65, 0.86, p < 0.001).[23] • CV death – HR 0.92 (95%CI: 0.75, 1.12) • All-cause mortality – HR 0.92 (95% CI: 0.77, 1.10, p >0.05) Therefore, AstraZeneca believes the strength of the available evidence in patients with HFrEF should not be considered equivalent across the SGLT2 inhibitor class, as similar evidence is not available for other SGTL2 inhibitors. There is also strong evidence for the treatment effect of dapagliflozin in CKD from the DAPA-CKD trial. DAPA-CKD was a double-blind, placebo-controlled phase III RCT with a median follow up of 2.4 years, that compared dapagliflozin (n=2,152) to placebo (n=2,152) alongside SOC in both arms, for the treatment of CKD in patients with and without comorbid T2DM. Dapagliflozin significantly reduced the risk of the primary composite endpoint of sustained decline in eGFR ≥50%, ESKD or death from renal or CV causes compared with placebo (9.2% versus 14.5%, respectively, HR 0.61 ;95% CI: 0.51, 0.72; p<0.001).[24] The positive treatment effect of dapagliflozin was also consistent in post hoc subgroup analyses of patients with or without T2DM (p-value for interaction: 0.24).[6] The current guidelines do not reflect the differences between the licenced populations, and consequently the strength of evidence, between the SGLT2 inhibitors. AstraZeneca therefore request that these considerations are reflected in the recommendations through additional wording or footnotes where appropriate and a table (such as table 4) to summarise the differences between the SGLT2 inhibitors to enable fully informed prescribing decisions. **<u>Summary</u>**	

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				AstraZeneca believes that it is important to reflect the differences highlighted above in the recommendations, and therefore requests that recommendations 1.7.5, 1.7.9 and 1.7.16 are updated in line with this: 1.7.5 Based on the person's cardiovascular risk assessment: • If they have congestive heart failure or established atherosclerotic cardiovascular disease, offer an SGLT2 inhibitor with proven CV and renal benefit in the relevant patient population in addition to metformin • If they are at high risk of developing cardiovascular disease, offer an SGLT2 inhibitor with proven CV benefit in this patient population in addition to metformin. 1.7.9 For first-line drug treatment in adults with type 2 diabetes, if metformin is contraindicated or not tolerated: • If they have congestive heart failure or established atherosclerotic cardiovascular disease, offer an SGLT2 inhibitor with proven CV and renal benefit in the patient population alone. • If they are at high risk of developing cardiovascular disease, offer an SGLT2 inhibitor with proven CV benefit in this patient population alone. 1.7.16 For adults with type 2 diabetes already on drug therapy: • If they have or develop congestive heart failure or established atherosclerotic cardiovascular disease, offer an SGLT2 inhibitor with proven CV and renal benefit in the relevant patient population in addition to current treatment or replace an existing drug with the SGLT2 inhibitor • If they are or become at high risk of developing cardiovascular disease, offer an SGLT2 inhibitor with proven CV and renal benefit in this patient population to current treatment or replacing an existing drug with the SGLT2 inhibitor.	
AstraZeneca	Guideline	General	General	**Concern** AstraZeneca believes that the statement in recommendation 1.7.13 "SGLT2 inhibitors have an adverse effect on renal function and this needs to be monitored, taking into account individual clinical factors and baseline renal function" is factually incorrect. This statement directly contradicts	Thank you for your comment. The committee discussed the stakeholder comments about the renal impact of SGLT2 inhibitors (SGLT2i). They agreed that the existing recommendation was unclear and potentially confusing because it gave no indication of the frequently or when the monitoring should take place. They also recognised that

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				evidence from Phase III clinical trials demonstrating the renal benefits associated with SGLT2 inhibitors and their effect on delaying CKD progression and NG10246 which is being developed in parallel to this guideline.[7, 24, 25] In addition, although AstraZeneca appreciate that healthcare providers (HCPs) must be aware of relevant safety information in order to make informed prescribing decisions, the current draft guideline over emphasises the potential side effects associated with SGLT2 inhibitors versus other oral antidiabetic drugs (OADs). No contextual information is presented on the risks associated with medicines currently used to treat T2DM, and this is thus not a fair and balanced representation of the safety profile of T2DM therapies. **Rationale** SGLT2 inhibitors are associated with long-term renal benefits in patients with T2DM and CKD and are licensed for the treatment of CKD, and a requirement for monitoring of renal function risks inappropriate and premature treatment discontinuation Data from two double-blind, placebo-controlled, dedicated renal outcomes RCTs supports a significant renal treatment benefit of dapagliflozin and canagliflozin, respectively, in patients with CKD, in contrast with the current statement that "SGLT2 inhibitors have an adverse effect on renal function". DAPA-CKD compared dapagliflozin (n=2,152) to placebo (n=2,152) alongside SOC in both arms, for the treatment of CKD in patients with and without comorbid T2DM. The trial demonstrated dapagliflozin significantly reduced the risk of the renal composite endpoint of ≥50% sustained decline in eGFR, ESKD, or renal death compared to SOC (HR 0.56; 95% CI: 0.45, 0.68; p<0.001).[24] CREDENCE compared canagliflozin (n=2,202) to placebo (n=2,199) in patients with T2DM and albuminuric CKD. The trial demonstrated the relative risk of the composite of end-stage kidney disease, doubling of the serum creatinine level, or renal death was lower by 34% in the canagliflozin group (HR 0.66; 95% CI, 0.53- 0.81; p<0.001).[7]	although SGT2i can have a negative effect on renal function this is usually a small reduction in function and not a reason to stop taking the SGLT2i. Taking these points into account the committee have now removed this draft recommendation. The committee declined to add extra safety information for other drugs used to treat type 2 diabetes because they expect the clinician to refer to the BNF, SPCs and MHRA alerts when making prescribing decisions. They retained some safety information for the SGLT2i because these drugs are relatively new to clinical practice, and especially primary care, in some places and prescribers may be unaware of some of the issues they need to check or discuss with people with type 2 diabetes before treatment with an SGLT2i is initiated. Links to NICE's new (2021) recommendations on the use of SGLT2i for adults with chronic kidney disease and type 2 diabetes have also been added to the start of the drug treatment section. The draft recommendation which included sick day rules was reviewed following stakeholder comments and the bullet point on sick day rules has now been removed as the committee agreed it would be inconsistent to present this information for one class of drugs but not any others. They expected that sick day rules and other safety related advice would be discussed with the individual with type 2 diabetes as part of the decision-making process regarding drug choice and wanted to keep the guidance as simple and clear as possible.

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				The mechanism of action of SGLT2 inhibitors causes an initial decline in eGFR, due to a reduction in glomerular pressure following vasoconstriction in the afferent arteriole induced by SGLT2 inhibition. In the long term, this helps to protect the glomerulus from damage caused by the high intra-glomerular pressure common to patients with CKD.[26] eGFR subsequently increases again over several months and henceforth the SGLT2 inhibitor treatment slows progressive eGFR decline as compared with individuals not taking SGLT2 inhibitors. In the DAPA-CKD trial, a greater initial drop in eGFR was observed with dapagliflozin vs. placebo (-3.97(± 0.15) vs. –0.82 ± 0.15 ml/minute/1.73 m^2) after two weeks of treatment. Thereafter, the annual change in the mean eGFR was smaller with dapagliflozin than with placebo (–1.67 ± 0.11 vs. –3.59 ± 0.11 ml/minute/1.73 m^2, respectively), giving a between-group difference of 1.92 ml/minute/1.73 m^2 per year (95% CI: 1.61, 2.24).[24] Similar results have been consistently demonstrated in the clinical trials of other SGLT2 inhibitors that measured change in eGFR.[15, 24, 27-29] In post-hoc analyses of the EMPA-REG and CREDENCE trials, it has been shown that even in patients experiencing a high initial drop in eGFR (>10%) this does not reduce the SGLT2 inhibitor induced risk reduction for CV and renal outcomes, and has no impact on adverse event rate.[30, 31] <u>Evidence is available that AKI rates are lower in patients treated with SGLT2 inhibitors compared with placebo</u> AstraZeneca feel that the potential risk of AKI adverse events associated with SGLT2 inhibitors are overstated in the current guideline. As outlined above, the mechanism of action of SGLT2 inhibitors causes an initial decline in eGFR, but this is followed by a gradual increase over several months and a slower rate of progressive eGFR decline as compared with individuals not taking SGLT2 inhibitors.[26] Evidence from several randomised placebo-controlled trials indicate that serious AKI risk is reduced by treatment with SGLT2 inhibitors, and this is illustrated by the results of a meta-analysis of four key SGLT2 inhibitor outcome trials (CANVAS, CREDENCE, EMPA REG OUTCOME and DECLARE-TIMI 58) which enrolled populations with conditions traditionally considered high	

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<tr><td></td><td></td><td></td><td></td><td>risk for AKI. This meta-analysis observed a 25% lower relative risk of AKI in patients treated with SGLT2 inhibitors compared with placebo (HR: 0.75; 95% CI: 0.66, 0.85; p<0.0001).[32]

Evidence from the randomised DAPA-CKD trial and the heart failure trials DAPA-HF and EMPORER-REDUCED have demonstrated similar results, with comparable rates of AKI and renal-related adverse events between the studied SGLT2 inhibitor and placebo (Table 6 and Table 7), and these results are supported by the results of DAPA-HF and EMPEROR-REDUCED which investigated SGLT2 inhibitors in patients with heart failure and a wide range of eGFR categories.

Table 6. Renal adverse events from key clinical trials involving dapagliflozin
<table>
<tr><th>Adverse events, n/N (%)</th><th>Dapagliflozin</th><th>Placebo</th><th>p-value</th></tr>
<tr><td>DAPA-HF</td><td></td><td></td><td></td></tr>
<tr><td>Any renal AE†</td><td>153/2,368 (6.5)</td><td>170/2,368 (7.2)</td><td>0.36</td></tr>
<tr><td>Serious renal AE</td><td>38/2,368 (1.6)</td><td>65/2,368 (2.7)</td><td>0.009</td></tr>
<tr><td>DAPA-CKD</td><td></td><td></td><td></td></tr>
<tr><td>Renal-related adverse event†</td><td>155/2,149 (7.2)</td><td>188/2,149 (8.7)</td><td>0.07</td></tr>
</table>
Footnotes: †Based on pre-defined list of preferred terms.
Sources: McMurray et al. 2019[22] and Heerspink 2020[24]

Table 7. Renal adverse events from EMPORER-REDUCED
<table>
<tr><th>Adverse events, n/N (%)</th><th>Empagliflozin</th><th>Placebo</th><th>p-value</th></tr>
<tr><td>Acute kidney injury</td><td>46/1,863 (2.5)</td><td>67/1,867 (3.6)</td><td>0.53</td></tr>
</table>
Source: Zannad 2021[33]

In addition, a retrospective cohort study by Rampersad et al. 2020 assessed whether SGLT2 inhibitor use (n=4,778), compared with all other</td><td></td></tr>
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<tr><td></td><td></td><td></td><td></td><td>glucose-lowering drugs (oGLDs; n=4,778), is associated with increased rates of AKI. The results (shown in Table 8) demonstrate that SGLT2 inhibitors are not associated with increased risk for AKI compared to oGLDs.[34]

Table 8. AKI events in patients with T2DM using SGLT2 inhibitors versus other glucose-lowering drugs in a retrospective cohort study
<table>
<tr><th>Outcome</th><th>SGLT2 inhibitor vs oGLD (9</th></tr>
<tr><td>AKI composite</td><td>HR = 0.64 (0.40 – 1.03</td></tr>
<tr><td>AKI hospitalisation</td><td>HR = 0.62 (0.33 – 1.15</td></tr>
<tr><td>AKI laboratory</td><td>HR = 0.56 (0.32 – 0.98</td></tr>
<tr><td>AKI within 30 days</td><td>OR = 0.70 (0.27 – 1.84</td></tr>
<tr><td>AKI within 90 days</td><td>OR = 0.64 (0.36 – 1.16</td></tr>
</table>
Source: Rampersand 2020[34]
Abbreviations: AKI: acute kidney injury; oGLD: other glucose-lowering drugs; SGLT2: sodium-glucose cotransporter-2.

As mentioned in AstraZeneca's response to the NICE CKD guideline consultation [NG203], there is considerable concern amongst nephrologists over the Committee's recommendation to monitor renal function following the initiation of an SGLT2 inhibitor in patients with T2DM. Clinical expert opinion is that conducting an eGFR test in the weeks following SGLT2 inhibitor initiation is not informative and may cause unnecessary concern that could result in termination of a proven renal-protective treatment if the clinician isn't aware of the mechanism of action for this drug class. eGFR monitoring should therefore not be recommended in this context. This is further supported by the draft UK Kidney Association (UKKA) Clinical Practice guideline which recommends that "individuals initiated on an SGLT2 inhibitor do not routinely require an early assessment of renal function or potassium following initiation of treatment", because it is important that the early changes in eGFR that occur following initiation of SGLT2 inhibitors do not routinely result in withdrawal of SGLT2 inhibition when people are likely to gain significant benefit from these therapies.[35]</td><td></td></tr>
</table>

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				<u>Undue emphasis is currently placed on the potential risk of volume depletion adverse events associated with SGLT2 inhibitors compared with other medications used to treat T2DM</u> AstraZeneca acknowledge that there is some clinical evidence that SGLT2 inhibition may be associated with an elevated risk of volume depletion compared with placebo and that is it important for clinicians to be aware of this. However, AstraZeneca feel that the adverse effects of SGLT2 inhibitors are currently overstated in the recommendations compared with other medicines used to treat T2DM. In order to support evidence-based prescribing, AstraZeneca request the committee also detail relevant adverse events of other medicines currently used to treat T2DM to provide a more balanced overview of the relevant safety information. AstraZeneca would suggest including a table summarising the most frequent adverse events associated with each drug class, similar to the table below adapted from the ADA guidelines for diabetes management for example. **Table 9. Additional considerations associated with available OADs highlighted in the 2021 ADA guidelines for diabetes management** **Drug Class** / **Additional Conside** Metformin: • Gastrointestinal side effects common (dia; • Potential for B12 deficiency SGLT-2 inhibitors: • Should be discontinued before any sched for DKA; • DKA risk (all agents, rare in T2DM); • Risk of bone fractures (canagliflozin); • Genitourinary infections; • Risk of volume depletion, hypotension; • Increased LDL cholesterol; • Risk of Fournier's gangrene GLP-1 RAs: • Risk of thyroid c-cell tumours in rodents: h determined (liraglutide, albiglutide, dulaglu release, semaglutide)	

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	• GI side effects common (nausea, vomiting, diarrhoea) • Injection site reactions • Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected
DPP-4 inhibitors	• Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Joint pain
Thiazolidinediones	• Congestive heart failure (pioglitazone, rosiglitazone) • Fluid retention (oedema, heart failure) • Benefit in NASH • Risk of bone fractures • Bladder cancer (pioglitazone) • Increased LDL cholesterol
Sulfonylureas	• Increased risk of CV mortality based on studies of an older sulfonylurea (tolbutamide) • Moderate risk of hypoglycaemia, as per Visual Summary 4 of NG28
Insulin	• Injection site reactions • High risk of hypoglycaemia with human insulin vs analogues

Source: Adapted from American Diabetes Association 2021.[10]

Sick day rules

SGLT2 inhibitors are also currently the only therapy in the guideline for which sick day rules are specifically called out: recommendation 1.7.14 states "Advise adults with type 2 diabetes who are taking an SGLT2 inhibitor: to stop taking the SGLT2 inhibitor temporarily if they become ill (for example, with fever, diarrhoea or vomiting". AstraZeneca requests that similar cautions are included in the guidelines for metformin, which has similar sick day rules for illnesses that pose a risk of dehydration, with reference to a suitable guidance document such as the Diabetes and Primary Care SADMANS Sick Day rules.[36]

AstraZeneca respectfully request that NICE consider updating recommendations 1.7.13 and 1.7.14 to reflect the well-established safety profile of SGLT2 inhibitors in patients with T2DM (proposed change in red):

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				• 1.7.13 Be aware that SGLT2 inhibitors can cause fluid volume depletion and ~~have an adverse effect on renal function and~~ this needs to be monitored, taking into account individual clinical factors and baseline renal function. • 1.7.14 Advise adults with type 2 diabetes who are taking metformin or SGLT2 inhibitors to stop taking these therapies ~~SGLT2 inhibitor~~ temporarily if they become ill (for example, with fever, diarrhoea or vomiting)".	
AstraZeneca	Guideline	General	General	**Concern** The current wording in recommendation 1.7.6 around introducing metformin and an SGLT2 inhibitor as first-line therapy sequentially based on the person's CV risk assessment may lead to confusion for prescribers and patients. The recommendation, as currently worded, could be interpreted as a recommendation to prescribe the two drugs sequentially which could be viewed as first- and second-line therapy. **AstraZeneca requests that the Committee simplify the recommendation for prescribers and patients, updating the recommendation to (proposed changes in red):** When starting dual therapy with metformin and an SGLT2 inhibitor as first-line therapy, ~~introduce~~ prescribe the drugs simultaneously, and advise the patient to initiate the drugs sequentially, starting with metformin, checking their tolerability.	Thank you for your comment. The committee discussed the stakeholder comments about this recommendation and have reworded it to make their intentions clearer. It was felt that an approach of prescribing treatments both simultaneously and starting sequentially could be potentially confusing. The committee have instead clarified that the SGLT2 inhibitor should be started without delay once metformin is tolerated in order to avoid people remaining on metformin alone for prolonged periods.
AstraZeneca	Guideline	General	General	**Concern** The grouping of SGLT2 inhibitors throughout the draft guideline, without differentiation based on licensed indication and dosage, has the potential to increase the risk of prescribing error due to lack of awareness of dose considerations for different patient subgroups. **Rationale** AstraZeneca would like to highlight that the recommended doses for glycaemic control, heart failure and CKD differ for some SGLT2 inhibitors, as demonstrated in Table 10. Therefore, AstraZeneca believe that dose variations between indications should be considered by clinicians when	Thank you for your comment. For first line treatment we are not recommending off-label use of the SGLT2 inhibitors (SGLT2i) because all currently available SGLT2i have a marketing authorisation for glycaemic control in adults with type 2 diabetes. Some SGLT2i (dapagliflozin and empagliflozin) have a marketing authorisation which includes symptomatic chronic heart failure with reduced ejection fraction alone, but we are not making recommendations for people who have heart failure with reduced ejection fraction who do not have type 2 diabetes. Symptomatic chronic heart failure with reduced ejection fraction is a subgroup of heart failure, which is one of the populations covered by the

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<tr><td></td><td></td><td></td><td></td><td>deciding the appropriate SGLT2 inhibitor to prescribe, in order to reduce risk of prescribing error.

Table 10: Licensed indication and dosage for SGLT2 inhibitors
<table>
<tr><th>SGLT2 inhibitor</th><th>Dosage for T2DM</th><th>Dosage for HF</th><th>Dosage for CKD</th></tr>
<tr><td>Canagliflozin[18]</td><td>The recommended starting dose is 100 mg once daily. In patients tolerating canagliflozin 100 mg once daily who have an eGFR ≥ 60 mL/min/1.73 m^2 or CrCl ≥ 60 mL/min and need tighter glycaemic control, the dose can be increased to 300 mg once daily*</td><td>Not licensed for use in this indication</td><td>Not licensed to use in this indication**</td></tr>
<tr><td>Dapagliflozin[19]</td><td>The recommended dose is 10 mg once daily*</td><td>The recommended dose is 10 mg once daily</td><td>The recommended dose is 10 mg once daily</td></tr>
<tr><td>Empagliflozin[20]</td><td>The recommended starting dose is 10 mg once daily. In patients</td><td>The recommended dose is 10 mg once daily</td><td>Not licensed to use in this indication</td></tr>
</table></td><td>recommendations for people who also have type 2 diabetes. The committee did not limit the recommendations to adults with type 2 diabetes and symptomatic chronic heart failure with reduced ejection fraction because they intended the recommendation to cover the broader heart failure population, which was defined based on the participants in the cardiovascular outcome trials.

In the recommendations for using SGLT2i for initial treatment in addition to metformin or in place of metformin if it is contraindicated / not tolerated, the SGLT2i is being used to provide glycaemic control and cardiovascular benefit. It is only if the use of an SGLT2i is retained despite not providing any glycaemic control that this would potentially be an off-label use. NICE expects that prescribers will use the drugs within the marketing authorisation over off-label use of a licensed medicine where appropriate. Please see additional information on prescribing medicines and off-label or unlicensed use.

Finally, there is additional information provided in the visual summary to highlight to prescribers where dose adjustments may be required.
.</td></tr>
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<table>
<tr><td></td><td>tolerating empagliflozin 10 mg once daily who have an eGFR ≥60 ml/min/1.73 m^2 and need tighter glycaemic control, the dose can be increased to 25 mg once daily. The maximum daily dose is 25 mg*</td><td></td><td></td></tr>
<tr><td>Ertugliflozin[21]</td><td>The recommended starting dose of ertugliflozin is 5 mg once daily. In patients tolerating ertugliflozin 5 mg once daily, the dose can be increased to 15 mg once daily if additional glycaemic control is needed*</td><td>Not licensed for use in this indication</td><td>Not licensed for use in this indication</td></tr>
</table>
Footnotes: *When is used as combination therapy with insulin or an insulin secretagogue (e.g. sulphonylurea), a lower dose of insulin or the insulin secretagogue may be considered to reduce the risk of hypoglycaemia. **Whilst canagliflozin is not specifically licenced for CKD, the CREDENCE trial demonstrated that a dose of 100 mg could be used for the treatment of
</td><td></td></tr>
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				patients with diabetic kidney disease and eGFR ≥30 to < 60 ml/min/1.73 m^2. Thiscan be increased to 300 mg in patients with eGFR ≥60 ml/min/1.73 m^2. Canagliflozin is not recommended to be initiated in patients with eGFR < 30 ml/min/1.73 m^2 but can be continued at 100 mg for patients already taking canagliflozin. **Abbreviations:** CKD: chronic kidney disease; CrCl: creatinine clearance; eGFR: estimated glomerular filtration rate; HFrEF: heart failure with reduced ejection fraction; SGLT2: sodium glucose co-transporter 2; T2D: type 2 diabetes mellitus. **Sources:** EMA Invokana® (Canagliflozin) Summary of Product Characteristics[18]; EMA Forxiga® (Dapagliflozin) Summary of Product Characteristics[19]; EMA Jardiance® (Empagliflozin) Summary of Product Characteristics[20]; EMA Steglatro® (Ertugliflozin) Summary of Product Characteristics[21]. **AstraZeneca requests the Committee include a footnote to highlight that the recommended doses for glycaemic control, heart failure or CKD differ for some SGLT2 inhibitors, and this should be factored into prescribing decisions. AstraZeneca suggest that a table summarising the differences in licensed indication and dosage between SGLT2 inhibitors should also be included in the appendices of the guideline.**	
AstraZeneca	Guideline	General	General	**Concern** AstraZeneca acknowledge that the update to this guideline will represent a substantial change to current clinical management for patients with T2DM, therefore AstraZeneca propose that it may be beneficial to develop a decision aid to support clinicians in interpreting a patients' CV risk status and hence treatment approach, similar to the decision aid already developed for patients. **AstraZeneca propose that a decision aid is developed for clinicians to support understanding and interpretation of the guideline.**	Thank you for your comment. The current update is accompanied by a series of visual summaries to help clinicians understand and interpretate the recommendations. We have no current plans to develop an additional tool to help clinicians determine CV risk. This is outside the scope of our current work.
Blackpool Teaching Hospitals NHS	General	General	General	The published draft guideline does not reflect the final scope published by NICE in July 2020. The scope was to include review of pharmacological therapies for cardiovascular (CV) and other benefits in addition to blood glucose control. This update has narrowly focused on health economic	Thank you for your comment. The original scope of the update to the drug treatment sections of NG28 was to fully update the treatment section of the guideline as your comment notes. However, once work on the topic

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Foundation Trust				modelling of cardiovascular outcomes data in isolation; glycaemic lowering has not been evaluated, while weight reduction & other complications such as hypoglycaemia have been treated simplistically. The rationale for amending the final scope is unclear.	commenced it was determined that updating evidence reviews and health economics for such a wide scope, within the resources available to NICE for this topic, would take an unacceptably lengthy period. Taking such an approach for this guideline update would have further delayed publication of updated treatment recommendations in this rapidly changing area. In view of the timescales involved and the appetite from the committee and stakeholders for an update within an acceptable time period, we worked with our committee members to identify the priority areas for this update. The committee members agreed that our initial focus should be on reviewing the evidence from trials looking at cardiovascular outcomes. This reflected the changing evidence base as a result of the significant investment in clinical trials to directly capture cardiovascular outcomes, feedback from stakeholders that assessing this evidence was a priority and the impact that this new evidence could have on recommendations for the treatment of people with diabetes. We therefore revised the scope to reflect this and carried out the current piece of work. However, the non-phamcological areas of the original scope have been retained in the amended scope and are still being addressed. They are being published as separate pieces of work. Please see the type 2 diabetes in adults: management website for more details of published work. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder

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					comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand.
Blackpool Teaching Hospitals NHS Foundation Trust	General	General	General	The draft guideline lacks clarity and patient centricity. It is unclear how to individualise care in the case of those patients where the greatest concerns are weight, hypoglycaemia, renal failure or microvascular complications. This partial update could bring unintended confusion and additional complexity when considering treatment decisions for patients.	Thank you for your comment. The original scope of the update to the drug treatment sections of NG28 was to fully update the treatment section of the guideline with the aim of providing more individualised care for people where there was evidence to support it. However, once work on the topic commenced it was determined that updating evidence reviews and health economics for such a wide scope, within the resources available to NICE for this topic, would take an unacceptably lengthy period. Taking such an approach for this guideline update would have further delayed publication of updated treatment recommendations in this rapidly changing area. In view of the timescales involved and the appetite from the committee and stakeholders for an update within an acceptable time period, we worked with our committee members to identify the priority areas for this update. The committee members agreed that our initial focus should be on reviewing the evidence from trials looking at cardiovascular outcomes to try to provide more personalised recommendations for people with a high risk of developing cardiovascular disease and people with established cardiovascular disease. This reflected the changing evidence base as a result of the significant investment in clinical trials to directly capture cardiovascular outcomes, feedback from stakeholders that assessing this evidence was a priority and the impact that this new evidence could

					have on recommendations for the treatment of people with diabetes. We therefore revised the scope to reflect this and carried out the current piece of work. Please note the renal benefits of using SGLT2 inhibitors in people with type 2 diabetes and CKD have been assessed in a separate piece of work that has recently been out for stakeholder consultation and was published in November 2021. The final recommendations on renal and cardiovascular benefits will be brought together in a single updated guideline document when this current work on cardiovascular benefits is published in 2022. In addition, to make it easier for prescribers to select appropriate treatment options that match the needs of each individual we have developed a summary table listing relevant factors such as whether the drug is associated with weight loss or weight gain. It is hoped that this table, together with the recommendation about factors to take into account when choosing drugs that includes tailoring drug choice to individual needs and circumstances, will support personalised care. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand.

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Blackpool Teaching Hospitals NHS Foundation Trust	General	General	General	The economic modelling has resulted in limited recommendations for reducing CV risk in high risk diabetes populations. The data in the economic model was limited to assessment of cardiovascular outcome trial data only and did not account for the totality of efficacy data of newer GLP-1RAs published since 2012. NICE have concluded that GLP-1RAs as a class are not cost effective for reducing cardiovascular risk and have not therefore recommended their use in the pathway for diabetes patients with high CV risk or established CVD. Novo Nordisk believe the analysis underpinning this conclusion is uncertain. While it is acknowledged that SGLT-2s will have an earlier position in the pathway than GLP-1RAs, Novo Nordisk believe that alternative recommendations to SGLT-2s in patients at high risk of CVD, where SGLT-2is are not tolerated or not suitable for individual patients, should be in place. This should include the recommendation of alternative medicines with clinical evidence of CV risk reduction.	Thank you for your comment. The original scope of the update to the drug treatment sections of NG28 was to fully update the treatment section of the guideline as your comment notes. However, once work on the topic commenced it was determined that updating evidence reviews and health economics for such a wide scope, within the resources available to NICE for this topic, would take an unacceptably lengthy period. Taking such an approach for this guideline update would have further delayed publication of updated treatment recommendations in this rapidly changing area. In view of the timescales involved and the appetite from the committee and stakeholders for an update within an acceptable time period, we worked with our committee members to identify the priority areas for this update. The committee members agreed that our initial focus should be on reviewing the evidence from trials looking at cardiovascular outcomes. This reflected the changing evidence base as a result of the significant investment in clinical trials to directly capture cardiovascular outcomes, feedback from stakeholders that assessing this evidence was a priority and the impact that this new evidence could have on recommendations for the treatment of people with diabetes. We therefore revised the scope to reflect this and carried out the current piece of work. Although there were a number of stakeholder comments asking for clarification of the treatment options for people with type 2 diabetes in whom SGLT2 inhibitors (SGLT2i) were contraindicated or not tolerated, there were no cardiovascular outcome trial style clinical trials identified that looked at the effectiveness of treatments for people at high cardiovascular (CV) risk in this population. The committee therefore used the evidence for effectiveness and cost

					effectiveness for other interventions from the same economic modelling scenarios as those looking at the cost-effectiveness of SGLT2i. The committee reviewed the stakeholder comments regarding the use of GLP-1 mimetics and examined the updated economic evidence relating to GLP-1 mimetic treatment for people with type 2 diabetes and high cardiovascular risk. In the NICE health economic analyses, when looking at GLP-1 mimetics as a class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of £20,000-£30,000/QALY. Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable

					semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors. In addition, the committee noted that there were differences in the clinical effectiveness of the 2 forms of semaglutide. Although the acquisition costs for injectable and oral semaglutide are similar they showed marked differences in cost-effectiveness in the economic analyses. This was caused by differences in the effect estimates for stroke, myocardial infarction and severe hypoglycaemia. From earlier discussions about the clinical evidence (see the discussion sections in the evidence review for more details) the committee had agreed that it was uncertain whether the observed differences in effect on all-cause mortality compared to placebo between the 2 forms of semaglutide were real and they therefore decided not to place undue weight on them. They had also noted that this uncertainty and any other differences in effects between the drugs for other outcomes was probably due to wide 95% confidence intervals for many outcomes with these drugs, due to the smaller numbers of participants and events in the trials compared to other CVOTs. The committee therefore agreed that they were unable to recommend injectable semaglutide for people with type 2

					diabetes and high cardiovascular risk who were unable to take an SGLT2i. As a result, the committee noted that people with high CV risk who could not take metformin with an SGLT2i would be offered metformin alone at treatment initiation. If they were also unable to take metformin then the clinician would select another treatment from the remaining options. Based on the CVOT evidence reviewed in this update, patients with high CV risk or with established CVD disease would be expected to be taking an SGLT2i for CV protection by the time they reach later stages of treatment. As discussed above the GLP-1 mimetics were not cost-effective alternatives for people in this population. In the absence of evidence from the CVOT studies for a different approach, the 2015 recommendations were retained for later stages of the treatment pathway. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand. The committee have taken stakeholder comments into account and agreed to remove the recommendation about not using GLP1-mimetic therapy solely for cardiovascular risk reduction in people with type 2 diabetes. Upon reviewing

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					the recommendation, the committee agreed that it was inappropriate to make a decision about treatment choice based solely on a single factor (cardiovascular risk) and that, as detailed in the recommendation about choosing drug treatments,, multiple factors should be taken into account instead.
Blackpool Teaching Hospitals NHS Foundation Trust	General	General	General	Instead, NICE has retained second and third line therapy recommendations from the 2015 guideline (DPP-4 inhibitors, pioglitazone, sulphonylureas), including for patients with high CV risk. This is despite some of these medicines not demonstrating a CV benefit and without assessing their overall risk-benefit for specific patient needs such as hypoglycaemia, weight reduction and CKD. GLP-1RAs are specifically mentioned as to be excluded for use solely for CV risk reduction. As none of the GLP-1RAs have a license to be used solely for CV risk reduction this statement could cause confusion and further restrict access to these medicines for patients who could benefit.	Thank you for your comment. Please see the response to your earlier comment for a full consideration of the issues you have raised here.
Blackpool Teaching Hospitals NHS Foundation Trust	General	General	General	The draft guideline does not reflect the totality of available published evidence to inform prescribing decisions for GLP-1RAs. This update has assessed the cardiovascular outcome data of the class in isolation and other 2015 recommendations have not been evaluated. The 2015 glycaemic - focused guidance was based on published evidence for GLP-1RAs prior to July 2012, over 9 years ago. Several newer GLP-1RAs (including semaglutide and dulaglutide) have been licensed for UK use since then. The evidence of these medicines and their significantly increased glycaemic efficacy, weight loss, associated CV benefits and cost effectiveness compared to earlier medicines in the GLP-1RA & other classes of medications has never been formally assessed by NICE either through an HTA or as part of this guideline update. As a result there has been no consideration or evaluation of the GLP-1RA stopping rules or review of where GLP-1RAs should be placed within the pathway, how they differentiate from each other and with reference to their use specifically prior to insulin. This is in contrast with the SGLT-2i class, all of which have been fully assessed through the extensive HTA process and placed in the pathway accordingly. It is therefore not known if the 2015 recommendations are still valid. By excluding assessment of the GLP-1RA class of medicines	Thank you for your comment. The original scope of the update to the drug treatment sections of NG28 was to fully update the treatment section of the guideline as your comment notes. However, once work on the topic commenced it was determined that updating evidence reviews and health economics for such a wide scope, within the resources available to NICE for this topic, would take an unacceptably lengthy period. Taking such an approach for this guideline update would have further delayed publication of updated treatment recommendations in this rapidly changing area. In view of the timescales involved and the appetite from the committee and stakeholders for an update within an acceptable time period, we worked with our committee members to identify the priority areas for this update. The committee members agreed that our initial focus should be on reviewing the evidence from trials looking at cardiovascular outcomes. This reflected the changing

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				from this update clinicians will not have access to key guidance and clear evidence of the full range of treatment options	evidence base as a result of the significant investment in clinical trials to directly capture cardiovascular outcomes, feedback from stakeholders that assessing this evidence was a priority and the impact that this new evidence could have on recommendations for the treatment of people with diabetes. We therefore revised the scope to reflect this and carried out the current piece of work. You are correct that the model does not contain every outcome that could potentially be of interest for modelling adults with type 2 diabetes. However, the committee agreed these were the most important outcomes for assessing the additional cardiovascular and other benefits associated with drug treatment for type 2 diabetes, for the majority of the type 2 diabetes population. The committee agreed the cardiovascular outcome trials were the most appropriate data source to assess cardiovascular benefits of these drugs, being powered to specifically detect differences in hard outcomes, rather than only surrogate outcomes. The committee noted these studies were not representative of the full population of people with type 2 diabetes, but agreed this was a lesser limitation than the need to extrapolate from surrogate endpoints to cardiovascular outcomes, particularly given the findings from those studies suggesting these surrogate extrapolations are often not very robust. They also agreed that taking data on weight and hypoglycaemic events from these cardiovascular outcome trials was the most appropriate approach, in order to match the data used for cardiovascular event rates. For hypoglycaemic events, the approach taken is broadly in line with that taken in many other evaluations in diabetes, attaching costs and quality of life outcomes to the incidence of severe hypoglycaemic events, as these are the ones that

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					make the most difference to a person's life. For changes in weight, it was noted it was important not to double count the impact of changes, as the effects on cardiovascular outcomes should already be captured in the outcomes of those trials. It was therefore agreed that the most appropriate approach was to only include the direct quality of life gains associated with reductions in weight, with the other benefits captured through the cardiovascular event data. The committee noted that if anything the approach taken in the guideline may overestimate the benefits of weight reduction, as some of the estimated quality of life gains may be the result of avoided cardiovascular events, but it was agreed to be the best data source available. There are of course other benefits that could have been considered as part of the modelling, including renal (or other microvascular) outcomes, or additional benefits directly related to improved glycaemic control, but the committee considered these to be of lower priority than those included in the model. They also noted that it would not be appropriate for any modelling approach to simply look at benefits on different outcomes from different trials or data sources, and assume those benefits are additive, and therefore increase the cost-effectiveness of drugs when included together. They noted that in many circumstances these benefits are not additive, and which benefits are likely to be realised may depend on the individual characteristics of the people included in studies. As an example, in the separate evaluation of SGLT2 inhibitors for people with CKD and type 2 diabetes, SGLT2 inhibitors were found to significantly improve renal outcomes, but this is a population in which a large benefit would not be expected for glycaemic control (hence why these agents were not originally licensed for use in people with impaired renal function).

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					It should also be noted that it is not the case that only additional outcomes beneficial to drug therapy were excluded from the modelling. As an example, adverse events related to drug treatment (excluding hypoglycaemia) were not included as part of the analysis. As a number of the analyses in the guideline explicitly compare the addition of new treatments (for example, using 3 drugs versus 2) rather than simply switching drugs, it would be expected that inclusion of adverse events would decrease the cost-effectiveness for any additional treatments, as they would add to the adverse event burden. Therefore, whilst it is likely there would be differences found in the results of the cost-effectiveness analysis were a different set of outcomes to be included, it is not clear in which direction the results would change for any given agent, and whether they would become more or less cost-effective. Please note that evidence for newer GLP-1 mimetics was included in this review. Cardiovascular outcome trial evidence for every currently licensed GLP-1 mimetic with a licensed indication for type 2 diabetes in the UK was included in both the evidence review and economic model including both oral and injectable semaglutide (PIONEER-6 and SUSTAIN-6 trials) and dulaglutide (REWIND trial) and the DPP-4 and sulfonylureas, please see Evidence Review A document for details. For people who do not have heart failure, established ASCVD or who are not at high risk of a CV events the committee agreed that the new CVOT evidence would not apply to them, Also, the alternative treatment options for people with and without increased cardiovascular risk remained the same for later treatment stages. Therefore, the committee agreed to retain the existing 2015 NG28 recommendations for treatment options for those at lower CV risk or if further interventions are required.

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					NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand.
Blackpool Teaching Hospitals NHS Foundation Trust	General	General	General	The economic modelling has resulted in limited recommendations for reducing CV risk in high risk diabetes populations. The data in the economic model was limited to assessment of cardiovascular outcome trial data only and did not account for the totality of efficacy data of newer GLP-1RAs published since 2012. NICE have concluded that GLP-1RAs as a class are not cost effective for reducing cardiovascular risk and have not therefore recommended their use in the pathway for diabetes patients with high CV risk or established CVD. Novo Nordisk believe the analysis underpinning this conclusion is uncertain. While it is acknowledged that SGLT-2s will have an earlier position in the pathway than GLP-1RAs, Novo Nordisk believe that alternative recommendations to SGLT-2s in patients at high risk of CVD, where SGLT-2is are not tolerated or not suitable for individual patients, should be in place. This should include the recommendation of alternative medicines with clinical evidence of CV risk reduction. Instead, NICE has retained second and third line therapy recommendations from the 2015 guideline (DPP-4 inhibitors, pioglitazone, sulphonylureas), including for patients with high CV risk. This is despite	Thank you for your comment. Please see the response to your earlier comment for a full consideration of the issues you have raised here.

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				some of these medicines not demonstrating a CV benefit and without assessing their overall risk-benefit for specific patient needs such as hypoglycaemia, weight reduction and CKD. GLP-1RAs are specifically mentioned as to be excluded for use solely for CV risk reduction. As none of the GLP-1RAs have a license to be used solely for CV risk reduction this statement could cause confusion and further restrict access to these medicines for patients who could benefit.	
Blackpool Teaching Hospitals NHS Foundation Trust	General	General	General	The guidance with respect to use of the GLP-1RA class in renal impairment is inaccurate. To say that the class should be avoided or used with caution in any renal impairment when four out of the seven formulations for the GLP-1RA class can be used without dose adjustment in severe renal impairment is not helpful, particularly when there are already such limited options for these patients.	Thank you for your comment. We have now provided this information specific for individual medicines rather than medicine classes.
Blackpool Teaching Hospitals NHS Foundation Trust	General	General	General	By limiting the scope of update to assessment of cardiovascular benefit only, the resulting guideline appears disjointed and could add confusion rather than clarity to individualised treatment decision-making. It is not clear how consideration of additional clinical characteristics, including those important to patients' quality of life such as weight, hypoglycaemia and frailty should influence prescribing decisions	Thank you for your comment. The original scope of the update to the drug treatment sections of NG28 was to fully update the treatment section of the guideline as your comment notes. However, once work on the topic commenced it was determined that updating evidence reviews and health economics for such a wide scope, within the resources available to NICE for this topic, would take an unacceptably lengthy period. Taking such an approach for this guideline update would have further delayed publication of updated treatment recommendations in this rapidly changing area. In view of the timescales involved and the appetite from the committee and stakeholders for an update within an acceptable time period, we worked with our committee members to identify the priority areas for this update. The committee members agreed that our initial focus should be on reviewing the evidence from trials looking at cardiovascular outcomes. This reflected the changing evidence base as a result of the significant investment in clinical trials to directly capture cardiovascular outcomes, feedback from stakeholders that assessing this evidence was a priority and the impact that this new evidence could

					have on recommendations for the treatment of people with diabetes. We therefore revised the scope to reflect this carried out the current piece of work. However, the non-phamcological areas of the original scope have been retained in the amended scope and are still being addressed. They are being published as separate pieces of work. Please see the type 2 diabetes in adults: management website for more details of published work. Please note that The renal benefits of using SGLT2 inhibitors in people with type 2 diabetes and CKD have been assessed in a separate piece of work that has recently been out for stakeholder consultation and was published in November 2021. The final recommendations on renal and cardiovascular benefits will be brought together in a single updated guideline document when this current work on cardiovascular benefits is published in 2022. To make it easier for prescribers to select appropriate treatment options that match the needs of each individual we have developed two visual summaries which contain a table listing relevant factors such as whether the drug is associated with weight loss or weight gain. It is hoped that this table, together with the recommendation on choosing drug treatments that includes tailoring drug choice to individual needs and circumstances, will support personalised care. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update

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					of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand.
Boehringer Ingelheim	General	General	General	We feel that the overall guideline provides a very thorough overview on how to manage type 2 diabetic patients. The use of SGLT2s will help to ensure better care for diabetes patients as well as ease of prescribing for health care professionals. As the therapeutic paradigm of type 2 diabetes management is changing, (i.e. glycaemic control is not the only factor to consider to type 2 diabetes management), we feel that it would be useful to include a section on 'goals of type 2 diabetes treatment' which will include considerations of the Cardio-Renal-Metabolic (CRM) conditions to improve patient outcomes and reduce healthcare resource use. This will be in line with recommendations from ADA/EASD guidelines that suggest a more expansive approach is needed in type 2 diabetes management.[1] Pharmacotherapeutic regimen should be tailored to the specific needs of the patient and not just on the basis of their glucose-lowering efficacy. The new guiding principle is that drugs should be selected based on the presence of comorbidities, particularly ASCVD, HF, or CKD, while also taking into account patients' clinical characteristics, risks for side effects, and socioeconomic factors.	Thank you for your comment and support of the SGLT2 recommendations. The committee agreed with the need to produce guidance to help promote personalised treatment. The original scope of this work covered additional groups of interest including people with renal impairment, people in specific ethnic groups, adults aged 65 years and older, as well as people in specific cardiovascular risk groups. It aimed to fully update the drug treatment sections of the NG28 guideline. However, once work on the topic commenced it was determined that updating evidence reviews and health economics for such a wide scope, within the resources available to NICE for this topic, would take an unacceptably lengthy period. The committee members agreed that our initial focus should be on reviewing the evidence from trials looking at cardiovascular outcomes. This reflected the changing evidence base as a result of the significant investment in clinical trials to directly capture cardiovascular outcomes, feedback from stakeholders that assessing this evidence was a priority and the impact that this new evidence could have on recommendations for the treatment of people with diabetes. We therefore revised the scope to reflect this and

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				Cardio-Renal-Metabolic (CRM) conditions are a major clinical and economic burden, as they coexist, amplify each other, are progressive and a major burden to health care systems. <u>Reference:</u> 1. Buse J, Wexler D, Tsapas A, et al. 2019 update to: Management of hyperglycaemia in type 2 diabetes, 2018: a consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 2020;63:221–228.	carried out the current piece of work looking at cardiovascular benefits. The renal benefits of using SGLT2 inhibitors in people with type 2 diabetes and CKD have been assessed in a separate piece of work that has recently been out for stakeholder consultation and was published in November 2021. The final recommendations on renal and cardiovascular benefits will be brought together in a single updated guideline document when this current work on cardiovascular benefits is published in 2022. Additionally, the committee believe that the addition of the visual summary to the guideline will help healthcare professionals make treatment more personalised and takes comorbidities into account. The committee were unable to add a section to the guideline covering goals of type 2 diabetes treatment because this was not included in the scope of the current update. However, as discussed above, the committee did make recommendations for people with type 2 diabetes and ASCVD or HF and another recent update covered people with CKD. The committee agreed that it is important to tailor the drug treatment regimen to the specific needs of the patient and not just on the basis of their glucose-lowering efficacy. To make it easier for prescribers to select appropriate treatment options that match the needs of each individual we have developed a summary table listing relevant factors such as whether the drug is associated with weight loss or weight gain. It is hoped that this table, together with the recommendation about choosing drug treatments that covers tailoring drug choice to individual needs and circumstances, will support personalised care.

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					NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs.
Boehringer Ingelheim	Guideline	013	018	We feel that that by adding there is safety advice from MHRA, it may be confusing for health care professionals as there has been no new guidance from MHRA since March 2020 and only relates to monitoring ketones. i.e. 'SGLT2 inhibitor treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses and ketone levels measured, preferably in blood rather than urine. Treatment may be restarted when the ketone values are normal and the patient's condition has stabilised' If this statement is to be kept, we suggest that advice needs to be balanced across other drug classes such as sulphonylureas and glp-1 receptor agonists. i.e. 1) GLP-1 receptor agonists: reports of diabetic ketoacidosis when concomitant insulin was rapidly reduced or discontinued, MHRA guidance 2019 found at: GLP-1 receptor agonists: reports of diabetic ketoacidosis when concomitant insulin was rapidly reduced or discontinued - GOV.UK (www.gov.uk)	Thank you for your comment. In response to stakeholder consultation comments the committee have removed the text boxes containing the MHRA safety advice because they agreed that prescribers are expected to consult MHRA alerts, the BNF and summary of product characteristics (SPC) for safety information and that it was therefore unnecessary and potentially confusing to refer to MHRA alerts in the guideline. .

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				2) SGLT2 inhibitors: monitor ketones in blood during treatment interruption for surgical procedures or acute serious medical illness, MHRA guidance 2020 found at: SGLT2 inhibitors: monitor ketones in blood during treatment interruption for surgical procedures or acute serious medical illness - GOV.UK (www.gov.uk) 3) Pioglitazone: risk of bladder cancer, MHRA guidance 2014 found at: Pioglitazone: risk of bladder cancer - GOV.UK (www.gov.uk) 4) Insulins (all types): risk of cutaneous amyloidosis at injection site - GOV.UK (www.gov.uk) 5) SGLT2 inhibitors: reports of Fournier's gangrene (necrotising fasciitis of the genitalia or perineum) - GOV.UK (www.gov.uk) 6) SGLT2 inhibitors: updated advice on increased risk of lower-limb amputation (mainly toes) - GOV.UK (www.gov.uk) 7) Canagliflozin (Invokana▼, Vokanamet▼): signal of increased risk of lower extremity amputations observed in trial in high cardiovascular risk patients - GOV.UK (www.gov.uk) 8) SGLT2 inhibitors: updated advice on the risk of diabetic ketoacidosis - GOV.UK (www.gov.uk)	
Boehringer Ingelheim	Guideline	013	019	We think it is useful to have the visuals alongside the recommendations summarised. It is easier for health care professionals to view the information easily when in consultation with patients and in day to day practice. A PDF of all the visual summaries would still be helpful as healthcare professionals would like to see the full algorithm easily.	Thank you for your comment. We have kept the visual summaries alongside the recommendations and as a separate PDF.
Boehringer Ingelheim	Guideline	014	013	In relation to the statement "- cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost)."	Thank you for your comment. We agree that the factors that guide healthcare professionals (and people with type 2 diabetes) about a decision to prescribe an SGLT2i or DPP-4i should not include consideration of treatment acquisition costs alone. When producing guidelines, NICE considers

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				BI does not believe that the decision to prescribe an SGLT2i nor DPP4i should include consideration of treatment acquisition costs alone. The wider value to the population and system should be the key consideration because in the case of type 2 diabetes, majority of NHS costs associated are related to T2D complications rather than drug acquisition costs. There is variation in effect size and statistical significance of the results from CVOTs within the SGLT2 inhibitor class. Although a naïve comparison between trials is not appropriate, we feel as though this variation also highlights a lack of face validity in some of the intra-class SGLT2 Health Economic results quoted in the HE report (see comments below). Therefore, we do not feel it is appropriate to draw conclusions on within-class cost-effectiveness of SGLT2 inhibitors based on the base case economic model results associated within these guidelines. i.e. • Empagliflozin showed superiority in reduction of 3-point MACE and significant reduction in all-cause mortality, as well as significant reduction in hospitalisation for heart failure. [1] • Canagliflozin showed superiority in 3-point MACE and hospitalisation for heart failure, but did not show reduction in all-cause mortality[2] • Dapagliflozin and ertugliflozin showed non-inferiority in reduction of 3-point MACE and reduced hospitalisation for heart failure, but did not show reduction in all-cause mortality.[3] Recommending the type 2 diabetes medicines with the greatest benefits in cardiovascular outcomes has the potential to lead to cost savings over the long-term, as well as preventing cardiovascular events. Since the cost associated with cardiovascular events is high), greater effect sizes can	both effectiveness and cost-effectiveness for all of the recommendations it makes. For this update committee reviewed the cost-effectiveness of the different drug options for treating people with type 2 diabetes. They then made class level recommendations for the SGLT2is and the DPP-4is. The committee reviewed the stakeholder comments but decided to continue treating SGLT2 inhibitors (SGLT2i) as a class for the following reasons: • There was a degree of uncertainty around whether there were real differences in cardiovascular (CV) benefits between the SGLT2i based on the clinical trial evidence and results from the NMAs. o Firstly, for hospitalisation for heart failure, the SGLT2i empagliflozin, canagliflozin, and dapagliflozin produced a clinically meaningful reduction compared with placebo in the random effects NMA model. However, in the sensitivity analyses using a fixed effect model ertugliflozin also showed a clinically meaningful reduction compared to placebo, which reflects the original clinical trial data. The NMA results could not differentiate between the SGLT2i for this outcome. o Secondly, for the 3 point MACE outcome, only canagliflozin and empagliflozin produced a statistically significant reduction compared to placebo but the SGLT2i could not be differentiated from each other in the NMA. o Thirdly for all cause and CV mortality empagliflozin showed a clinically meaningful reduction compared to placebo and the other SGLT2i, but the remaining SGLT2i could not

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				lead to reductions in the costs incurred due to clinical events, which may in turn offset a higher acquisition cost. Regarding the DPP4 class, it is not clear that the guidelines recognise some of the potential capacity and cost offsets that may result from variation in dosing regimens. We do not believe that these potential differences would be captured by the economic model as described in the HE report. For example, no dose adjustment is needed for linagliptin in patients with renal impairment, but this is not noted in the document. As renal function deterioration should result in dosing or medication changes for sitagliptin, alogliptin, saxagliptin and vildagliptin, there maybe resource implications due to the intervention and follow-up consultations required. Therefore, the reference to acquisition casts alone undermines the recommendation stated by NG28 to base the choice of drug treatments on the person's individual circumstance, safety & tolerability, and monitoring requirements. With respect to making recommendations that consider wider value to the population, we refer to the NHS reform. This describes a shift towards managing populations and pathways and treating multiple patient architypes in a more holistic way to provide a broader population benefit . The NHS and Directors of Public Health are working together to develop more sophisticated approaches to population health management. Leading with cost does not allow for the right medicines with the best outcomes to be given to those appropriate patient profiles, and therefore does not align with the 'sophisticated approach' when treating diabetic patients[5]	be differentiated from each other or placebo in the NMA. ○ Fourthly, for non-fatal MI and non-fatal stroke the NMAs could not differentiate between empagliflozin, canagliflozin, ertugliflozin and placebo. The data for dapagliflozin was reported differently and could not be included in the NMAs. From the clinical trial data dapagliflozin could not be differentiated from placebo for MI and was not meaningfully different from placebo for stroke. ○ Finally, only dapagliflozin showed a clinically meaningful improvement in severe hypoglycaemia compared to placebo but the remaining SGLT2i could not be differentiated from each other and placebo in the NMA. • There was also a degree of uncertainty around the cost-effectiveness of individual SGLT2i in the economic modelling. Although only dapagliflozin was cost-effective at a threshold of £20,000/quality-adjusted life year (QALY) across all model scenarios and CV risk groups it could not be differentiated from the other SGLT2i in the NMA apart from for the all-cause and CV mortality outcomes where it was clinically meaningfully worse than empagliflozin. The ranking of ICERs for the other SGLT2i varied across model scenarios and risk groups. The committee agreed that there was sufficient uncertainty in the economic modelling (caused in turn by uncertainty in the underlying clinical data) to mean that they were not sufficiently confident that these different ICERs represented true underlying differences in cost-effectiveness, as opposed to simply random variation in the results between different SGLT2 trials. • Taking the cost-effectiveness and clinical results into account the committee decided against only recommending dapagliflozin and instead made

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				We also refer to the NHS Long-Term Plan, which notes that each encounter with the health service should not be treated as a single, unconnected 'episode' of care,[2] and that care of patients with diabetes should aim to minimize patients' risk of future complications.[3] References: 1. Zinman B, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes N Engl J Med 2015; 373:2117–2128. 2. Neal B, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. New England Journal of Medicine. 2017;377(7):644-657. 3. Wiviott S et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. New England Journal of Medicine. 2019;380(4):347-357. 4. Cannon C, Pratley R, Dagogo-Jack S, Mancuso J, Huyck S, Masiukiewicz U et al. Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. New England Journal of Medicine. 2020;383(15):1425-1435. 5. Department of Health and Social Care. *Policy paper Integration and innovation: working together to improve health and social care for all (HTML version)*. Updated 11 February 2021. Available at: https://www.gov.uk/government/publications/working-together-to-improve-health-and-social-care-for-all/integration-and-innovation-	recommendations for the SGLT2i as a class. However, they recognised that there was a greater degree of uncertainty around the CV benefit associated with ertugliflozin because, depending on the choice of model used in the NMA, it did not consistently show a clinically meaningful reduction in hospitalisation for heart failure compared to placebo, unlike empagliflozin, canagliflozin and dapagliflozin. It was also not statistically significantly better than placebo for the 3-point MACE outcome unlike canagliflozin and empagliflozin. The committee therefore recommended SGLT2i with proven CV benefit because this wording would enable the prescribers to select a particular drug from within the SGLT2 class if they thought this was clinically justified based on the individual characteristics of their patient, whilst future proofing the recommendation should additional evidence or new SGLT2s be made available. As per the recommendation on choosing drug treatment, once the clinical circumstances and needs of the person with type 2 diabetes, including their need for CV protection, have been taken into account, if 2 drugs in the same class are suitable for that individual then the prescriber is still expected to choose the option with the lowest acquisition cost to help use NHS resources wisely. Please see evidence review A for more a more detailed explanation of the analyses that were carried out and the committee's discussion of the results. With reference to your point about the DPP-4i's, the visual summary that accompanies this guideline provides additional information to help prescribers with their choice of medicine. Recommendation 1.7. 1 covers factors to take into account when choosing drug treatments. These include the individual's clinical needs as well as their needs and

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				working-together-to-improve-health-and-social-care-for-all-html-version (Accessed October 2021). 6. NHS Long-Term Plan. *Chapter 1: A new service model for the 21st century*. Available at: https://www.longtermplan.nhs.uk/online-version/chapter-1-a-new-service-model-for-the-21st-century/. (Accessed October 2021). 7. NHS Long-Term Plan. C*hapter 3: Further progress on care quality and outcomes*. Available at: https://www.longtermplan.nhs.uk/online-version/chapter-3-further-progress-on-care-quality-and-outcomes/better-care-for-major-health-conditions/diabetes/ (Accessed October 2021).	preferences, monitoring licensing and safety issues. The point about lowest acquisition cost is intentionally the last bullet point and is only relevant if 2 drugs within the same class are appropriate having taken all the earlier points into account. This point not meant to be taken in isolation. The contents of this recommendation and the recommendation about reviewing treatments are intended to support personalised care by ensuring that the choice of drug is tailored to individual needs and circumstances.
Boehringer Ingelheim	Guideline	014	014	Please add in additional bullet point regarding adherence/concordance especially with respect to polypharmacy	Thank you for your comment. It is unclear why a new bullet on adherence and concordance should be included in a list of factors on which to base the drug choice decision. It unlikely that a healthcare professional would be able predict who would be/ not be adherent or concordant until the person has tried taking a medicine. This is appropriately referred to in the recommendation on reviewing drug treatments, which also refers back to this recommendation as part of that process.
Boehringer Ingelheim	Guideline	015	006	From a prescriber and patient perspective, we are glad to see this being incorporated within the NICE guidance. T2D patients have an increased risk of cardiovascular events which can incur a resource impact to the NHS. By recommending SGLT2s in those with a risk of developing cardiovascular disease, this will enable patients to have better outcomes and save cost to the NHS. We suggest that 'cardiovascular risk' should be a factor that healthcare professionals should consider when treating type 2 diabetic patients.	Thank you for your comment. As you note recommendation 1.7.4 in the consultation version of this guideline recommends assessing cardiovascular risk in people with type 2 diabetes. The committee decided against adding this to recommendation 1.7.1 as the listed factors to take into account when choosing drug treatments already cover the person's individual clinical circumstances. The committee agreed that this would include CV risk and that they could not list every possible clinical circumstance to be considered. They also noted that the recommendation already mentions the effectiveness of the drug treatments in terms of metabolic response and cardiovascular protection.

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Boehringer Ingelheim	Guideline	015	008	We fully support that SGLT2s are recommended in addition to metformin when patients have congestive heart failure or established atherosclerotic cardiovascular disease. In line with international guidelines such as the ADA/EASD[1], the assessment should also consider whether the patient has CKD[2] This is because in relation to the renal outcomes from the CVOTs, the SGLT2 inhibitors class have been shown to reduce the rate of eGFR decline despite the initial drop in egfr on drug initiation.[3 -10 ,11, 12] This also falls in line with the Cardio-Renal-Metabolic benefits that the SGLT2i, provides to patients in addition to glycaemic control. Please also ask health care professionals to view the T2D and CKD guidelines. Initial increases in creatinine and initial decreases in estimated glomerular filtration rates in patients treated with SGLT2s are generally transient during continuous treatment or reversible after drug discontinuation of treatment.[3-10] References: 1. Buse JB et al. 2020 Update to: Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) Diabetes Care 2020, 43(2) 487-493 2. Khunti et al, Diabetic medicine 2021 Doi 10.1111/dme.14697 3. Jardiance (Empagliflozin) 10mg Summary of product characteristics found at: Jardiance 10 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 4. Jardiance (Empagliflozin) 10mg Summary of product characteristics found at: Jardiance 25 mg film-coated tablets -	Thank you for your comment. The renal benefits of using SGLT2 inhibitors in people with type 2 diabetes and CKD have been assessed in a separate piece of work that has recently been out for stakeholder consultation and was published in November 2021. The final recommendations on renal and cardiovascular benefits will be brought together in a single updated guideline document when this current work on cardiovascular benefits is published in 2022. Please note that a recommendation in the section on chronic kidney disease refers the reader to the NICE guidance on chronic kidney disease.

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				Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 5. Forxiga (Dapagliflozin) 5mg Summary of product characteristics found at: Forxiga 5 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 6. Forxiga (Dapagliflozin) 10mg Summary of product characteristics found at: Forxiga 10 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 7. Steglatro (Ertugliflozin) 5mg Summary of product characteristics found at: Steglatro 5 mg Film-Coated Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 8. Steglatro (Ertugliflozin) 15mg Summary of product characteristics found at: Steglatro 15 mg Film-Coated Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 9. Invokana (Canagliflozin) 100mg Summary of product characteristics found at: Invokana 100 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 10. Invokana (Canagliflozin) 300mg Summary of product characteristics found at: Invokana 300 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 11. McGuire D et al Jama Cardiology 2021 6(2) 148-158 12. Wanner C et al J Am Soc Nephrol 2018 doi.org/10.1681/ASN.2018010103	
Boehringer Ingelheim	Guideline	015	012	We welcome this addition to the guidelines as SGLT2s have proven to reduce the risk of cardiovascular disease. This is positive for patients and will help to reduce significant costs in the NHS. Around one third of people worldwide with type 2 diabetes also have cardiovascular disease[1] (CVD). CVD is responsible for almost half of all deaths in people with type 2 diabetes[1] and many of these deaths are premature[2]. Patients with cardiovascular disease and diabetes die earlier than those patients without[3]. Evidence shows the importance of	Thank you for your comment and support for the SGLT2i recommendations.

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				intervening early to reduce CV risk in patients with type 2 diabetes as shown in the STENO-2 trial[4], which demonstrated long-term mortality benefits. In the UKPDS trial, epidemiological analysis of the data demonstrated a continuum link between better glycaemic control and reduction in macro-vascular complications.[5] References: 1. Einarson TR *et al. Cardiovasc Diabetol.* 2018;17:83 2. Fisher M, Shaw KM. *Pract Diab Int.* 2001;18:183–184 3. Emerging risk factors collaboration. *JAMA*. 2015;314:52–60 4. Gæde P *et al. Diabetologia*. 2016;59:2298–2307; 5. American Diabetes Association: Implications of the United Kingdom Prospective Diabetes Study. *Diabetes Care* 22 (Suppl. 1): S27–31, 1999	
Boehringer Ingelheim	Guideline	015	013	This is positive for patients needing dual therapy as both metformin and SGLT2 will help reduce blood glucose levels and SGLT2 will provide long term benefits such as cardio- renal protection	Thank you for your comment and support for the SGLT2i recommendations.
Boehringer Ingelheim	Guideline	015	022	This is positive for patients and will provide ease of prescribing for health care professionals.	Thank you for your comment.
Boehringer Ingelheim	Guideline	016	019	The wording should reflect to say that taking a SGLT2i 'can increase the risk of DKA'. This would be in line with the SMPC's where the frequency of DKA is rare. [1-8] References: 1. Jardiance (Empagliflozin) 10mg Summary of product characteristics found at: Jardiance 10 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 2. Jardiance (Empagliflozin) 10mg Summary of product characteristics found at: Jardiance 25 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 3. Forxiga (Dapagliflozin) 5mg Summary of product characteristics found at: Forxiga 5 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)	Thank you for your comment. The recommendation has been amended to state that before starting an SGLT2 inhibitor the prescriber should check whether the person may be at increased risk of diabetic ketoacidosis (DKA) if they take an SGLT2 inhibitor, for example if they have modifiable or non-modifiable risk factors such as having had a previous episode of DKA, they are currently unwell or they are following a very low carbohydrate or ketogenic diet. The recommendations also ask the prescriber to address modifiable risks for DKA (for example, for people who are following a very low carbohydrate or ketogenic diet, may need to delay treatment until they have changed their diet).

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				4. Forxiga (Dapagliflozin) 10mg Summary of product characteristics found at: Forxiga 10 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 5. Steglatro (Ertugliflozin) 5mg Summary of product characteristics found at: Steglatro 5 mg Film-Coated Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 6. Steglatro (Ertugliflozin) 15mg Summary of product characteristics found at: Steglatro 15 mg Film-Coated Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 7. Invokana (Canagliflozin) 100mg Summary of product characteristics found at: Invokana 100 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 8. Invokana (Canagliflozin) 300mg Summary of product characteristics found at: Invokana 300 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)	
Boehringer Ingelheim	Guideline	016	025	This paragraph may be misleading as there are additional benefits for the SGLT2 inhibitor class (i.e. cardio-renal-metabolic benefits). We suggest this to be reworded to 'SGLT2 inhibitors can cause fluid volume depletion and require monitoring of renal function prior to initiation and individual clinical factors need to be considered.' Initial increases in creatinine and initial decreases in estimated glomerular filtration rates in patients treated with SGLT2s are generally transient during continuous treatment or reversible after drug discontinuation of treatment. [1-8] In relation to the renal outcomes from the CVOTs, the SGLT2 inhibitors class have been shown to reduce the rate of eGFR decline despite the initial drop in egfr on drug initiation.[1-8, 9, 10], This also falls in line with the Cardio-Renal-Metabolic benefits that the SGLT2i, provides to patients in addition to glycaemic control.	Thank you for your comment. The committee discussed the stakeholder comments about the renal impact of SGLT2 inhibitors (SGLT2i). They agreed that the existing recommendation was unclear and potentially confusing because it gave no indication of the frequency or when the monitoring should take place. They also recognised that although SGT2i can have a negative effect on renal function this is usually a small reduction in function and not a reason to stop taking the SGLT2i. Taking these points into account the committee have now removed this draft recommendation.

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				Monitoring of this is not required per the SMPCs [1-8] and guidelines such a KDIGO[11] and ADA/EASD[12]. References: 1. Jardiance (Empagliflozin) 10mg Summary of product characteristics found at: Jardiance 10 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 2. Jardiance (Empagliflozin) 10mg Summary of product characteristics found at: Jardiance 25 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 3. Forxiga (Dapagliflozin) 5mg Summary of product characteristics found at: Forxiga 5 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 4. Forxiga (Dapagliflozin) 10mg Summary of product characteristics found at: Forxiga 10 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 5. Steglatro (Ertugliflozin) 5mg Summary of product characteristics found at: Steglatro 5 mg Film-Coated Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 6. Steglatro (Ertugliflozin) 15mg Summary of product characteristics found at: Steglatro 15 mg Film-Coated Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 7. Invokana (Canagliflozin) 100mg Summary of product characteristics found at: Invokana 100 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 8. Invokana (Canagliflozin) 300mg Summary of product characteristics found at: Invokana 300 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 9. McGuire D et al Jama Cardiology 2021 6(2) 148-158	

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				10. Wanner C et al J Am Soc Nephrol 2018 doi.org/10.1681/ASN.2018010103 11. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2020;98(4S):S1-S11. 12. Buse JB et al. 2020 Update to: Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) Diabetes Care 2020, 43(2) 487-493.	
Boehringer Ingelheim	Guideline	017	008	We suggest including a statement that 'patients discuss with their healthcare professionals first before suspending any SGLT2 treatment'.	Thank you for your comment. The committee agreed that this is probably impractical due to the availability of healthcare professionals to respond to requests for such consultations. The committee agreed that it is more practical to give sick day advice. However, the draft recommendation which included sick day rules was reviewed following stakeholder comments and the bullet point on sick day rules has now been removed as the committee agreed it would be inconsistent to present this information for one class of drugs but not any others. They expected that sick day rules and other safety related advice would be discussed with the individual with type 2 diabetes as part of the decision-making process regarding drug choice and wanted to keep the guidance as simple and clear as possible. We have therefore been unable to include the additional information you suggested.
Boehringer Ingelheim	Guideline	018	001	Visual summary 2. First-line treatment We note that ertugliflozin is listed to be equivalent to empagliflozin, canagliflozin and dapagliflozin. However, in the VERTIS CV trial [1] (Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes) trial, showed that ertugliflozin, as compared with placebo, reduced the risk of hospitalization for heart failure, without statistically significant reduction in risk of MACE, death from cardiovascular causes, or other cardiovascular outcomes. As noted above, although a naïve comparison	Thank you for your comment. The committee reviewed the stakeholder comments but decided to continue treating SGLT2 inhibitors (SGLT2i) as a class for the following reasons: • There was a degree of uncertainty around whether there were real differences in cardiovascular (CV)

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				of individual study results is not appropriate, there is variation amongst the SGLT2 class with respect to the demonstration of superiority regarding CVOT trial outcomes. We wanted to also highlight that regarding the SGLT2 cardiovascular outcome trials (CVOT) only empagliflozin[2] and canagliflozin[3] were superior to 3P MACE in the class. Empagliflozin also showed further benefits in CV death and all-cause mortality. We also want to highlight empagliflozin CVOT trial had over 99% of patients with established cardiovascular disease (eCVD) as did VERTIS CVOT[3] The recommendations do not reflect the use of empagliflozin as per international guidelines such as ADA/EASD and ESC. Therefore, aside from the positive effects on glycaemic control, patients at high risk of CV disease or established CV disease will not get the early additional benefits of empagliflozin on top of standard of care. From a long-term perspective, it is important for NICE and the NHS to take this into consideration. We feel that the use of ertugliflozin in this table should be reconsidered and only reserved for patients 'not at high CVD risk' References: 1. Cannon C, Pratley R, Dagogo-Jack S, Mancuso J, Huyck S, Masiukiewicz U et al. Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. New England Journal of Medicine. 2020;383(15):1425-1435. 2. Zinman B, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes N Engl J Med 2015; 373:2117–2128. 3. Neal B et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. New England Journal of Medicine. 2017;377(7):644-657.	benefits between the SGLT2i based on the clinical trial evidence and results from the NMAs. o Firstly, for hospitalisation for heart failure, the SGLT2i empagliflozin, canagliflozin, and dapagliflozin produced a clinically meaningful reduction compared with placebo in the random effects NMA model. However, in the sensitivity analyses using a fixed effect model ertugliflozin also showed a clinically meaningful reduction compared to placebo, which reflects the original clinical trial data. The NMA results could not differentiate between the SGLT2i for this outcome. o Secondly, for the 3 point MACE outcome, only canagliflozin and empagliflozin produced a statistically significant reduction compared to placebo but the SGLT2i could not be differentiated from each other in the NMA. o Thirdly for all cause and CV mortality empagliflozin showed a clinically meaningful reduction compared to placebo and the other SGLT2i, but the remaining SGLT2i could not be differentiated from each other or placebo in the NMA. o Fourthly, for non-fatal MI and non-fatal stroke the NMAs could not differentiate between empagliflozin, canagliflozin, ertugliflozin and placebo. The data for dapagliflozin was reported differently and could not be included in the NMAs. From the clinical trial data dapagliflozin could not be differentiated from placebo for MI and was not meaningfully different from placebo for stroke. o Finally, only dapagliflozin showed a clinically meaningful improvement in severe hypoglycaemia compared to placebo but the

					remaining SGLT2i could not be differentiated from each other and placebo in the NMA. • There was also a degree of uncertainty around the cost-effectiveness of individual SGLT2i in the economic modelling. Although only dapagliflozin was cost-effective at a threshold of £20,000/quality-adjusted life year (QALY) across all model scenarios and CV risk groups it could not be differentiated from the other SGLT2i in the NMA apart from for the all-cause and CV mortality outcomes where it was clinically meaningfully worse than empagliflozin. The ranking of ICERs for the other SGLT2i varied across model scenarios and risk groups. The committee agreed that there was sufficient uncertainty in the economic modelling (caused in turn by uncertainty in the underlying clinical data) to mean that they were not sufficiently confident that these different ICERs represented true underlying differences in cost-effectiveness, as opposed to simply random variation in the results between different SGLT2 trials. • Taking the cost-effectiveness and clinical results into account the committee decided against only recommending dapagliflozin and instead made recommendations for the SGLT2i as a class. However, they recognised that there was a greater degree of uncertainty around the CV benefit associated with ertugliflozin because, depending on the choice of model used in the NMA, it did not consistently show a clinically meaningful reduction in hospitalisation for heart failure compared to placebo, unlike empagliflozin, canagliflozin and dapagliflozin. It was also not statistically significantly better than placebo for the 3-point MACE outcome unlike canagliflozin and empagliflozin. The committee therefore recommended SGLT2i with proven CV benefit because this wording would enable the prescribers to select a particular drug from within the SGLT2 class if they thought this was clinically justified based on the individual characteristics of their patient, whilst future proofing the recommendation should

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					additional evidence or new SGLT2s be made available. As per the recommendation on choosing drug treatment, once the clinical circumstances and needs of the person with type 2 diabetes, including their need for CV protection, have been taken into account, if 2 drugs in the same class are suitable for that individual then the prescriber is still expected to choose the option with the lowest acquisition cost to help use NHS resources wisely. Please see evidence review A for more a more detailed explanation of the analyses that were carried out and the committee's discussion of the results.
Boehringer Ingelheim	Guideline	019	001	Visual summary, medicines table. The draft text states that for DPP4 inhibitors, ketoacidosis is a contraindication. The SmPCs for drugs within the DPP4 inhibitor class do not state ketoacidosis nor diabetic ketoacidosis as a contraindication or as a warning References 1. Trajenta (Linagliptin) SmPC: Trajenta 5 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 2. Saxagliptin SmPC - Onglyza 2.5mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 3. Sitagliptin SmPC JANUVIA 100mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 4. Vldagliptin SmPC - Galvus 50 mg Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 5. Alogliptin SMPC - Vipidia 12.5mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)	Thank you for your comment. We have used contraindication content from the BNF (checked November 2021) and have highlighted this to the BNF regarding the BNF content discrepancy with the SPCs.

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Boehringer Ingelheim	Guideline	019	001	Visual summary, medicines table. The draft text states that DPP4 inhibitors need dose adjustment for renal considerations. Linagliptin does not need does adjustment at any stage of renal impairment or liver impairment. This difference should be stated.	Thank you for your comment. The content in the table has been updated for specific medicines rather than for medicine classes.
Boehringer Ingelheim	Guideline	020	003	We think it is very positive for health care professionals to work with the patient when reviewing or considering changing treatments for adults with type 2 diabetes. However, we think it may be beneficial to provide healthcare professionals with advice as to how they might ascertain whether a medication is working or not. Management of type 2 diabetes involves more than just glycaemic control; this is clear from the evidence considered in the draft guideline update. For SGLT2 inhibitors such as empagliflozin, the clinical benefits go beyond that which is expected through glycaemic control alone. This is reflected in section 5.1 of empagliflozin SmPC where 'both improvement of glycaemic control and reduction of cardiovascular morbidity and mortality are an integral part of the treatment of type 2 diabetes.' There have been many published cardiovascular outcome trials over the last five years which have demonstrated proven cardiovascular benefit for patients with type 2 diabetes and CVD treated with SGLT2 inhibitors or GLP-1 receptor agonists. Other international guidelines and consensus recommendations e.g. ADA/EASD[1] and ESC[2] have been updated based on this evidence. Within the UK, SIGN[3] guidelines and many local hospital trust guidelines within NHSE have already incorporated the evidence from these trials. The first of the CVOT trials in the SGLT2i class, EMPA-REG OUTCOME[4], met its primary composite endpoint (CV death, non-fatal myocardial infarction and non-fatal stroke) which was driven by a statistically significant reduction in cardiovascular death. From the EMPA-REG OUTCOME trial[4] the reduction in cardiovascular death was statistically significant with a relative risk reduction of 38% with an absolute risk reduction of 2.2%. These cardiovascular and overall mortality results remain unsurpassed across all safety cardiovascular	Taking stakeholder feedback into account the committee have amended the recommendation on reviewing drug treatment. The committee clarified that they by stopping drugs that were not effective they meant stopping medicines that have had no impact on glycaemic control or weight unless they are expected to have less apparent or measurable benefits such as cardiovascular and renal protection.

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				outcome trials within type 2 diabetes. These results were achieved on top of standard of care with 98% already being treated with glucose lowering agents and 95% taking anti-hypertensive therapy. There are additional metabolic advantages which were demonstrated in the EMPA-REG OUTCOME trial.[4] These include a reduction in blood pressure, weight reduction, and renal benefits. More recently in the SUGAR-DM-HF study5 (an investigator-initiated study evidence of left ventricular mass reduction and remodelling were discovered. All of these additional benefits are of value in treatment of type 2 diabetes. Empagliflozin is a potent oral hypoglycaemic agent and its efficacy has been established through a number of studies (EMPA-REG clinical development programme). With a once daily dosing regimen this medication has a variety of positive cardio-renal-metabolic effects as highlighted above. Therefore, we suggest adding some clarification on how HCPs can ascertain whether a treatment has worked or not. As the committee has acknowledged on page 40, line 6 of the draft guidance 'However, some drugs, such as SGLT2 inhibitors, may be continued because they provide additional cardiovascular protective benefits' we feel that this statement provided by the committee articulates the fact that the additional, and often unseen, cardiovascular benefits of SGLT2 inhibitors need to be taken into account when assessing whether a treatment has 'worked' (not just glycaemic control in isolation). <u>References</u>: 1. Buse JB et al. 2020 Update to: Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) Diabetes Care 2020, 43(2) 487-493.	

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				2. Cosentino F, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020;41(2):255–323. 3. Scottish Intercollegiate Guidelines Network (SIGN). SIGN 154, Pharmacological management of glycaemic control in people with type 2 diabetes. Available at: https://www.sign.ac.uk/our-guidelines/management-of-diabetes/ (Accessed October 2021). 4. Zinman B, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes N Engl J Med 2015; 373:2117–2128.	
Boehringer Ingelheim	Guideline	020	010	We suggest that it would be beneficial if we could also add long terms benefits of staying on the treatment is taken into consideration. E.g. presence or high risk for ASCVD, CKD, and heart failure (HF), as well as patients' needs, preferences, sociodemographic characteristics, and access limitations. These all now take a place alongside A1C as key considerations in designing the most appropriate diabetes management plan for each patient and is in line with recommendations from international guidelines such as ADA/EASD.[1] Reference: Buse JB et al. 2020 Update to: Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) Diabetes Care 2020, 43(2) 487-493.	Thank you for your comment. After reviewing stakeholder comments the committee have amended the recommendation on reviewing drug treatments to take account of the less apparent or measurable benefits such as cardiovascular and renal protection.
Boehringer Ingelheim	Guideline	021	005	This is very positive for patients living with type 2 diabetes because the management of diabetes goes beyond glycaemic control alone and there is a greater emphasis on the prevention of CV events in those at high risk. The cardiovascular benefits of SGLT2 inhibitors such as empagliflozin	Thank you for your comment in support of the SGLT2 inhibitor recommendations.

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				have demonstrated cardiovascular benefits which have led to recommendations being made in international guidelines such as ADA/EASD[1] and ESC.[2] References: 1. Buse JB et al. 2020 Update to: Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) Diabetes Care 2020, 43(2) 487-493. 2. Cosentino F, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020;41(2):255–323.	
Boehringer Ingelheim	Guideline	024	General	Visual summary 3, Disease progression, insulin therapy box. It appears that empagliflozin is not recommended for use alongside canagliflozin and dapagliflozin. We recommend that empagliflozin should also be added to this list alongside the two other SGLT2s listed. This is because empagliflozin can be used with insulin as per the SmPC.[1] Furthermore, there are studies that have shown that using empagliflozin with insulin leads to positive benefits for the patient such as reduced Hba1c, reduced weight and more importantly reduced insulin dose.[2,3] References: 1. Jardiance 10 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk). 2. Rosenstock J, et al. mpact of empagliflozin added on to basal insulin in type 2 diabetes inadequately controlled on basal insulin: a 78-week randomized, double-blind, placebo-controlled trial. *Diabetes Obes Metab*. 2015; 17: 936–948.	Thank you for your comment. This was an omission and empagliflozin has now been added.

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				Vaduganathan M, et al. 30-OR: Empagliflozin Delays Need for Insulin Initiation in Patients with Type 2 Diabetes and Cardiovascular Disease: Findings from EMPA-REG OUTCOME. *Diabetes* 2020;69(Supplement 1).	
Boehringer Ingelheim	Guideline	025	General	Visual summary, medicines table, it states that for DPP4 inhibitors, ketoacidosis is a contraindication. The SmPCs for drugs within the DPP4 inhibitor class do not state ketoacidosis nor diabetic ketoacidosis as a contraindication or warning 1. Trajenta (Linagliptin) SmPC: Trajenta 5 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 2. Saxagliptin SmPC - Onglyza 2.5mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 3. Sitagliptin SmPC JANUVIA 100mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 4. Vldagliptin SmPC - Galvus 50 mg Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 5. Alogliptin SMPC - Vipidia 12.5mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)	Thank you for your comment. According to the BNF (November 2021), ketoacidosis is listed as a contraindication. We have highlighted this to the BNF regarding the BNF content discrepancy with the SPCs.
Boehringer Ingelheim	Guideline	035	006 – 009	The copy here notes that "The evidence from the clinical trials looking at cardiovascular benefits, the network meta-analyses, and the economic modelling, showed that some treatments were effective at improving cardiovascular outcomes and were likely to be cost effective." We would like to highlight that, due to significant limitations in the methodology (as acknowledged in the HE report), it is not appropriate to draw conclusions on within-class cost-effectiveness of SGLT2 inhibitors based on the economic model base case.	Thank you for your comment. Please note that page 35 lines 6 to 9 make a general statement about all the interventions (SGLT2 inhibitors, DPP-4 inhibitors, GLP-1 mimetics, thiazolidinediones and sulfonylureas) included in each of the CV outcome trials and does not make specific reference to the effectiveness or cost-effectiveness of the SGLT2 inhibitors as a class. The uncertainty surrounding the results of the economic analysis has been taken into account by the committee when making the recommendations. Nevertheless, we have made amendments to the discussion of results in our HE report so that we discuss the ICERs for each treatment as a result of the modelling, and assessment

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					of cost-effectiveness takes into account wider elements of the analysis including uncertainty in model inputs and results and results across different scenarios. Please see the health economic report for details.
Boehringer Ingelheim	Guideline	039	021	For the SGLT2 SmPC's there are no recommendations to monitor for eGFR decline nor additional renal function monitoring for these agents other than routine renal function testing. From the empagliflozin SmPC, the recommendation is to check eGFR before initiation and then at least annually, and again if any agent is added to the patients regimen that could effect their eGFR. For other SGLT2 inhibitors such as dapagliflozin, there is no recommendation to monitor for eGFR decline except for those at risk of volume depletion. The initial dip in eGFR is transient and reversible upon treatment discontinuation, and does not cause adverse effects on renal function. With appropriate support and education of the healthcare professional, there should not be an increase in renal function testing thus leading to increased resource use. Importantly, evidence from the EMPA-REG OUTCOME trial demonstrated that the extent of eGFR dip at the start of treatment did not effect the CV or renal outcomes observed in the trial.[1] Reference: 1. Kraus BJ, et al. Characterization and implications of the initial estimated glomerular filtration rate 'dip' upon sodium-glucose cotransporter-2 inhibition with empagliflozin in the EMPA-REG OUTCOME trial. *Kidney International* 2021;99,750–762.	Thank you for your comment. The committee discussed the stakeholder comments about the renal impact of SGLT2 inhibitors (SGLT2i). They agreed that the existing recommendation was unclear and potentially confusing because it gave no indication of the frequently or when the monitoring should take place. They also recognised that although SGT2i can have a negative effect on renal function this is usually a small reduction in function and not a reason to stop taking the SGLT2i. Taking these points into account the committee have now removed this draft recommendation.The text your comment relates to in the rationale has also been removed.
Boehringer Ingelheim	Guideline	General	General	Boehringer Ingelheim welcomes the opportunity to comment on these guidelines. We are pleased to see NICE recognising the latest developments in the treatment of patients with T2D in particular the wealth of evidence from CVOT trials which has been published since the last update. We feel as though these changes have the potential to benefit both patients and the NHS system. We hope that these additions are recognised in the final NICE guideline. SGLT2's have been on the market for several years and their safety and efficacy are well understood by primary care clinicians.	Thank you for your comments and support of the SGLT2 inhibitor recommendations.

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Boehringer Ingelheim	Health economic report	020	032 +	Upon our reading, it was not clear how and why (or why not) between trial population differences or other heterogeneity was controlled for in the model. Use of trial point estimates alone in making between trial treatment comparisons is typically regarded as having limitations. We suggest addressing this (or cross referencing to a section of the document) where this is explained to aid reader understanding.	Thank you for your comment. Treatment effects used from the trials have not been adjusted for heterogeneity due to the absence of individual patient data, with the committee agreeing that there were no established methods for adjusting these data that could be conducted that would increase their confidence in the effect estimated. They noted that simply having populations at different risk levels in different trials would not be a source of bias in the results, as this should not impact on the relative effects estimated in the trials and subsequently used to populate the model. A concern would only arise if there were systematic differences between the trials in characteristics that would affect relative (and not just absolute) treatment effectiveness and, while the data did not allow the committee to completely rule out this possibility, there were not clear clinical reasons they were aware of to suspect that such a pattern would exist. Nonetheless, the committee agreed the between trial heterogeneity was a source of uncertainty in the analysis, and considered this as part of their decision-making, as detailed in the committee discussion-section of the evidence review. In particular, they noted this uncertainty was one factor leading towards making class level recommendations, rather than interpreting relatively small overall differences in cost-effectiveness between drugs within the same class as clinically meaningful. They also noted that uncertainty would in general lead towards making weaker rather than stronger recommendations, and therefore any factors that led them to be more uncertain would lead to a smaller number of treatment options being recommended as cost-effective, rather than a larger number of options. It is also worth noting that while point estimates were used for base case analysis, the uncertainty around these estimates were considered in the probabilistic sensitivity

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					analysis, where the treatment decisions did not change from the base case analysis.
Boehringer Ingelheim	Health economic report	020	035	Table HE010 - The numeric difference in stroke between empagliflozin and placebo in the modified intent-to-treat analysis was primarily because of 18 patients in the empagliflozin group with a first event >90 days after last intake of study drug (versus 3 on placebo). In a sensitivity analysis based on events during treatment or ≤90 days after last dose of drug, the hazard ratio for stroke with empagliflozin versus placebo was 1.08 (95% confidence interval, 0.81–1.45; P=0.60). There were no differences in risk of recurrent, fatal, or disabling strokes, or transient ischemic attack, with empagliflozin versus placebo. Patients with the largest increases in hematocrit or largest decreases in systolic blood pressure did not have an increased risk of stroke.[1] The EMPAREG OUTCOME study demonstrated that in patients with type 2 diabetes mellitus and high cardiovascular risk, there was no significant difference in the risk of cerebrovascular events with empagliflozin versus placebo Therefore the data used in the economic model has potentially introduced misleading artefacts into the economic modelling results. We recognise that a pragmatic approach was needed, given the complexity of the overall between class decision problem. However, we believe that this example maybe illustrative, and adds further limitation to the validity of the model in making intra-class comparisons. As a result, we believe that the economic model report should highlight these limitations and avoid drawing firm conclusions within the SGLT2 class, as highlighted in our responses below. <u>Reference:</u> Zinman B, et al. Empagliflozin and cerebrovascular events in patients with type 2 diabetes mellitus at high cardiovascular risk. *Stroke*. 2017;48:1218–1225	Thank you for your comment. NICE disagree with the comment that we have introduced misleading artefacts. The network meta-analyses (NMA) and NICE economic model accounted for stroke events in 2 ways. Firstly, mortality from stroke was captured as part of the cardiovascular mortality outcome in the cardiovascular outcome trials (CVOTs), it would be double counting to then incorporate the same deaths as part of the stroke outcome. Secondly non-fatal stroke events were reported as a separate NMA outcome and the same data (as reported in Table HE010) was used in the NICE economic model (Hazard ratio 1.24, 95% CI 0.92 to 1.67[1]) for EMPA-REG. Additionally, it was important that we use the sufficiently similar intention-to-treat data for each study included in the network meta-analyses and economic model to have consistency between trials. Not doing so would risk introducing clinical and statistical heterogeneity in the network and economic models. Further the use modified intention-to-treat data in the sensitivity analyses (adjusted based on a first event >90 day after last dose threshold) would not maintain the initial trial randomisation so increasing the risk of biases such as non-random attrition bias. We have therefore not included this study in our analyses. [1] Zinman et al (2015) Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. The New England journal of medicine 373(22): 2117-28
Boehringer Ingelheim	Health economic report	021	009 – 031	The base-case analysis does not fully capture the mortality benefit of treatment demonstrated in clinical trials which is derived indirectly through the reduction in the occurrence of an intermediate event (e.g. myocardial infarction, stroke, heart failure, etc). An additional option considered by NICE was to make a further adjustment to the modelling of mortality and	Thank you for your comment. The committee spent some time considering the relative merits of the two possible approaches (modelling cardiovascular mortality directly, or as a function of cardiovascular events). Ultimately, they decided the later was preferable, as the higher number of

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				calibrate the estimates to align with the evidence on cardiovascular mortality extracted from the clinical review, however this was only a sensitivity analysis. This calibration was inadequate because the adjustment was based on hazard ratios from the evidence synthesis that had wide confidence intervals which overlapped 1. This resulted in the modelling of point estimates of non-significant outcomes which are associated with considerable uncertainty. In turn, this led to an artificially big ICER difference between dapagliflozin and empagliflozin that is not consistent with the evidence base. EMPA-REG demonstrated a statistically significant CV-death benefit which was not fully reflected in the economic model.	cardiovascular events in the studies (compared to the number of cardiovascular events) meant that more precise estimates could be obtained, in turn leading to reduced uncertainty in the analyses. The committee did also consider the results of the sensitivity analysis you discuss, and concluded that, given they had decided to make recommendations at the class rather than individual drug level, the results of that analysis did not substantially change the conclusions they had drawn from the base-case analysis. It is true that wide confidence intervals did surround the hazard ratios referred to. Whilst a PSA was not performed to look at the impact of uncertainty caused by these wide confidence intervals in the base case across all treatment paths, the committee did keep in mind the uncertainty surrounding these hazard ratios and the potential limitations it causes to our analysis when making recommendations. It is also worth noting that while point estimates were used for base case analysis, the uncertainty around these estimates were considered in the probabilistic sensitivity analysis for second intensification replacement, where the treatment decisions did not change from the base case analysis.
Boehringer Ingelheim	Health economic report	022	001 – 009	The report notes here that the modelled cardiovascular mortality hazard ratio did not fall within the trial hazard ratio for two treatments: empagliflozin and oral semaglutide. Looking specifically at empagliflozin, the report notes that 'EMPA-REG found that empagliflozin is associated with a cardiovascular mortality HR of 0.62 (compared with a modelled 0.94)'. The model used in the base case grossly underpredicts the cardiovascular mortality benefit seen with empagliflozin. We do not feel it is appropriate to make any intra-class conclusions around this base case, in which two treatments do not have CV benefits appropriately modelled. The results and conclusions should highlight this when mentioning base	Thank you for your comment. The committee considered the different assumptions underlying the two possible approaches to mortality and noted that a priori they were both reasonably approaches to take. Both assumptions (that differences in cardiovascular mortality are mediated through differences in rates of cardiovascular events, or that they are not) are currently unprovable with the available data, and therefore the committee considered the practical implications of each choice. In particular, they noted that the cardiovascular outcomes trials, whilst large, were not powered to detect differences in cardiovascular mortality, and therefore there was considerable uncertainty around those results (since rates of cardiovascular events are

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				case SGLT2 results. As it is currently written, the report has the potential to be misleading.	necessarily higher than rates of cardiovascular mortality, the data on vents will necessarily be more precise). They therefore felt the data on cardiovascular event rates were more robust, and thus favoured an approach to modelling mortality based on those data. The committee did, however, consider both sets of results when making recommendations, and in particular noted they would have more confidence in a treatment that was shown to be cost-effective under both sets of assumptions, than one where the cost-effectiveness was very sensitive to the choice of assumption. The committee reviewed the stakeholder comments but decided to continue treating SGLT2 inhibitors (SGLT2i) as a class for the following reasons: 1. There was a degree of uncertainty around whether there were real differences in cardiovascular (CV) benefits between the SGLT2i based on the clinical evidence and results from the NMAs. 2. There was also a degree of uncertainty around the cost-effectiveness of individual SGLT2i in the economic modelling. Although dapagliflozin was cost-effective across all model scenarios and CV risk groups it could not be differentiated from the other SGLT2i in the NMA apart from for CV mortality where it was worse than empagliflozin. The ranking of ICERs for the other SGLT2i varied across model scenarios and risk groups. The committee agreed that there was sufficient uncertainty in the economic modelling (caused in turn by uncertainty in the underlying clinical data) to mean that they were not sufficiently confident that these different ICERs represented true underlying differences in cost-effectiveness, as opposed to simply random variation in the results between different SGLT2 trials.

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					Given the uncertainty in clinical data informing of differences in CV outcomes, and the economic analysis that the clinical evidence fed into, class level recommendations were made to allow the freedom to select a SGLT2 based on circumstances.
Boehringer Ingelheim	Health economic report	022	010 – 014	The report notes the following "The committee recognised that there were limitations to each approach to modelling cardiovascular mortality. On balance it decided not to calibrate the results in the base-case, on the premise that cardiovascular mortality was likely to be mediated by events already captured in the model. The alternative calibration approach was explored as a sensitivity analysis." Thus, the report acknowledges there are limitations to the different modelling approaches (including both the base case and the sensitivity analyses). We feel the base case itself should be treated as a sensitivity analysis and that no intra-class SGLT2 conclusions – or even the suggestion of conclusions – should be made on it. Rather, the sensitivity analysis which is calibrated for CV mortality would be a more appropriate base case for this specific comparison. As it is currently written, the report has the potential to be misleading.	Thank you for your comment. The committee spent some time considering the relative merits of the two possible approaches (modelling cardiovascular mortality directly, or as a function of cardiovascular events). Ultimately, they decided the later was preferable, as the higher number of cardiovascular events in the studies (compared to the number of cardiovascular events) meant that more precise estimates could be obtained, in turn leading to reduced uncertainty in the analyses. A sensitivity analysis was performed where cardiovascular mortality was modelled using information from the trials. The committee did also consider the results of this sensitivity analysis, and concluded that, given they had decided to make recommendations at the class rather than individual drug level, the results of that analysis did not substantially change the conclusions they had drawn from the base-case analysis. The results in this sensitivity analysis being very similar to the base case, also signalled of good model fit. The committee reviewed the stakeholder comments but decided to continue treating SGLT2 inhibitors (SGLT2i) as a class for the following reasons: 1. There was a degree of uncertainty around whether there were real differences in cardiovascular (CV) benefits between the SGLT2i based on the clinical evidence and results from the NMAs. 2. There was also a degree of uncertainty around the cost-effectiveness of individual SGLT2i in the economic modelling. Although dapagliflozin was cost-effective across

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					all model scenarios and CV risk groups it could not be differentiated from the other SGLT2i in the NMA apart from for CV mortality where it was worse than empagliflozin. The ranking of ICERs for the other SGLT2i varied across model scenarios and risk groups. The committee agreed that there was sufficient uncertainty in the economic modelling (caused in turn by uncertainty in the underlying clinical data) to mean that they were not sufficiently confident that these different ICERs represented true underlying differences in cost-effectiveness, as opposed to simply random variation in the results between different SGLT2 trials. Given the uncertainty in clinical data informing of differences in CV outcomes, and the economic analysis that the clinical evidence fed into, class level recommendations were made to allow the freedom to select a SGLT2 based on circumstances.
Boehringer Ingelheim	Health economic report	043	015 – 018	The report here makes conclusions drawn on the base-case analysis which has severe limitations (as detailed elsewhere in the report), specifically it claims "with dapagliflozin being the most cost-effective amongst the SGLT2s, being the only CVOT to have an ICER below £20,000". As per comments above, this phrase should be modified given that the current base case is not the most appropriate analysis for informing SGLT2 comparisons. As it is currently written, the report has the potential to be misleading.	Thank you for your comment. As discussed in our response to your previous points, any limitations having a significant impact on the results, especially relating to the uncertainty around the treatment effects sourced from CVOTs and the different approaches of modelling CV related mortality have been considered by the committee when making recommendations with the committee accounting for this by looking at the treatments and associated results at a class level (as outlined by the class level recommendation made with regard SLGT2s). A discussion of the limitations of the analysis has been provided in the committee discussion of the evidence in the relevant evidence review.
Boehringer Ingelheim	Health economic report	047	013 - 014	The report states "Dapagliflozin continues to be the only CVOT to have an ICER below £20,000 in all subgroups, and hence remains as the most cost-effective treatment option." As per comments above, this phrase should be modified given that the current base case is not the most appropriate analysis for informing	Thank you for your comment. As discussed in our response to your previous points, any limitations having a significant impact on the results, especially relating to the uncertainty around the treatment effects sourced from CVOTs and the different approaches of modelling CV related mortality have been considered by the committee when making recommendations with the committee accounting for this by

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				SGLT2 comparisons. As it is currently written, the report has the potential to be misleading.	looking at the treatments and associated results at a class level (as outline by the class level recommendation made with regard SLGT2s). A discussion of the limitations of the analysis has been provided in the committee discussion of the evidence in the relevant evidence review.
Boehringer Ingelheim	Health economic report	051	013 - 015	The report states "However, dapagliflozin remained the most cost-effective treatment option and the only one to have an ICER below £20,000." As per comments above, this phrase should be modified given that the current base case is not the most appropriate analysis for informing SGLT2 comparisons. As it is currently written, the report has the potential to be misleading.	Thank you for your comment. As discussed in our response to your previous points, any limitations having a significant impact on the results, especially relating to the uncertainty around the treatment effects sourced from CVOTs and the different approaches of modelling CV related mortality have been considered by the committee when making recommendations with the committee accounting for this by looking at the treatments and associated results at a class level (as outline by the class level recommendation made with regard SLGT2s). A discussion of the limitations of the analysis has been provided in the committee discussion of the evidence in the relevant evidence review.
Boehringer Ingelheim	Health economic report	062	012 - 13	The discussion notes that "Across all subgroups in the base-case dapagliflozin is the SGLT2 most commonly associated with an ICER of less than £20,000." As per comments above, this phrase should be modified given that the current base case is not the most appropriate analysis for informing SGLT2 comparisons. As it is currently written, the report has the potential to be misleading.	Thank you for your comment. As discussed in our response to your previous points, any limitations having a significant impact on the results, especially relating to the uncertainty around the treatment effects sourced from CVOTs and the different approaches of modelling CV related mortality have been considered by the committee when making recommendations with the committee accounting for this by looking at the treatments and associated results at a class level (as outline by the class level recommendation made with regard SLGT2s). A discussion of the limitations of the analysis has been provided in the committee discussion of the evidence in the relevant evidence review.
Boehringer Ingelheim	Health economic report	General	General	The overall methodology for the HE modelling is well thought through and addresses a very complex decision problem. The base case analysis is suitable for informing decision-making at a class level; consistent with the pull through of 'class effect' economic modelling results into the updated treatment guidelines.	Thank you for your comments. As correctly pointed out, differences in CV mortality has been explored in the sensitivity analysis with the results in this sensitivity analysis

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				However, key limitations of the modelling make it inappropriate for making intra-class comparison for the SGLT2 class. In particular, the base-case analysis does not well represent all CV mortality benefits demonstrated in clinical trials. For example, in EMPA-REG, empagliflozin was associated with a cardiovascular mortality HR of 0.62, compared with a modelled 0.94. A sensitivity analysis was performed that included a calibration approach to align estimates with CV mortality rates seen in the clinical trials. We feel this analysis should be considered the base-case for informing intra-class decision-making, as it better represents clinical data relevant for the decision problem. The HE modelling report draws conclusions from the base-case analysis that we feel are inappropriate. Such conclusions are repeated throughout the report and, without the context of the limitations of the base-case analysis, are potentially misleading. It appears there is a lack of face validity in the base-case analysis modelling results. While we acknowledge a naïve comparison between trials must be treated with caution, empagliflozin demonstrated favourable CV outcomes in EMPA-REG, and is priced equivalent to most other medicines with the class, therefore we would expect it to dominate other SGLT2s. As described above: • Empagliflozin showed superiority in reduction of 3-point MACE and significant reduction in all-cause mortality, as well as significant reduction in hospitalisation for heart failure. • Canagliflozin showed superiority in 3-point MACE and hospitalisation for heart failure, but did not show reduction in all-cause mortality. • Dapagliflozin and ertugliflozin showed non-inferiority in reduction of 3-point MACE and reduced hospitalisation for heart failure, but did not show reduction in all-cause mortality.	being very similar to the base case, thereby signalling good model fit. With regard to discrepancies between trial results and cost-effectiveness results when looking at SGLT-2's it is worth keeping in mind that while the 3 point MACE outcome is a strong indicator for clinical effectiveness, the CV outcomes are considered separately in a cost-effectiveness analysis. This results in us using separate HRs for each of the CV outcomes as reported in the evidence review (point estimates used in the economic evaluation are reported in Table HE010 in the economic report). As an example Empagliflozin has the highest point estimate for stroke which amongst CV events has the highest impact on quality of life amongst CV outcomes considered according to the literature.

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				This opinion is supported by clinical experts we have heard from, who expressed surprise that the HE report appeared to claim dapagliflozin is the most cost-effective SGLT2, and questioned the modelling methods.	
Boehringer Ingelheim	Health economic report	General	General	A limitation of the T2D economic model is that it focuses on cardiovascular outcomes, ignoring the impact of poor renal function, and the impact of this on health-related quality of life. As described in the EMPA REG OUTCOME trial, the percentage of patients with acute renal failure (including acute kidney injury) was lower in the empagliflozin groups than in the placebo group, and renal function was maintained with empagliflozin. Complications of diabetes, including renal complications, have been defined in the NICE scoping of previous T2D medicines; for instance TA390.	Thank you for your comment. In addition to this update looking at cardiovascular outcomes, NICE has also undertaken a separate piece of work looking at the renal benefits of SGLT-2 inhibitors in people with chronic kidney disease, which considered evidence from EMPA-REG. The published version of the guidance now contains both sets of recommendations.
British Association for Nutrition and Lifestyle Medicine (BANT)	Guideline	006	014 - 015	Ref 1.3.3 In light of the May 2021 Scientific Advisory Committee on Nutrition report on Lower Carbohydrates diets for overweight/obese adults living with T2D suggest that this should now read: *"Encourage adults with type 2 diabetes to follow general healthy eating principles, which includes;"*	Thank you for your comment. The section of the guideline covering dietary advice and bariatric surgery was not prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest existing recommendations needed amending. The surveillance team at NICE monitor whether guidelines are up to date. The surveillance process includes reacting to events at any time after guideline publication (for example, publication of a key study) as well as a standard check every 5 years. Stakeholders can help with this process by letting us know which parts of the guideline stakeholders believe out-of-date and why during scope consultations.. As these are evidence-based guidelines it is useful if stakeholders can provide links to important evidence sources that they believe would necessitate an update of a particular area of the guideline. We can then pass these references onto the NICE surveillance team for evaluation and a decision about whether an update is justified.
British Association for Nutrition and Lifestyle	Guideline	006	016 - 017	Amend to: "eating high-fibre, low glycaemic sources of carbohydrate such as whole fruit, whole vegetables, pulses and minimally processed whole grains [two words, not 'wholegrain']".	Thank you for your comment. The section of the guideline covering dietary advice and bariatric surgery was not prioritised at the scoping stage as no evidence was identified

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Medicine (BANT)					in the surveillance review to suggest existing recommendations needed amending. The surveillance team at NICE monitor whether guidelines are up to date. The surveillance process includes reacting to events at any time after guideline publication (for example, publication of a key study) as well as a standard check every 5 years. Stakeholders can help with this process by letting us know which parts of the guideline stakeholders believe out-of-date and why during scope consultations.. As these are evidence-based guidelines it is useful if stakeholders can provide links to important evidence sources that they believe would necessitate an update of a particular area of the guideline. We can then pass these references onto the NICE surveillance team for evaluation and a decision about whether an update is justified.
British Association for Nutrition and Lifestyle Medicine (BANT)	Guideline	006	018	Amend to: "choosing full-fat dairy products in moderation. When choosing low-fat alternatives ensure that product does not contain high GI calorific maltodextrins or artificial sweeteners." Refs: 1) Cara B Ebbeling, Amy Knapp, Ann Johnson, Julia M W Wong, Kimberly F Greco, Clement Ma, Samia Mora, David S Ludwig, Effects of a low-carbohydrate diet on insulin-resistant dyslipoproteinemia—a randomized controlled feeding trial, *The American Journal of Clinical Nutrition*, 2021;, nqab287, https://doi.org/10.1093/ajcn/nqab287 2) Mitri J, Tomah S, Furtado J, Tasabehji MW, Hamdy O. Plasma Free Fatty Acids and Metabolic Effect in Type 2 Diabetes, an Ancillary Study from a Randomized Clinical Trial. *Nutrients*. 2021;13(4):1145. Published 2021 Mar 31. doi:10.3390/nu13041145 3) Maltodextrin - an overview | ScienceDirect Topics	Thank you for your comment. The section of the guideline covering dietary advice and bariatric surgery was not prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest existing recommendations needed amending.
British Association for Nutrition	Guideline	006	020	New bullet point:	Thank you for your comment. The section of the guideline covering dietary advice and bariatric surgery was not prioritised at the scoping stage as no evidence was identified

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and Lifestyle Medicine (BANT)				"- avoiding extruded breakfast cereals and other ultra-processed foods, sugar sweetened beverages and low calorie drinks with artificial sweeteners." Refs: 1) Mathur K, Agrawal RK, Nagpure S, Deshpande D. Effect of artificial sweeteners on insulin resistance among type-2 diabetes mellitus patients. *J Family Med Prim Care*. 2020;9(1):69-71. Published 2020 Jan 28. doi:10.4103/jfmpc.jfmpc_329_19 2) Vinoy S, Normand S, Meynier A, et al. Cereal processing influences postprandial glucose metabolism as well as the GI effect. *J Am Coll Nutr*. 2013;32(2):79-91. doi:10.1080/07315724.2013.789336	in the surveillance review to suggest existing recommendations needed amending.
British Association for Nutrition and Lifestyle Medicine (BANT)	Guideline	007	001 - 004	1.3.6 Amend to read: "Individualise recommendations for carbohydrate and alcohol intake, and meal patterns. Advise patients on lower carbohydrate diets or very low energy diets according to their preferences. Make reducing the risk of hypoglycaemia a particular aim for people using insulin or an insulin secretagogue."	Thank you for your comment. The section of the guideline covering dietary advice and bariatric surgery was not wasn't prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest existing recommendations needed amending.
British Association for Nutrition and Lifestyle Medicine (BANT)	Guideline	007	005 - 008	1.3.7 Delete this item – sucrose is a high-glycaemic carbohydrate and this item is inconsistent with advice to eat low glycaemic sources of carbohydrate.	Thank you for your comment. The section of the guideline covering dietary advice and bariatric surgery was not prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest existing recommendations needed amending.
British Association for Nutrition and Lifestyle Medicine (BANT)	Guideline	056	Gene ral	Patient Decision Aid - This document refers to patients having options to change their diet and lifestyle. Following the May 2021 report of the Scientific Advisory Committee on Nutrition on Lower Carbohydrate diets for overweight/obese adults with type 2 diabetes, which looked at evidence with Hba1C and weight as primary outcomes, the recommendations are: *1) that a lower carbohydrate diet can be recommended by clinicians as an effective short-term option (up to 6 months) for improving glycaemic control and serum triacylglycerol concentrations.*	Thank you for your comment. The PDA is not a general information leaflet but is focussed on the decision about the person's target HbA1c. It reflects the guideline recommendations and the evidence reviewed. The section of the guideline covering diet was not prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest existing recommendations needed amending. The PDA doses state that diet and

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				2) *Since the majority of individuals living with T2D have overweight or obesity, weight management remains the primary goal for improving glycaemic control and reducing CVD risk. Health professionals should support any evidence-based dietary approach that helps individuals with T2D to achieve long-term weight reduction.* A section on Diet should be in the Guideline which sets out both strategies so that patients can make an informed decision. Additionally reference ought to be made to the NHS adoption of the DiRECT trial 'evidence-based' protocol using very low calories soups/shakes followed by the Counterweight lower starch dietary guidelines.	lifestyle measures can help the person manage their blood glucose and reduce their cardiovascular risk. The section of the guideline covering diet was not prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest existing recommendations needed amending.
CaReMe UK	Guideline	008	006	We acknowledge that the evidence for anti-platelet therapy has not been reviewed, however we urge the panel to consider reviewing the evidence and updating this section. Several studies relevant to anti-platelet and anti-thrombotic therapy in type 2 diabetes have been published since 2015. In secondary prevention, the PEGASUS trial demonstrated that extended anti-platelet therapy with aspirin and ticagrelor reduced the risk of major adverse cardiovascular events in people with prior myocardial infarction who are high risk of a further event – including people with diabetes (TA420). The COMPASS trial indicates that people with stable cardiovascular disease and risk factors including diabetes or peripheral arterial disease may be offered aspirin and rivaroxaban for prevention of atherothrombotic events (TA607).	Thank you for your comment. The section of the guideline covering antiplatelet therapy was not prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest existing recommendations needed amending. However, we will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
CaReMe UK	Guideline	009	007	We suggest that specific values of HbA1c as examples of appropriate targets are included to aid prescribers.	Thank you for your comments. The starting point is the targets given in recommendations 1.6.7 and 1.6.8. The aim of the PDA is to support an individualised discussion between the healthcare professional and person with diabetes. PDAs should not be used in place of the conversation. The committee felt that putting specific target values in the PDA or visual analogue scale could be too restrictive and counter-productive to the aim of support shared decision making. They emphasised the need for dialogue that is tailored to the person's individual circumstances, preferences, goals and values.
CaReMe UK	Guideline	010	001	We are concerned that Figure 1 does not accurately convey the clinical benefit of a lower target in preventing future microvascular and	Thank you for your comment. The figure relates to reasons for thinking about relaxing the HbA1c target mentioned in

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				macrovascular disease – particularly in younger people with recently diagnosed type 2 diabetes. The terms and phrasing used appear weighted against drug therapy and fail to convey the message that for many people, using appropriate drug selection, it is possible to achieve tight glycaemic control without the risk of hypoglycaemia or medication side effects.	recommendation 1.6.9. The guideline did not consider any new evidence on this topic so it is not possible to include disease duration per se, but it does include life expectancy ('thinking about my age and my health overall') and multimorbidity ('health issues apart from my diabetes'). The PDA (appendix A) discusses the issue of side effects including hypoglycaemia in a fair and balanced way. We hope that providing a tool to support discussions between the healthcare professional and person with diabetes will support informed decision making and a better shared understanding of concerns and the potential benefits and harms of a higher or lower target HbA1c.
CaReMe UK	Guideline	011	012	We are concerned that this recommendation promotes therapeutic inertia in treatment escalation and relies on failure of initial therapy to secure glycaemic control before adding a second agent. We argue that more aggressive treatment escalation or better still, initial combination therapy is indicated, especially in younger individuals (eg aged <40 years) with type 2 diabetes, to maintain HbA1c <53mmol/mol/. In the VERIFY trial, early combination therapy delayed treatment escalation in newly-diagnosed young-onset type 2 diabetes and reduced time to initial treatment failure (Chan JCN, et al. Early combination therapy delayed treatment escalation in newly diagnosed young-onset type 2 diabetes: A subanalysis of the VERIFY study. Diabetes Obes Metab. 2021;23:245-251). In the EDICT trial, initial combination therapy with metformin, pioglitazone and exenatide was more effective than sequential add-on therapy in subjects with new-onset diabetes. (Abdul-Ghani MA, et al. Initial combination therapy with metformin, pioglitazone and exenatide is more effective than sequential add-on therapy in subjects with new-onset diabetes. Results from the Efficacy and Durability of Initial Combination Therapy for Type 2 Diabetes (EDICT): a randomized trial. Diabetes Obes Metab. 2015;17:268-7).	Thank you for your comment. This recommendation and the section on targets were not prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest existing recommendations needed amending. However, we will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
CaReMe UK	Guideline	012	001	We find the recommendation to consider relaxing HbA1c targets in those 'with significant co-morbidities to be misleading'. We suggest that this should only apply to people with co-morbidities in whom stricter targets are inappropriate due to age or frailty. This point is not made clear in the	Thank you for your comment. The figure relates to reasons for thinking about relaxing the HbA1c target mentioned in recommendation 1.6.9. The guideline did not consider any new evidence on this topic as it was out of scope of the

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				recommendation. Younger people with co-morbidities (for example CVD or CKD) may benefit substantially from stricter HbA1c control to prevent adverse clinical events and we suggest that a statement to clarify this point is included.	current update so it is not possible to include disease duration per se, but it does include life expectancy ('thinking about my age and my health overall') and multimorbidity ('health issues apart from my diabetes').
CaReMe UK	Guideline	013	001	We suggest including advice that steroid therapy, as well as intercurrent illness, may worsen hyperglycaemia. The JBDS document Management of Hyperglycaemia and Steriod (Glucocorticoid) Therapy (Revised May 2021) provides useful information.	Thank you for your comment. The section of the guideline covering self-monitoring of blood glucose was not prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest existing recommendations needed amending.
CaReMe UK	Guideline	014	008	Data from the CVOT for SGLT2 inhibitors, and subsequent trials in CKD, indicate clinical benefits in renal protection as well as cardiovascular protection. We suggest that reference to 'cardiovascular protection' should be expanded to 'cardiovascular and renal protection' throughout.	Thank you for your comment. Following committee discussion of stakeholder comments the recommendation on choosing drug treatments has been amended to include consideration of cardiovascular and renal protection (third bullet). The renal benefits of using SGLT2 inhibitors in people with type 2 diabetes and CKD have been assessed in a separate piece of work that has recently been out for stakeholder consultation and was published in November 2021. The final recommendations on renal and cardiovascular benefits will be brought together in a single updated guideline document when this current work on cardiovascular benefits is published in 2022.
CaReMe UK	Guideline	014	013 - 014	We disagree that the drug with the lower acquisition cost should always be selected if there is choice between drugs in the same class. Evidence of clinical benefit also needs to be taken into account. As the panel acknowledges, evidence for cardiovascular benefit of SGLT2 inhibitors is inconsistent across the class. The SGLT2 inhibitor with the lowest acquisition cost (ertugliflozin) did not demonstrate a significant reduction in major adverse cardiovascular events in its cardiovascular outcome trial. We urge the panel to recommend agents with proven cardiovascular benefit in patients with established cardiovascular disease or high cardiovascular risk.	Thank you for your comment. We agree that the factors that guide healthcare professionals (and people with type 2 diabetes) about a decision to prescribe any particular drug should not include consideration of treatment acquisition costs alone and it is for this reason that recommendation 1.7. 1 covers multiple factors to take into account when choosing drug treatments. These include the individual's clinical needs as well as their needs and preferences, monitoring licensing and safety issues. The point about lowest acquisition cost is intentionally the last bullet point and is only relevant if 2 drugs within the same class are appropriate having taken all the earlier points into account. This point is not meant to be taken in isolation. The contents

					of this recommendation and the recommendation on reviewing treatments are intended to support personalised care by ensuring that the choice of drug is tailored to individual needs and circumstances. The committee reviewed the stakeholder comments but decided to continue treating SGLT2 inhibitors (SGLT2i) as a class for the following reasons: • There was a degree of uncertainty around whether there were real differences in cardiovascular (CV) benefits between the SGLT2i based on the clinical trial evidence and results from the NMAs. o Firstly, for hospitalisation for heart failure, the SGLT2i empagliflozin, canagliflozin, and dapagliflozin produced a clinically meaningful reduction compared with placebo in the random effects NMA model. However, in the sensitivity analyses using a fixed effect model ertugliflozin also showed a clinically meaningful reduction compared to placebo, which reflects the original clinical trial data. The NMA results could not differentiate between the SGLT2i for this outcome. o Secondly, for the 3 point MACE outcome, only canagliflozin and empagliflozin produced a statistically significant reduction compared to placebo but the SGLT2i could not be differentiated from each other in the NMA. o Thirdly for all cause and CV mortality empagliflozin showed a clinically meaningful reduction compared to placebo and the other SGLT2i, but the remaining SGLT2i could not be differentiated from each other or placebo in the NMA. o Fourthly, for non-fatal MI and non-fatal stroke the NMAs could not differentiate between empagliflozin, canagliflozin, ertugliflozin and placebo. The data for dapagliflozin was

					reported differently and could not be included in the NMAs. From the clinical trial data dapagliflozin could not be differentiated from placebo for MI and was not meaningfully different from placebo for stroke. ○ Finally, only dapagliflozin showed a clinically meaningful improvement in severe hypoglycaemia compared to placebo but the remaining SGLT2i could not be differentiated from each other and placebo in the NMA. • There was also a degree of uncertainty around the cost-effectiveness of individual SGLT2i in the economic modelling. Although only dapagliflozin was cost-effective at a threshold of £20,000/quality-adjusted life year (QALY) across all model scenarios and CV risk groups it could not be differentiated from the other SGLT2i in the NMA apart from for the all-cause and CV mortality outcomes where it was clinically meaningfully worse than empagliflozin. The ranking of ICERs for the other SGLT2i varied across model scenarios and risk groups. The committee agreed that there was sufficient uncertainty in the economic modelling (caused in turn by uncertainty in the underlying clinical data) to mean that they were not sufficiently confident that these different ICERs represented true underlying differences in cost-effectiveness, as opposed to simply random variation in the results between different SGLT2 trials. • Taking the cost-effectiveness and clinical results into account the committee decided against only recommending dapagliflozin and instead made recommendations for the SGLT2i as a class. However, they recognised that there was a greater degree of uncertainty around the CV benefit associated with ertugliflozin because, depending on the choice of model used in the NMA, it did not consistently show a clinically meaningful reduction in hospitalisation for heart failure compared to placebo, unlike empagliflozin, canagliflozin and dapagliflozin. It was also not statistically

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					significantly better than placebo for the 3-point MACE outcome unlike canagliflozin and empagliflozin. The committee therefore recommended SGLT2i with proven CV benefit because this wording would enable the prescribers to select a particular drug from within the SGLT2 class if they thought this was clinically justified based on the individual characteristics of their patient, whilst future proofing the recommendation should additional evidence or new SGLT2s be made available. As per the recommendation on choosing drug treatment, once the clinical circumstances and needs of the person with type 2 diabetes, including their need for CV protection, have been taken into account, if 2 drugs in the same class are suitable for that individual then the prescriber is still expected to choose the option with the lowest acquisition cost to help use NHS resources wisely. Please see evidence review A for more a more detailed explanation of the analyses that were carried out and the committee's discussion of the results.
CaReMe UK	Guideline	014	029	The term congestive heart failure is outmoded and not in routine clinical use. We suggest the term 'chronic heart failure with reduced ejection fraction' is used for consistency with other NICE guidance (NG106, TA679)	Thank you for your comment. The committee discussed the stakeholder comments about the use of the term 'congestive' heart failure. They agreed that it would be inappropriate to change this to say symptomatic chronic heart failure with reduced ejection fraction because people with heart failure are a larger group of people than those with heart failure with reduced ejection fraction. In addition, the recommendations deliberately cover people with type 2 diabetes and heart failure to match the clinical and economic evidence. Based on stakeholder requests the committee decided to change congestive heart failure to chronic heart failure. This change was made because this term refers to the same population of people with heart failure as congestive heart failure does and it was thought that the

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					wider medical society will understand this term better because it is in wider use currently.
CaReMe UK	Guideline	015	003 - 006	We acknowledge that QRISK2 is a pragmatic tool to assess cardiovascular risk, however it should be recognised that QRISK2 was not used as an inclusion criterion for the cardiovascular outcome trials of SGLT2 inhibitors.	Thank you for your comment. The committee deliberated over the definition of high risk of developing CV risk disease (high risk of future major adverse cardiovascular event such as an MI or stroke) to capture this population. They. They were aware that this tool was not used as an inclusion criterion for the cardiovascular outcome trials of SGLT2 inhibitors but agreed that a QRISK2 score of >10% would be appropriate because this score takes into account most of the factors that were used to define this population in the economic model (and factors such as age, gender and ethnicity).They noted that QRISK2 is recommended for the assessment of CV risk in people with the 2 diabetes in the NICE guideline on NICE guideline on Cardiovascular disease: risk assessment and reduction, including lipid modification and is widely used and accepted in current general practice. Although other algorithms for assessing CVD risk exist, such as QRISK3, they are not in widespread use currently.
CaReMe UK	Guideline	015	008	The term congestive heart failure is outmoded and not in routine clinical use. We suggest the term 'chronic heart failure with reduced ejection fraction' is used for consistency with other NICE guidance (NG106, TA679)	Thank you for your comment. The committee discussed the stakeholder comments about the use of the term 'congestive' heart failure. They agreed that it would be inappropriate to change this to say symptomatic chronic heart failure with reduced ejection fraction because people with heart failure are a larger group of people than those with heart failure with reduced ejection fraction. In addition, the recommendations deliberately cover people with type 2 diabetes and heart failure to match the clinical and economic evidence. Based on stakeholder requests the committee decided to change congestive heart failure to chronic heart failure. This change was made because this term refers to the same population of people with heart failure as congestive heart failure does and it was thought that the wider medical society will understand this term better because it is in wider use currently.

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CaReMe UK	Guideline	015	008	We suggest including CKD as another criterion for SGLT2 inhibitor therapy in addition to heart failure and atherosclerotic cardiovascular disease.	Thank you for your comment. The renal benefits of using SGLT2 inhibitors in people with type 2 diabetes and CKD have been assessed in a separate piece of work that has recently been out for stakeholder consultation and was published in November 2021. The final recommendations on renal and cardiovascular benefits will be brought together in a single updated guideline document when this current work on cardiovascular benefits is published in 2022.
CaReMe UK	Guideline	015	008 - 0012	We welcome the recommendation to initiate SGLT2 inhibitor therapy, after metformin, in people with heart failure or established atherosclerotic cardiovascular disease or high cardiovascular risk. We suggest that clarification is provided that SGLT2 inhibitors should be started 'routinely' in this setting independently of glycaemic control, and not as a therapy escalation after exceeding HbA1c threshold.	Thank you for your comment. Following stakeholder comments the committee have reworded this recommendation to emphasise the need introduce the SGLT2 inhibitor without delay once metformin is tolerated. This is aimed at reducing the risk of clinical inertia delaying the introduction of the SGLT2. The recommendation about adding an SGLT2 inhibitor at any stage after first-line treatment has been started makes it clear that if the person with type 2 diabetes has or develops CVD or high CVD risk after they have started treatment then an SGLT2 can be added to their drug regimen or they can be switched onto an SGLT2. The SGLT2s are not licensed for use for CV protection independently of glycaemic control and it is expected that they would contribute to glycaemic control in most cases. However, we have included a note to the reviewing treatment recommendation to refer to this off license use.
CaReMe UK	Guideline	015	013	We agree that metformin and SGLT2 inhibitor should be initiated sequentially, however we recommend that a suggested timeline for the initiation of SGLT2 inhibitor is specified. We are mindful that the cardiovascular benefits of SGLT2 inhibitors were manifest early after commencing treatment in the CVOTs. We are concerned that the absence of specific advice on the timing of initiation may lead to delayed initiation due to therapeutic inertia.	Thank you for your comment. Following stakeholder comments the committee have reworded this recommendation to emphasise the need introduce the SGLT2 inhibitor without delay once metformin is tolerated. This is aimed at reducing the risk of clinical inertia delaying the introduction of the SGLT2i.
CaReMe UK	Guideline	015	024 - 025	We suggest including CKD as another criterion for SGLT2 inhibitor therapy in addition to heart failure and atherosclerotic cardiovascular disease.	Thank you for your comment. The renal benefits of using SGLT2 inhibitors in people with type 2 diabetes and CKD have been assessed in a separate piece of work that has recently been out for stakeholder consultation and was

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					published in November 2021. The final recommendations on renal and cardiovascular benefits will be brought together in a single updated guideline document when this current work on cardiovascular benefits is published in 2022.
CaReMe UK	Guideline	016	025	The statement that SGLT2 inhibitors can have an adverse effect on renal function is misleading. Although a small, transient, decline in eGFR can be observed after initiation of an SGLT2 inhibitor, the class is protective to the kidneys and reduces the incidence of adverse renal events. We refer the panel to the advice of the Association of British Clinical Diabetologists and the Renal Association, in which routine monitoring of renal function after initiation of an SGLT2 inhibitor is not considered necessary: ABCD and Renal Association Clinical practice guidelines for management of hyperglycaemia in adults with diabetic kidney disease (2021 update): 'We do not recommend routine assessment of renal function (creatinine and/or eGFR) within six weeks of SGLT2 initiation as there is likely to be a transient deterioration and this is not a reason to discontinue the drug'. This recommendation will add unnecessary workload to primary care and increase service utilisation, thus rendering the intervention less cost effective.	Thank you for your comment. The committee discussed the stakeholder comments about the renal impact of SGLT2 inhibitors (SGLT2i). They agreed that the existing recommendation was unclear and potentially confusing because it gave no indication of the frequency or when the monitoring should take place. They also recognised that although SGT2i can have a negative effect on renal function this is usually a small reduction in function and not a reason to stop taking the SGLT2i. Taking these points into account the committee have now removed this draft recommendation.
CaReMe UK	Guideline	017	012	We suggest inclusion of CKD in the 'Choosing treatments' box of the visual summary, given the compelling evidence that SGLT2i inhibitors are protective in this group of patients.	Thank you for your comment. We have added 'renal protection' to bullet 3 in the prescribing guidance in the visual summary.
CaReMe UK	Guideline	017	012	We suggest that a caveat is added to the statement 'stop medicines that have not worked or are not tolerated' to indicate that SGLT2 inhibitors should not be stopped in people with CVD or high CVD risk if HbA1c fails to improve. It is important to note that cardiovascular and renal benefits of SGLT2 inhibitors are accrued independently of glycaemic control.	Thank you for your comment. We have added 'stopping medicines that have had no impact on glycaemic control or weight, unless there is an additional clinical benefit, such as cardiovascular or renal protection, from continued treatment (see the note below on off-label use)' to the bullet.
CaReMe UK	Guideline	018	001	Visual summary 2 advises to assess HbA1c, cardiovascular risk and renal function. However, there is no indication of how renal function should influence treatment selection.	Thank you for your comment. At the time of consultation, the CKD recommendations were not available. We have now linked to these from the visual summaries.
CaReMe UK	Guideline	018	001	Visual summary 2 lists members of the SGLT2 inhibitor class which should be considered in people not at high CVD risk. We suggest that only SGLT2 inhibitors with evidence of reduction of cardiovascular events should be recommended for use in people at high CVD risk or with established CVD.	Thank you for your comment. The committee reviewed the stakeholder comments but decided to continue treating SGLT2 inhibitors (SGLT2i) as a class for the following reasons: • There was a degree of uncertainty around whether there were real differences in cardiovascular (CV)

					benefits between the SGLT2i based on the clinical trial evidence and results from the NMAs. ○ Firstly, for hospitalisation for heart failure, the SGLT2i empagliflozin, canagliflozin, and dapagliflozin produced a clinically meaningful reduction compared with placebo in the random effects NMA model. However, in the sensitivity analyses using a fixed effect model ertugliflozin also showed a clinically meaningful reduction compared to placebo, which reflects the original clinical trial data. The NMA results could not differentiate between the SGLT2i for this outcome. ○ Secondly, for the 3 point MACE outcome, only canagliflozin and empagliflozin produced a statistically significant reduction compared to placebo but the SGLT2i could not be differentiated from each other in the NMA. ○ Thirdly for all cause and CV mortality empagliflozin showed a clinically meaningful reduction compared to placebo and the other SGLT2i, but the remaining SGLT2i could not be differentiated from each other or placebo in the NMA. ○ Fourthly, for non-fatal MI and non-fatal stroke the NMAs could not differentiate between empagliflozin, canagliflozin, ertugliflozin and placebo. The data for dapagliflozin was reported differently and could not be included in the NMAs. From the clinical trial data dapagliflozin could not be differentiated from placebo for MI and was not meaningfully different from placebo for stroke. ○ Finally, only dapagliflozin showed a clinically meaningful improvement in severe hypoglycaemia compared to placebo but the remaining SGLT2i could not be differentiated from each other and placebo in the NMA.

					• There was also a degree of uncertainty around the cost-effectiveness of individual SGLT2i in the economic modelling. Although only dapagliflozin was cost-effective at a threshold of £20,000/quality-adjusted life year (QALY) across all model scenarios and CV risk groups it could not be differentiated from the other SGLT2i in the NMA apart from for the all-cause and CV mortality outcomes where it was clinically meaningfully worse than empagliflozin. The ranking of ICERs for the other SGLT2i varied across model scenarios and risk groups. The committee agreed that there was sufficient uncertainty in the economic modelling (caused in turn by uncertainty in the underlying clinical data) to mean that they were not sufficiently confident that these different ICERs represented true underlying differences in cost-effectiveness, as opposed to simply random variation in the results between different SGLT2 trials. • Taking the cost-effectiveness and clinical results into account the committee decided against only recommending dapagliflozin and instead made recommendations for the SGLT2i as a class. However, they recognised that there was a greater degree of uncertainty around the CV benefit associated with ertugliflozin because, depending on the choice of model used in the NMA, it did not consistently show a clinically meaningful reduction in hospitalisation for heart failure compared to placebo, unlike empagliflozin, canagliflozin and dapagliflozin. It was also not statistically significantly better than placebo for the 3-point MACE outcome unlike canagliflozin and empagliflozin. The committee therefore recommended SGLT2i with proven CV benefit because this wording would enable the prescribers to select a particular drug from within the SGLT2 class if they thought this was clinically justified based on the individual characteristics of their patient, whilst future proofing the recommendation should additional evidence or new SGLT2s be made available. As per the recommendation on choosing drug

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					treatment, once the clinical circumstances and needs of the person with type 2 diabetes, including their need for CV protection, have been taken into account, if 2 drugs in the same class are suitable for that individual then the prescriber is still expected to choose the option with the lowest acquisition cost to help use NHS resources wisely. Please see evidence review A for more a more detailed explanation of the analyses that were carried out and the committee's discussion of the results.
CaReMe UK	Guideline	018	001	In people at high CVD risk or with established CVD, we suggest that a maximum recommended timescale for initiation of SGLT2 inhibitor after metformin therapy is stated (e.g. within 4-6 weeks).	Thank you for your comment. We have added the wording 'Start the SGLT2 inhibitor as soon as metformin tolerability is confirmed' to the recommendation.
CaReMe UK	Guideline	018	001	SGLT2 is misspelled in the box at the lower left of the summary as 'SLGT2'.	Thank you for your comment. The typo has been amended.
CaReMe UK	Guideline	019	001	Visual summary 4 is included out of sequence and appears in the document before visual summary 3.	Thank you for your comment. This was intentional but the visual summaries have now been combined into either first line treatment or treatment options when further interventions are needed.
CaReMe UK	Guideline	019	001	Visual summary 4 states that GLP-1 receptor agonists should be avoided or used with caution in renal impairment. This is incorrect. Some GLP-1 receptor agonists can be used in people with CKD and eGFR 15 or above.	Thank you for your comment. This content has been updated for specific medicines rather than for medicine classes.
CaReMe UK	Guideline	019	001	We disagree that sulphonylureas have a 'moderate' hypoglycaemia risk. Sulphonyureas can cause severe and prolonged hypoglycaemia leading to hospitalisation.	Thank you for your comment. The committee agreed that, compared with insulin, the risk of hypoglycaemia is moderate for sulphonylureas. We have added text to say that the risk is high in older people in accordance with the BNF.
CaReMe UK	Guideline	020	005	We suggest that a caveat is added to the statement 'stopping medicines that have not worked or are not tolerated' to indicate that SGLT2 inhibitors should not be stopped in people with CVD or high CVD risk if HbA1c fails to improve. It is important to note that cardiovascular and renal benefits of SGLT2 inhibitors are accrued independently of glycaemic control.	Thank you for your comment. As requested the committee have amended the recommendation on reviewing drug treatments, to take account of the less apparent or measurable benefits such as cardiovascular and renal protection.

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CaReMe UK	Guideline	022	019	We disagree that GLP-1 mimetic therapy should not be offered to adults with type 2 diabetes for cardiovascular risk reduction. GLP-1 mimetics are recommended specifically for this purpose in other guidelines including ESC/EASD, ADA and our own CaReMe-UK guidance. We argue that the economic modelling reviewed by the panel to make this decision is flawed – see comment 38. We also urge the panel to review the evidence for reduction in stroke associated with use of GLP-1 mimetic therapy and consider whether these agents should be recommended specifically in people with type 2 diabetes at high risk of stroke. Bellastella G, et al. Glucagon-like peptide-1 receptor agonists and prevention of stroke systematic review of cardiovascular outcome trials with meta-analysis. Stroke. 2020;51:666-9.Malhotra K, Katsanos AH, Lambadiari V, Goyal N, Palaiodimou L, Kosmidou M, Krogias C, Alexandrov AV, Tsivgoulis G. GLP-1 receptor agonists in diabetes for stroke prevention: a systematic review and meta-analysis. Journal of neurology. 2020;267:2117-22.	Thank you for your comment. The committee have taken stakeholder comments into account and agreed to remove the recommendation about not using GLP1-mimetic therapy solely for cardiovascular risk reduction in people with type 2 diabetes. Upon reviewing the recommendation, the committee agreed that it was inappropriate to make a decision about treatment choice based solely on a single factor (cardiovascular risk) and that, as detailed in the recommendation on choosing drug treatments, multiple factors should be taken into account instead. Please see our separate response to your earlier comment about the economic modelling. Given the focus on looking at treatments reducing all CV risks, the current economic model looks at the cost-effectiveness of these treatments in both the total diabetic population, and across three other subgroups which have varying levels of high cardio vascular risk (the definitions of which are listed in section 3.1 in the economic report). A cost-effectiveness analysis looking at a population at risk of only one particular CV outcome such as stroke was thought to be inappropriate as the risk factors contributing towards stroke will likely contribute towards other CV events as well, hence resulting in populations similar to the three subgroups modelled in our analysis. The committee were therefore unable to make separate recommendations for people at risk of stroke, as a population as risk of stroke is likely to be at risk of other CV events as well.
CaReMe UK	Guideline	023	013	Visual summary 1 is duplicated here – it has already been included in the document on page 17.	Thank you for your comment. This was intentional but the visual summaries have now been combined following feedback from users.
CaReMe UK	Guideline	024	General	We are concerned that the visual summary fails to convey information in an easy-to-follow manner. Inclusion of NICE TA numbers in association with the SGLT2 inhibitors listed in the figure appears clumsy and does not offer any advantage over sampling naming the medications. The TA for	Thank you for your comment. The TAs have been included as they may be useful for people who are not at a high risk of CVD. We have tried to make this clearer visually. We have corrected the error on the empagliflozin TA.

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				empagliflozin is incorrect listed as TA366 (it is TA 336). We are confused by the statement 'This guideline update (2021) recommends SGLT2 inhibitor use in a wider population than the technology appraisals published before August 2021'. Does this indicate that the technology appraisals have been superseded?	
CaReMe UK	Guideline	024	General	Inclusion of only dapagliflozin and canagliflozin in the box labelled 'Insulin therapy' is misleading. Other SGLT2 inhibitors (empagliflozin and ertugliflozin) can be prescribed with insulin therapy.	Thank you for your comment. Empagliflozin has been added to the insulin therapy box. Insulin is not given as an option for combination with ertugliflozin in the TAs so this has not been included.
CaReMe UK	Guideline	024	General	We are concerned that the visual summary does not provide the prescriber with any advice on which drug should be selected in which circumstance. We are particularly concerned that there is no indication of which drugs are preferred in people with CVD or high cardiovascular risk and which should be avoided.	Thank you for your comment. The guideline update has recommended SGLT2 inhibitors as first line treatment for people with a high risk or established CVD. Contraindications have also been included in the table in the visual summary.
CaReMe UK	Guideline	024	General	We suggest adding to visual summary 3 a statement that SGLT2 inhibitors should not be discontinued if people with CVD or CKD if glycaemic control does not improve but should be continued for their protective cardiovascular and renal effects.	Thank you for your comment. The following wording has been added to the reviewing treatment recommendation: 'stopping medicines that have had no impact on glycaemic control or weight, unless there is an additional clinical benefit, such as cardiovascular or renal protection, from continued treatment (see the note below on off-label use)'.
CaReMe UK	Guideline	024	General	We disagree that GLP-1 treatments should be reserved for use only in the restricted criteria listed in the 'GLP-1 treatments' box. This recommendation contradicts guidance by organisations including ESC/EASD, PCDE and ADA in which GLP-1 treatments are prioritised in people with CVD or high cardiovascular risk. Frontline clinicians over the past three years are now or have changed practices based on these guidelines, in the vacuum left as a result of the lack of updates from NICE. We are concerned that basing the updates of NG28 on modelling on CV risk reduction alone will create significant confusion in primary care where over 90% of patients with type 2 diabetes are managed. We argue that the economic modelling which led to the panel's decision not to recommend GLP-1 treatments in people with CVD to reduce cardiovascular risk are flawed (discussed in comment 37).	Thank you for your comment. The committee reviewed the stakeholder comments regarding the use of GLP-1 mimetics and examined the updated economic evidence relating to GLP-1 mimetic treatment for people with type 2 diabetes and high cardiovascular risk. In the NICE health economic analyses, when looking at GLP-1 mimetics as a class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable

					semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of £20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the intervention as an effective use of NHS resources will specifically take account of the following factors." and • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis." Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable

					semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors. In addition, the committee noted that there were differences in the clinical effectiveness of the 2 forms of semaglutide. Although the acquisition costs for injectable and oral semaglutide are similar they showed marked differences in cost-effectiveness in the economic analyses. This was caused by differences in the effect estimates for stroke, myocardial infarction and severe hypoglycaemia. From earlier discussions about the clinical evidence (see the discussion sections in the evidence review for more details) the committee had agreed that it was uncertain whether the observed differences in effect on all-cause mortality compared to placebo between the 2 forms of semaglutide were real and they therefore decided not to place undue weight on them. They had also noted that this uncertainty and any other differences in effects between the drugs for other outcomes was probably due to wide 95% confidence intervals for many outcomes with these drugs, due to the smaller numbers of participants and events in the trials compared to other CVOTs. Due to the higher level of uncertainty surrounding the cost-effectiveness of the GLP-1 mimetics as a class compared to

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					the SGLT2 inhibitors, the committee considered whether to recommend injectable semaglutide for people at high cardiovascular risk in whom an SGLT2 is contraindicated or not tolerated. However, taking into account the uncertainty in the cost-effectiveness and clinical effectiveness the committee decided against recommending injectable semaglutide for this population. In the absence of the GLP-1s being cost-effective treatments for people with high CV risk or established cardiovascular disease, the existing 2015 recommendations for when to use GLP-1s were retained.
CaReMe UK	Guideline	025	General	Visual summary 4 is duplicated here.	Thank you for your comment. This was intentional but the visual summaries have now been combined into either first line treatment or treatment options when further interventions are needed.
CaReMe UK	Guideline	037	013 - 020	In relation to avoidance of diabetic ketoacidosis in people treated with SGLT2 inhibitors, we are surprised that the panel focus on people with very low carbohydrate or ketogenic diets. Selection of this group appears to be based on anecdote rather than scientific evidence.	Thank you for your comment. Following stakeholder consultation, the committee have reworded the draft recommendation on what to check before starting an SGLT2 inhibitor. The first bullet now covers whether the person may be at increased risk of diabetic ketoacidosis (DKA) if they take an SGLT2 inhibitor and includes some examples of when a person might have a higher risk of DKA. This list includes a previous episode of DKA, they are unwell with intercurrent illness, or are following a very low carbohydrate or ketogenic diet, but is not intended to be exhaustive.
CaReMe UK	Guideline	038	001 - 005	"Because of the relatively recent introduction of SGLT2 inhibitors, the committee were concerned that drug-induced renal damage could become widespread if monitoring is not carried out appropriately". We consider this statement to be alarmist, misleading and implies a misunderstanding of the mechanism of action of these drugs and the totality of the clinical trial evidence. SGLT2 inhibitors protect against declining renal function and reduce the incidence of adverse renal events. They do not cause 'drug-induced renal damage'. Clinical trials in the setting of heart failure and CKD, in people with and without type 2 diabetes, provide reassurance that SGLT2 inhibitors can be used safely in	Thank you for your comment. The committee discussed the stakeholder comments about the renal impact of SGLT2 inhibitors (SGLT2i). They agreed that the existing recommendation was unclear and potentially confusing because it gave no indication of the frequently or when the monitoring should take place. They also recognised that although SGT2i can have a negative effect on renal function this is usually a small reduction in function and not a reason to stop taking the SGLT2i. Taking these points into account

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				people with established CKD and that 'drug-induced renal damage' will not 'become widespread'.	the committee have now removed this draft recommendation.
CaReMe UK	Guideline	042	012 - 015	We are concerned that GLP-1 mimetics were excluded from the recommendations for drugs to use in people with established CVD to reduce cardiovascular risk. Prescription of GLP-1 mimetics should not be predicated 'solely to reduce cardiovascular risk'. GLP-1 mimetics have several other advantages, including weight loss and absence of hypoglycaemia risk, which argue for use in people with CVD in preference to other therapies (e.g. sulphonyureas). We disagree that GLP-1 mimetics are not cost effective in this scenario and consider that the economic modelling is flawed – see comment 38. Lack of HbA1c data in the modelling for GLP1RA will have significant impact in primary care. A substantial proportion of diabetes management in primary care is still hinged on HbA1c reduction and this is remains an integral part of QOF. Basing the update of NG28 on modelling on CV risk reduction alone will create significant confusion over the clinical use of GLP1-RAs in primary care. .The effects of obesity and overweight issues in with people with T2DM are under-estimated in the modelling. Therefore, the clinical benefits of weight loss associated with GLPR1RAs is also not adequately captured. Over 90% of people with T2DM are obese or overweight.	Thank you for your comment. The committee have taken stakeholder comments into account and agreed to remove the recommendation about not using GLP1-mimetic therapy solely for cardiovascular risk reduction in people with type 2 diabetes. Upon reviewing the recommendation, the committee agreed that it was inappropriate to make a decision about treatment choice based solely on a single factor (cardiovascular risk) and that, as detailed in the recommendation on choosing drug treatments, multiple factors should be taken into account instead. You are correct that the model does not contain every outcome that could potentially be of interest for modelling adults with type 2 diabetes. However, the committee agreed these were the most important outcomes for assessing the additional cardiovascular and other benefits associated with drug treatment for type 2 diabetes, for the majority of the type 2 diabetes population. The committee agreed the cardiovascular outcome trials were the most appropriate data source to assess cardiovascular benefits of these drugs, being powered to specifically detect differences in hard outcomes, rather than only surrogate outcomes. The committee noted these studies were not representative of the full population of people with type 2 diabetes, but agreed this was a lesser limitation than the need to extrapolate from surrogate endpoints to cardiovascular outcomes, particularly given the findings from those studies suggesting these surrogate extrapolations are often not very robust. They also agreed that taking data on weight and hypoglycaemic events from these cardiovascular outcome trials was the most appropriate approach, in order to match the data used for cardiovascular event rates. For hypoglycaemic events, the approach taken is broadly in line

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					with that taken in many other evaluations in diabetes, attaching costs and quality of life outcomes to the incidence of severe hypoglycaemic events, as these are the ones that make the most difference to a person's life. For changes in weight, it was noted it was important not to double count the impact of changes, as the effects on cardiovascular outcomes should already be captured in the outcomes of those trials. It was therefore agreed that the most appropriate approach was to only include the direct quality of life gains associated with reductions in weight, with the other benefits captured through the cardiovascular event data. The committee noted that if anything the approach taken in the guideline may overestimate the benefits of weight reduction, as some of the estimated quality of life gains may be the result of avoided cardiovascular events, but it was agreed to be the best data source available. There are of course other benefits that could have been considered as part of the modelling, including renal (or other microvascular) outcomes, or additional benefits directly related to improved glycaemic control, but the committee considered these to be of lower priority than those included in the model. They also noted that it would not be appropriate for any modelling approach to simply look at benefits on different outcomes from different trials or data sources, and assume those benefits are additive, and therefore increase the cost-effectiveness of drugs when included together. They noted that in many circumstances these benefits are not additive, and which benefits are likely to be realised may depend on the individual characteristics of the people included in studies. As an example, in the separate evaluation of SGLT2 inhibitors for people with CKD and type 2 diabetes, SGLT2 inhibitors were found to significantly improve renal outcomes, but this is a population in which a large benefit would not be expected for glycaemic control (hence why these agents were not originally licensed for use in people with impaired renal function).

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					It should also be noted that it is not the case that only additional outcomes beneficial to drug therapy were excluded from the modelling. As an example, adverse events related to drug treatment (excluding hypoglycaemia) were not included as part of the analysis. As a number of the analyses in the guideline explicitly compare the addition of new treatments (for example, using 3 drugs versus 2) rather than simply switching drugs, it would be expected that inclusion of adverse events would decrease the cost-effectiveness for any additional treatments, as they would add to the adverse event burden. Therefore, whilst it is likely there would be differences found in the results of the cost-effectiveness analysis were a different set of outcomes to be included, it is not clear in which direction the results would change for any given agent, and whether they would become more or less cost-effective.
CaReMe UK	Health Economic Report	008	029 - 039	We consider the economic modelling to be flawed because the regimen chosen as 'standard care', against which other therapies are compared, does not represent contemporary standard care of adults with type 2 diabetes. Serial intensification of treatment using metformin, sulphonylurea and NPH insulin is not typical of contemporary practice. Because these are all medications with low acquisition costs, their selection as standard of care prejudices comparison with medications with higher acquisition costs. In our experience, few prescribers would pursue this treatment intensification regime in their patients with type 2 diabetes. Reference to recommendations made in NG28 as 'standard of care' is inappropriate because this guidance is outdated and inconsistent with other more contemporary clinical guidelines. This is particularly the case in patients with established CVD or high CVD risk, in whom sulphonylureas would not generally be selected as second line therapy now due to the significant risk of hypoglycaemia; and the increasing awareness of the association between hypoglycaemia and cardiovascular mortality. It is noteworthy that many prescribers initiate a DPP4 inhibitor in preference to a sulphonylurea to avoid the risk of hypoglycaemia. This is reflected in UK prescribing trends, where prescriptions for sulphonylureas have declined over the last	Thank you for your comment. Throughout the scoping and development process, the committee considered DPP4 inhibitors to be one of the treatment comparators within the model as per the scope of the evidence review. The SoC arm in the model was generated in order to provide a baseline rate of events to which the treatment effects from the evidence review could be applied. In our analyses, we estimate the relative cost-effectiveness of all treatment comparators in the model, therefore enabling a comparison between any treatments of interest (such as between DPP4 inhibitors and any other treatment strategies in the model. You are correct that CVOTs predominantly include high CV risk patients. However, a separate subgroup analysis was performed on patients deemed at having a high CV risk, and

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				few years, whereas prescriptions for DPP4 inhibitors have increased and have almost reached parity with sulphonylureas (Farmer RE et al. Prescribing in Type 2 Diabetes Patients With and Without Cardiovascular Disease History: A Descriptive Analysis in the UK CPRD. Clin Ther. 2021 Feb;43(2):320-335). We urge the panel to commission revised economic modelling in which CVOT-medications are compared with 'standard care' regimes including a DPP4 inhibitor. We argue that a compelling indication for GLP-1 therapy is in people with CVD, or high cardiovascular risk, who are already prescribed an SGLT2 inhibitor and in whom treatment escalation is required to maintain glycaemic control. In this scenario, in which sulphonylureas are often avoided because of hypoglycaemia risk, GLP-1 mimetics represent a logical choice. This sequencing, which is advocated by clinical guidelines including those of the ESC/EASD, ADA and PCDE, has now become the 'standard of care'. We suggest that health economic modelling is employed to assess the ICER of GLP-1 therapies in this scenario. Finally, the Health Economic model is based on data from CVOTs. The CVOTs predominately include patients at high-risk/established CV but 70 to 80 percentage of the patients in primary care are not in this category, therefore the generalisation of the model results for the primary care population will be inappropriate. Additionally, the CVOTs were all very different in the baseline characteristics of participants and duration of follow up - as evidenced in the differential event rates in control arms of the studies. Therefore, treating patients as the same, and as similar to our primary care patients is not clinically appropriate. Standard arms of the CVOTs are completely different. If they were comparable, we would expect to see similar rates of MACE in the placebo arms of these trials, but this is not the case. MACE varies widely between 2.7 (REWIND) and 4.4 (SUSTAIN-6) events per 100 patient years.	the interpretation of results not deferring to that of the total population. You are correct that there were differences in the baseline characteristics between the CVOTs. However in the absence of individual patient data, the committee agreed that there were no established methods for adjusting these data that could be conducted that would increase their confidence in the effect estimated. They noted that simply having populations at different risk levels in different trials would not be a source of bias in the results, as this should not impact on the relative effects estimated in the trials and subsequently used to populate the model. A concern would only arise if there were systematic differences between the trials in characteristics that would affect relative (and not just absolute) treatment effectiveness and, while the data did not allow the committee to completely rule out this possibility, there were not clear clinical reasons they were aware of to suspect that such a pattern would exist. Nonetheless, the committee agreed the between trial heterogeneity was a source of uncertainty in the analysis, and considered this as part of their decision-making.
Dexcom	Guideline	012	011	It is surprising that NICE have taken the decision to omit continuous glucose monitoring (CGM) systems from the guideline update due to both the high clinical need and evidence base surrounding CGM.	Thank you for your comment. We agree that this is an important topic and that there is new evidence available that supports an update. The updates to the type 2 diabetes guideline are being carried out as a series of independent reviews. This current work is focused on the drug treatment

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				At present across the UK 4.1 million people live with diabetes, 90% of these individuals have Type 2 diabetes (T2D). In addition to the diagnosed T2D population, it has been estimated that a further 850,000 individuals have undiagnosed T2D and that by 2030 the number of people living with diabetes is estimated to be 5.5 million[1]. The proposed update to the T2D treatment guidelines makes it clear that education, diet and lifestyle advice are key components of a treatment plan[2]. They also clearly state that for adults with T2D who have not been able to achieve or maintain their individually agreed HbA1c threshold, further interventions should be considered, one of these being insulin therapy[2]. It has been estimated that 12.5% of the UK diagnosed T2D population require insulin to manage their diabetes[3]. This equates to a T2D insulin dependent population of 461,250 across the UK. People with diabetes that require insulin to manage their diabetes are at risk for developing hypoglycaemia. Hypoglycaemia is an important risk factor of insulin therapy as it can result in serious acute complications such as seizures, coma, and even death[4]. Numerous randomized clinical trials (RCTs) have shown that intensive diabetes therapy, which aims to achieve lower average blood glucose, increases the risk of severe hypoglycaemia by 2- to 3-fold in patients with T1D and T2D[5-8].	pathway, and the CGM work is being carried out separately. It will be be published by March 31st 2022.

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				Nocturnal hypoglycaemia, which are severe hypoglycaemic events occurring at night, are particularly dangerous. Nocturnal hypoglycaemia is estimated to be a contributing factor to patients dying while asleep, which has been found to occur at an incidence of 2.5 events/patient-year inT2D patients[9]. In addition to hypoglycaemia, there is a growing body of evidence demonstrating that CGM has the ability to lower HbA1c thus reducing the probability of the user developing long-term complications associated with elevated HbA1c. Since the publication of the last NICE update in 2015, the Advanced Technologies & Treatments for Diabetes (ATTD) consensus statement[10] has been produced on CGM and additional studies have been completed evaluating CGM in patients with T2 Diabetes. This growing body of evidence regarding the benefit of CGM in lowering HbA1c, reduction of hypoglycaemia, and the potential behavioural changes seen in people with T2D requires a thorough review for consideration in this guideline. **Clinical Evidence** Martens et al (2021) published a multicentre, randomized, open-labelled, parallel group clinical trial to determine the effectiveness of CGM in adults with T2D treated with basal insulin without prandial insulin in a **primary**	

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				care setting[11]. This study included 175 T2D patients with HbA1c levels between 7.8% and 11.5% [mean 9.1%] who used 1-2 daily injections of long- or intermediate-acting basal insulin for at least 6 months. This study demonstrated that CGM users achieved a -0.4% decrease in HbA1c levels vs SMBG users [8.0% vs 8.4%, respectively, at 8-months]. A far greater proportion of CGM users (63%) obtained an HbA1c of <8% at 8-months compared to SMGB users (39%). In addition, Martens and colleagues also found 63% of CGM users compared to 41% of the SMBG group achieved a ≥10% improvement in HbA1c, a 54% relative greater improvement, which based on the DCCT trial, equates to a 40% reduction in the development of retinopathy[12]. A retrospective propensity match cohort study of Type 2 IIT diabetes patients found a significant 0.6% difference-in-difference reduction in HbA1c for CGM users (8.2% to 7.6%) compared to non-CGM users (8.3% to 8.2%)[13]. Aleppo et al conducted a 6-month follow-up analysis to Marten study that assessed the clinical value for sustained use for CGM in insulin using type 2 diabetics, This analysis randomised CGM using participants, to either continue or discontinue CGM. The participants that discontinued CGM were placed on blood glucose monitoring (BGM). The results of this analysis clearly demonstrated that a significant proportion of the benefits such as time in range (TIR) derived through use of CGM were lost when CGM was withdrawn[14]. The study findings clearly demonstrate that with	

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				the use of CGM, poorly controlled patients with T2D on basal insulin can improve glycaemic control in the primary care setting. Billings et al (2018)[15] conducted a post hoc analysis to investigate whether the DIAMOND study participants at progressively higher baseline HbA1c levels benefit from using CGM. In this analysis, 120 T2D patients (CGM, n=63; control, n=57) with baseline HbA1c ≥ 8.0% – 10% were included. The study observed that change in HbA1c was significantly greater among participants in the CGM group compared to SMBG at all predefined HbA1c thresholds at 12 and 24 weeks. Reductions in HbA1c ranged in magnitude from 0.8% to 1.4% (8 to 15 mmol/mol) depending on baseline HbA1c with the greatest change being in ≥ 9.0% subgroup. This is a significant finding as it demonstrates that using of CGM, significant reductions in HbA1c can be achieved among elevated baseline HbA1c levels Ehrhardt et al (2011)[16] conducted a prospective, 52-week, two-arm, randomized trial comparing CGM versus self-monitoring of blood glucose (SMBG) in 50 people with T2D not taking prandial insulin. Baseline HbA1c was 8.4% (68 mmol/mol) and 8.2% (66 mmol/mol) respectively. Mean reduction in HbA1c at 12 weeks was 1.0% in the CGM group and 0.5% in the SMBG group. The participants who used the CGM for ≥48 days reduced their HbA1c by 1.2% versus 0.6% in those who used it <48 days. The finding suggests that the real-time feedback provided by CGM	

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				enables people with T2D to see the glycaemic effects of meals and exercise, which may teach lifestyle skills. Pazos-Couselo et at (2015)[17] conducted an observational prospective study. Included in the study were 63 stable, insulin treated patients with type 2 diabetes. The results showed significantly higher percentages of hyperglycemic and hypoglycemic episodes detected by CGM than by capillary blood glucose measurements 61.1% vs. 50.8% and 3.8% vs. 1.7% respectively. A total of 33% patients experienced nocturnal hypoglycemia, and 19% of patients who had no hypoglycemia data recorded in the capillary blood glucose diary, had experienced hypoglycemia as measured by CGM. Hypoglycemia occurred mainly during the nocturnal period. These data highlight that insulin using people with T2D require a CGM to alert them to potentially dangerous glucose excursions. Preventing CGM access to these patients may negatively impact patient safety. This was further highlighted by Ishikawa et al (2018)[18]. The author concluded that patients aged ≥ 65 years with T2D have a higher glucose variability and lower average glucose levels indicating a greater hypoglycemia risk. It is therefore necessary to ensure comprehensive blood glucose control in such patients to prevent hypoglycemia. The growing body of evidence in this area lead to the following:	

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				ATTD International Consensus on Use of Continuous Glucose Monitoring[19], recommending that "*CGM should be considered in conjunction with HbA1c for glycemic status assessment and therapy adjustment in all patients with type 1 diabetes, and patients with type 2 diabetes treated with intensive insulin therapy who are not achieving glucose targets, especially if the patient is experiencing problematic hypoglycaemia."* (Danne et al 2017, p1631- 1640) The American Diabetes Association's (ADA) 2021 Standards of Medical Care in Diabetes[20] do not differentiate between insulin dependent Type 2 diabetics and Type 1 diabetes in regard to the use of CGM. The ADA recommend that CGM should be used for insulin dependent diabetics, without differentiating between T1D and T2D Reference list 1) Diabetes UK, diabetes diagnoses double in the last 15 years, 2021 2) National Institute of Health and Care, Type 2 diabetes in adults: management, Guideline, Draft for consultation, September 2021 3) Basu,s. et al, Estimation of global Insulin use for Type 2 diabetes Mellitus, 2018 -2030, Health Action International, 2018 4) American Diabetes Association. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes	

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				Association Workgroup on Hypoglycemia. *Diabetes care.* 2005;28(5):1245-1249 5) The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977-986. 6) Reichard P, Pihl M, Rosenqvist U, Sule J. Complications in IDDM are caused by elevated blood glucose level: the Stockholm Diabetes Intervention Study (SDIS) at 10-year follow up. Diabetologia. 1996;39(12):1483-1488. 7) UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352(9131):837-853. 8) Gerstein HC, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358(24):2545-2559. 9) Khunti K, et al. Rates and predictors of hypoglycaemia in 27 585 people from 24 countries with insulin-treated type 1 and type 2 diabetes: the global HAT study. *Diabetes Obes Metab.* 2016;18(9):907-915. 10) Danne, T. (2017). International Consensus of Use of Continuous Glucose Monitoring. Diabetes Care, 40(12), 1631–1640.doi:10.2337/dc17-1600	

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				11) T. Martens, et al. Effect of Continuous Glucose Monitoring on Glycemic Control in Patients With Type 2 Diabetes Treated With Basal Insulin: A Randomized Clinical Trial, JAMA 2021 Vol. 325 Issue 22. 12) Beck, R. Continuous Glucose Monitoring for Type 2 Diabetes: How Does It Compare with Type 1 Diabetes? Diabetes Technology and Therapeutics, DOI: 10.1089/dia.2021.0374 13) Karter, A. J., et al. (2021). "Association of Real-time Continuous Glucose Monitoring With Glycemic Control and Acute Metabolic Events Among Patients With Insulin-Treated Diabetes." JAMA 325(22): 2273-2284. 14) G. Aleppo, R. et al. The Effect of Discontinuing Continuous Glucose Monitoring in Adults With Type 2 Diabetes Treated With Basal Insulin, Diabetes Care 2021 Pages dc211304 15) Billings, L.K et al, Baseline Glycated Hemoglobin Values Predict the Magnitude of Glycemic Improvement in Patients with Type 1 and Type 2 Diabetes: Subgroup Analyses from the DIAMOND Study Program. Diabetes Technol Ther, 2018. **20**(8): p. 561-565 16) Ehrhardt, N. M et al. (2011). *The Effect of Real-Time Continuous Glucose Monitoring on Glycemic Control in Patients with Type 2 Diabetes Mellitus. Journal of Diabetes Science and Technology, 5(3), 668–675.*doi:10.1177/193229681100500320 17) Pazos-Couselo, M et al. (2015). High Incidence of Hypoglycemia in Stable Insulin-Treated Type 2 Diabetes Mellitus: Continuous	

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				Glucose Monitoring vs. Self-Monitored Blood Glucose. Observational Prospective Study. Canadian Journal of Diabetes, 39(5), 428–433.doi:10.1016/j.jcjd.2015.05.007 18) Ishikawa, Tet al. (2017). Continuous glucose monitoring reveals hypoglycemia risk in elderly patients with type 2 diabetes mellitus. Journal of Diabetes Investigation, 9(1), 69–74.doi:10.1111/jdi.12676 19) Danne, T et al. (2017). International Consensus on Use of Continuous Glucose Monitoring. Diabetes Care, 40(12), 1631–1640.doi:10.2337/dc17-1600 20) American Diabetes Diabetes Technology (ADA): Standards of Medical Care in Diabetes-2021, Diabetes Care 2021;44(Suppl. 1):S85–S99	
Diabetes Specialist Nurse Forum UK ltd	Guideline	General	General	Amazed that they have not put GLP's higher up in the pathway in line with ADA/EASD. Why is NPH still first choice insulin?" "GLP-1 still so far down the line, I was hoping to see more of a similar approach to ADA/EASD" "GLP-1's was only reviewed in light of CV benefit due to time. No other benefits were considered. A full review should be asked as this would potentially alter the GLP-1's place in the pathway." Amazed to see that the option of GLP-1's has not been included as primary treatment with Metformin for those at high risk of ACVD. It goes against the ADA/EASD guidance and would like to know what the rationale for this is."	Thank you for your comment. The committee reviewed the stakeholder comments regarding the use of GLP-1 mimetics and examined the updated economic evidence. In the NICE health economic analyses, when looking at GLP-1 mimetics as a class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of

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					£20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the intervention as an effective use of NHS resources will specifically take account of the following factors." and • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis." Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors.

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					Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors. In addition, the committee noted that there were differences in the clinical effectiveness of the 2 forms of semaglutide. Although the acquisition costs for injectable and oral semaglutide are similar they showed marked differences in cost-effectiveness in the economic analyses. This was caused by differences in the effect estimates for stroke, myocardial infarction and severe hypoglycaemia. From earlier discussions about the clinical evidence (see the discussion sections in the evidence review for more details) the committee had agreed that it was uncertain whether the observed differences in effect on all-cause mortality compared to placebo between the 2 forms of semaglutide were real and they therefore decided not to place undue weight on them. They had also noted that this uncertainty and any other differences in effects between the drugs for other outcomes was probably due to wide 95% confidence intervals for many outcomes with these drugs, due to the smaller numbers of participants and events in the trials compared to other CVOTs. Due to the higher level of uncertainty surrounding the cost-effectiveness of the GLP-1 mimetics as a class compared to the SGLT2 inhibitors, the committee considered whether to

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					recommend injectable semaglutide for people at high cardiovascular risk in whom an SGLT2 is contraindicated or not tolerated. However, taking into account the uncertainty in the cost-effectiveness and clinical effectiveness the committee decided against recommending injectable semaglutide for this population. The section of the guideline covering insulins was not within the scope of this update. The current committee did not review any evidence on this topic and were therefore unable to update the recommendations in this section. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand. The committee were aware of the ADA guidance, but their decisions were made according to the NICE guideline manual and took into account the evidence relevant to our review question. Although the NICE guidance may differ to the guidance provided by ADA, the committee were confident that their recommendations reflected the evidence they reviewed and their clinical judgement. It is of particular importance to note that the NICE guideline used an original

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					economic model as the basis to recommend the most clinically and cost-effective options while the ADA guidance did not systematically take cost-effectiveness into account. When producing guidelines, NICE considers both effectiveness and cost-effectiveness for all of the recommendations it makes. As well as helping to ensure the recommendations made represent the best use of NHS resources (in particular, the opportunity costs of spending additional resources), this is also required by the legislation that originally established NICE (the Health and Social Care Act 2012), which states that when exercising its functions, NICE must have regard to "the broad balance between the benefits and costs of the provision of health services or of social care in England." NICE's principles further refine this by explicitly stating that "if possible, NICE considers value for money by calculating the incremental cost-effectiveness ratio" and "interventions with an ICER of less than £20,000 per QALY gained are generally considered to be cost effective." This guidance was developed in line with both these statutory requirements, and NICE's stated principles, methods and processes.
Diabetes Specialist Nurse Forum UK ltd	Guideline	General	General	"The guidelines are more concerned with cost saving as opposed to efficacy and benefit based on current evidence."	Thank you for your comment. When producing guidelines, NICE considers both effectiveness and cost-effectiveness for all of the recommendations it makes. As well as helping to ensure the recommendations made represent the best use of NHS resources (in particular, the opportunity costs of spending additional resources), this is also required by the legislation that originally established NICE (the Health and Social Care Act 2012), which states that when exercising its functions, NICE must have regard to "the broad balance between the benefits and costs of the provision of health services or of social care in England." NICE's principles further refine this by explicitly stating that "if possible, NICE considers value for money by calculating the incremental cost-effectiveness ratio" and "interventions with an ICER of

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					less than £20,000 per QALY gained are generally considered to be cost effective." This guidance was developed in line with both these statutory requirements, and NICE's stated principles, methods and processes. This responsibility does not solely extend to NICE as under the NHS Constitution those providing NHS services should also take into account the cost and benefit of the treatments they use. The current update has taken both effectiveness and cost-effectiveness into account and this has resulted in recommendations for SGLT2s for people at high CV risk/ established CVD who are likely to benefit from CV protection, whilst not recommending treatments where the CE is more uncertain. The GLP-1s were not cost-effective for people at high CV risk/ established CVD and the committee were therefore unable to recommend them.
Diabetes Specialist Nurse Forum UK ltd	Guideline	General	General	"Very disappointed that the guidelines are not similar to the ADA/EASD guidance" "I am very disappointed that the GLP-1 therapies remain so far down the treatment line when the ADA/EASD guidelines are completely different in terms of when to add GLP-1 therapy to those patients with CKD/HF/CVD. How 2 pathways can be so different is astonishing, especially when the ADA/EASD guidance is based on recent evidence and trials. This will only confuse our colleagues more to determine which pathway they should follow. If cost is an implication, surely the cost of starting insulin and the need to monitor blood glucose levels (cost of testing strips and lancets) along with the time spent on insulin start education and intensive follow up would work out higher that the cost of initiating a GLP-1 RA." "My main comment would be the treatment recommendations not aligning with the ADA/EASD guidance. SGLT-2's are recommended as first line treatment for those at risk of CVD (alongside Metformin), but not GLP-1 treatment."	Thank you for your comment. The committee were aware of the ADA guidance, but their decisions were made according to the NICE guideline manual and took into account the evidence relevant to our review question. Although the NICE guidance may differ to the guidance provided by ADA, the committee were confident that their recommendations reflected the evidence they reviewed and their clinical judgement. It is of particular importance to note that the NICE guideline used an original economic model as the basis to recommend the most clinically and cost-effective options while the ADA guidance did not systematically take cost-effectiveness into account. When producing guidelines, NICE considers both effectiveness and cost-effectiveness for all of the recommendations it makes. As well as helping to ensure the recommendations made represent the best use of NHS resources (in particular, the opportunity costs of spending additional resources), this is also required by the legislation

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				"So from what I can see the committee they are basing their decision around the position of GLP-1 RA treatment not justified to solely reduce CVD and not seen as cost effective. However they said that they did not evaluate evidence around glycaemic control, which we know has significant benefits. My question would be, what is the cost benefit around the reduction in glycaemic control on long term complications, additional health care support etc. NICE also state about GLP-1's: These recommendations set tight limits 29 on who should be offered a GLP-1 mimetic, based on the lack of cost effectiveness of this treatment for most people in the 2015 guideline. However if they have not reviewed all metabolic values then how can they fully established the physiological and cost effectiveness of the treatment? Overall I must say that I am disappointed with the review as they have not yet reviewed the full effectiveness of GLP-1's so left it to remain unchanged meaning the guideline has not been fully and holistically reviewed."	that originally established NICE (the Health and Social Care Act 2012), which states that when exercising its functions, NICE must have regard to "the broad balance between the benefits and costs of the provision of health services or of social care in England." NICE's principles further refine this by explicitly stating that "if possible, NICE considers value for money by calculating the incremental cost-effectiveness ratio" and "interventions with an ICER of less than £20,000 per QALY gained are generally considered to be cost effective." This guidance was developed in line with both these statutory requirements, and NICE's stated principles, methods and processes. The committee reviewed the stakeholder comments regarding the use of GLP-1 mimetics and examined the updated economic evidence. In the NICE health economic analyses, when looking at GLP-1 mimetics as a class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of £20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the intervention as an effective use of NHS resources will specifically take account of the following factors." And

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					• "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis." Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-

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					effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors. In addition, the committee noted that there were differences in the clinical effectiveness of the 2 forms of semaglutide. Although the acquisition costs for injectable and oral semaglutide are similar they showed marked differences in cost-effectiveness in the economic analyses. This was caused by differences in the effect estimates for stroke, myocardial infarction and severe hypoglycaemia. From earlier discussions about the clinical evidence (see the discussion sections in the evidence review for more details) the committee had agreed that it was uncertain whether the observed differences in effect on all-cause mortality compared to placebo between the 2 forms of semaglutide were real and they therefore decided not to place undue weight on them. They had also noted that this uncertainty and any other differences in effects between the drugs for other outcomes was probably due to wide 95% confidence intervals for many outcomes with these drugs, due to the smaller numbers of participants and events in the trials compared to other CVOTs. Due to the higher level of uncertainty surrounding the cost-effectiveness of the GLP-1 mimetics as a class compared to the SGLT2 inhibitors, the committee considered whether to recommend injectable semaglutide for people at high cardiovascular risk in whom an SGLT2 is contraindicated or not tolerated. However, taking into account the uncertainty in the cost-effectiveness and clinical effectiveness the committee decided against recommending injectable semaglutide for this population.

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					The original scope of the update to the drug treatment sections of NG28 was to fully update the treatment section of the guideline as your comment notes. However, once work on the topic commenced it was determined that updating evidence reviews and health economics for such a wide scope, within the resources available to NICE for this topic, would take an unacceptably lengthy period. Taking such an approach for this guideline update would have further delayed publication of updated treatment recommendations in this rapidly changing area. In view of the timescales involved and the appetite from the committee and stakeholders for an update within an acceptable time period, we worked with our committee members to identify the priority areas for this update. The committee members agreed that our initial focus should be on reviewing the evidence from trials looking at cardiovascular outcomes. This reflected the changing evidence base as a result of the significant investment in clinical trials to directly capture cardiovascular outcomes, feedback from stakeholders that assessing this evidence was a priority and the impact that this new evidence could have on recommendations for the treatment of people with diabetes. We therefore revised the scope to reflect this and carried out the current piece of work. You are correct that the model does not contain every outcome that could potentially be of interest for modelling adults with type 2 diabetes. However, the committee agreed these were the most important outcomes for assessing the additional cardiovascular and other benefits associated with drug treatment for type 2 diabetes, for the majority of the type 2 diabetes population. The committee agreed the cardiovascular outcome trials were the most appropriate data source to assess

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					cardiovascular benefits of these drugs, being powered to specifically detect differences in hard outcomes, rather than only surrogate outcomes. The committee noted these studies were not representative of the full population of people with type 2 diabetes, but agreed this was a lesser limitation than the need to extrapolate from surrogate endpoints to cardiovascular outcomes, particularly given the findings from those studies suggesting these surrogate extrapolations are often not very robust. They also agreed that taking data on weight and hypoglycaemic events from these cardiovascular outcome trials was the most appropriate approach, in order to match the data used for cardiovascular event rates. For hypoglycaemic events, the approach taken is broadly in line with that taken in many other evaluations in diabetes, attaching costs and quality of life outcomes to the incidence of severe hypoglycaemic events, as these are the ones that make the most difference to a person's life. For changes in weight, it was noted it was important not to double count the impact of changes, as the effects on cardiovascular outcomes should already be captured in the outcomes of those trials. It was therefore agreed that the most appropriate approach was to only include the direct quality of life gains associated with reductions in weight, with the other benefits captured through the cardiovascular event data. The committee noted that if anything the approach taken in the guideline may overestimate the benefits of weight reduction, as some of the estimated quality of life gains may be the result of avoided cardiovascular events, but it was agreed to be the best data source available. There are of course other benefits that could have been considered as part of the modelling, including renal (or other microvascular) outcomes, or additional benefits directly related to improved glycaemic control, but the committee

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					considered these to be of lower priority than those included in the model. They also noted that it would not be appropriate for any modelling approach to simply look at benefits on different outcomes from different trials or data sources, and assume those benefits are additive, and therefore increase the cost-effectiveness of drugs when included together. They noted that in many circumstances these benefits are not additive, and which benefits are likely to be realised may depend on the individual characteristics of the people included in studies. As an example, in the separate evaluation of SGLT2 inhibitors for people with CKD and type 2 diabetes, SGLT2 inhibitors were found to significantly improve renal outcomes, but this is a population in which a large benefit would not be expected for glycaemic control (hence why these agents were not originally licensed for use in people with impaired renal function). It should also be noted that it is not the case that only additional outcomes beneficial to drug therapy were excluded from the modelling. As an example, adverse events related to drug treatment (excluding hypoglycaemia) were not included as part of the analysis. As a number of the analyses in the guideline explicitly compare the addition of new treatments (for example, using 3 drugs versus 2) rather than simply switching drugs, it would be expected that inclusion of adverse events would decrease the cost-effectiveness for any additional treatments, as they would add to the adverse event burden. Therefore, whilst it is likely there would be differences found in the results of the cost-effectiveness analysis were a different set of outcomes to be included, it is not clear in which direction the results would change for any given agent, and whether they would become more or less cost-effective. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we

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					have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand.
Diabetes Specialist Nurse Forum UK ltd	Guideline	General	General	a. We note that the evidence for GLP-1 RA was only limited to cardiovascular benefits and weight loss and glycaemic management were not examined. In light of the EASD/ADA guidance and the evidence that was examined for their comprehensive guideline, this in our view will make the new NICE guidance outdated even with its proposed update, since the guidance has not been reviewed in full. When will this further data be examined and what time frame does this give for a full review? The current guidance for GLP-1 RA is almost 7 years old and with the EASD/ADA guidance being updated in 2018 and 2019, why would people opt to follow UK guidance that is still outdated? Many local areas and CCG's out of frustration are formulating their own guidance in light of the evidence of the effectiveness of GLP-1 RA's in all areas such as CVD, weight loss and HbA1c. Two examples from Liverpool (appendix 1) and Medway (appendix 2) have been included. b. We would like to request a full review of the position of GLP-1 RA's in the guidance and believe that a full review would change their position more in line with the current EASD/ADA guidance.	Thank you for your comment. The original scope of the update to the drug treatment sections of NG28 was to fully update the treatment section of the guideline as your comment notes. However, once work on the topic commenced it was determined that updating evidence reviews and health economics for such a wide scope, within the resources available to NICE for this topic, would take an unacceptably lengthy period. Taking such an approach for this guideline update would have further delayed publication of updated treatment recommendations in this rapidly changing area. In view of the timescales involved and the appetite from the committee and stakeholders for an update within an acceptable time period, we worked with our committee members to identify the priority areas for this update. The committee members agreed that our initial focus should be on reviewing the evidence from trials looking at cardiovascular outcomes. This reflected the changing evidence base as a result of the significant investment in clinical trials to directly capture cardiovascular outcomes, feedback from stakeholders that assessing this evidence was a priority and the impact that this new evidence could

					have on recommendations for the treatment of people with diabetes. We therefore revised the scope to reflect this and carried out the current piece of work. The current update has therefore focused on CV benefits of the drugs included in the cardiovascular outcome trials. These included the GLP-1 mimetics. The committee agreed the cardiovascular outcome trials were the most appropriate data source to assess cardiovascular benefits of these drugs, being powered to specifically detect differences in hard outcomes, rather than only surrogate outcomes. They also agreed that taking data on weight and hypoglycaemic events from these cardiovascular outcome trials was the most appropriate approach, in order to match the data used for cardiovascular event rates. For changes in weight, it was noted it was important not to double count the impact of changes, as the effects on cardiovascular outcomes should already be captured in the outcomes of those trials. It was therefore agreed that the most appropriate approach was to only include the direct quality of life gains associated with reductions in weight, with the other benefits captured through the cardiovascular event data. The committee noted that if anything the approach taken in the guideline may overestimate the benefits of weight reduction, as some of the estimated quality of life gains may be the result of avoided cardiovascular events, but it was agreed to be the best data source available. Evidence regarding weight loss and glycaemic management from new non- CVOT style trials that have been completed since the 2015 update were not included but the data from 2015 was used in the economic modelling. The committee reviewed the stakeholder comments regarding the use of GLP-1 mimetics and examined the updated economic evidence. In the NICE health economic analyses, when looking at GLP-1 mimetics as a class, the

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					results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of £20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the intervention as an effective use of NHS resources will specifically take account of the following factors." and • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis." Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly

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					robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors. In addition, the committee noted that there were differences in the clinical effectiveness of the 2 forms of semaglutide. Although the acquisition costs for injectable and oral semaglutide are similar they showed marked differences in cost-effectiveness in the economic analyses. This was caused by differences in the effect estimates for stroke, myocardial infarction and severe hypoglycaemia. From earlier discussions about the clinical evidence (see the discussion sections in the evidence review for more details) the committee had agreed that it was uncertain whether the observed differences in effect on all-cause mortality

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					compared to placebo between the 2 forms of semaglutide were real and they therefore decided not to place undue weight on them. They had also noted that this uncertainty and any other differences in effects between the drugs for other outcomes was probably due to wide 95% confidence intervals for many outcomes with these drugs, due to the smaller numbers of participants and events in the trials compared to other CVOTs. Due to the higher level of uncertainty surrounding the cost-effectiveness of the GLP-1 mimetics as a class compared to the SGLT2 inhibitors, the committee considered whether to recommend injectable semaglutide for people at high cardiovascular risk in whom an SGLT2 is contraindicated or not tolerated. However, taking into account the uncertainty in the cost-effectiveness and clinical effectiveness the committee decided against recommending injectable semaglutide for this population. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand..

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					The committee were aware of the ADA guidance, but their decisions were made according to the NICE guideline manual and took into account the evidence relevant to our review question. Although the NICE guidance may differ to the guidance provided by ADA, the committee were confident that their recommendations reflected the evidence they reviewed and their clinical judgement. It is of particular importance to note that the NICE guideline used an original economic model as the basis to recommend the most clinically and cost-effective options while the ADA guidance does not take cost-effectiveness into account. When producing guidelines, NICE considers both effectiveness and cost-effectiveness for all of the recommendations it makes. As well as helping to ensure the recommendations made represent the best use of NHS resources (in particular, the opportunity costs of spending additional resources), this is also required by the legislation that originally established NICE (the Health and Social Care Act 2012), which states that when exercising its functions, NICE must have regard to "the broad balance between the benefits and costs of the provision of health services or of social care in England." NICE's principles further refine this by explicitly stating that "if possible, NICE considers value for money by calculating the incremental cost-effectiveness ratio" and "interventions with an ICER of less than £20,000 per QALY gained are generally considered to be cost effective." This guidance was developed in line with both these statutory requirements, and NICE's stated principles, methods and processes.
Diabetes Specialist Nurse Forum UK ltd	Guideline	General	General	With reference to the patient decision making tool "Target HbA1c: Weighing it up" although it is a great way to approach individualised care and agreeing a person centred approach, there is no guide for clinicians with regard to what those individualised targets could be. Diabetes Specialist clinicians will use their clinical judgment as to what individualised HbA1c is an appropriate target, taking into account frailty	Thank you for your comment. The starting point is the targets given in recommendations 1.6.7 and 1.6.8. The aim of the PDA is to support an individualised discussion between the healthcare professional and person with diabetes. The committee felt that putting specific target values in the PDA or visual analogue scale could be too

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				and hypoglycaemia avoidance or impaired hypoglycaemia awareness for example, but non specialists will be guided by QOF targets which are not always appropriate given a patients individual circumstances. We would therefore like to see some reference to HbA1c targets that can be used for different groups of people whereby strict glycaemic management may not be appropriate. We would also like to see reference made to the new indicators added to NICE indicators (NM157-NM164) in 2018 as a guide for those with frailty (see appendix 3).	restrictive and counter-productive to the aim of support shared decision making. They emphasised the need for dialogue that is tailored to the person's individual circumstances, preferences, goals and values. The guideline update did not consider any new evidence on this topic because it was not prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest existing recommendations needed amending. Therefore it has not been possible to include reference to the NICE indicators.
Diabetes Specialist Nurse Forum UK ltd	Guideline	General	General	As a Forum we would like to call for a full review of the Type 2 Diabetes guidance. The current guidance are referred to nationally amongst primary and secondary care and it becomes confusing when our guidance is so very outdated to that of real world evidence, as well as European and American guidelines. We would also recommend a review of the data with regards technology in T2DM such as flash glucose monitoring particularly in those who use insulin for their treatment. We would welcome a full review of the guidance.	Thank you for your comment. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand. The type 2 guideline went through a surveillance review prior to the start of this work and another area that was highlighted for update was concerning continuous glucose monitoring, including flash glucose monitoring, in adults with type 2 diabetes. This work has now been completed and is expected to be published by March 31st 2022.
Diabetes UK	Guideline	009	006	Diabetes UK welcomes the inclusion of a decision support tool and educational leaflet for people with diabetes when discussing and agreeing a target HbA1c with their healthcare professional through a care planning	Thank you for your comments. Both PDA and visual analogue scale (VAS) are tools that can be used if appropriate, neither is mandatory. We agree that the prime

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				conversation, but believe this recommendation along with the associated 'Appendix A' are not fit for purpose as described. Given that predominantly non-diabetes specialists will be discussing these drugs with people with diabetes, we are concerned about the risk for health care professionals to be led "by paper" in their practice, rather than having a personalised conversation. If fit for purpose, these can be helpful to prompt a more holistic and person-centred approach, which is key to both maximising the physical benefits of these treatments and in considering the psychological and emotional impact of these treatments for people with diabetes. We also think the length and text-heavy nature of 'Appendix A' risk rendering it inappropriate for certain patient groups. This includes individuals for whom English is not their first language or where literacy levels are low. We strongly suggest the Committee reviews this decision aid in light of the above to understand the potential health inequalities it may risk embedding. We also recommend that they are properly tested with people living with type 2 diabetes. A clear rationale for why this decision aid is deemed appropriate should be provided to ensure these tools are used in the most effective way.	aim must be for a person-centred conversation. However, we do believe that, used judiciously, PDAs and other decision support tools can be helpful to support those conversations, in line with the NICE guidelines on shared decision making (NG197) and medicines optimisation (NG5). As these guidelines make clear, PDAs should not be used to replace the conversation. If use of a PDA is appropriate to the individual situation, the discussion during the clinical encounter can focus on the VAS. If the healthcare professional and person with diabetes do not want to go through the PDA in detail during the consultation, it can be provided to support shared decision making either before or after the consultation, in line with the NICE guideline on shared decision making. We would support further evaluation of the PDA and VAS in practice and we are planning to collate feedback on the PDA and VAS when published. The Flesch-Kincaid reading ease score suggests it will be understandable by people with a reading age of 11-13. This is in line with the NICE PDA standards. As you have noted certain patient groups, including individuals for whom English is not their first language or where literacy levels are low, may have difficulty using the PDA without support. However, this should not be a problem because it is intended that they should be guided through it as part of a shared decision making conversation with their healthcare professional, as stated on the PDA. If the person with type 2 diabetes has a low level of literacy their healthcare professional can explain it to them during the discussion. If they don't speak English or have a low level of understanding of English then their healthcare professional could involve translation services to support this discussion in the same way that they would for other discussions with the person.

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Diabetes UK	Guideline	010	001	We are particularly concerned that some of the responses offered in the decision support tool are potentially very dangerous. For example, the statement: "Thinking about things like driving, severe hypos would not be a severe problem for me" is inaccurate. Severe hypos whilst driving are a significant safety concern for the person with diabetes driving and others on the road. A person with diabetes who has a severe hypo whilst driving is legally required to inform the DVLA of this. The wording currently implies they can tell a healthcare professional without informing the DVLA and considering it a "severe problem", which is troubling. There is also a lack of specific guidance for people with diabetes for whom weight and hypoglycaemia may be an issue. We recommend a thorough review of the tool and have made recommendations below. To improve the decision aid tool further clarity could be provided for rows one and two and we suggest changing the wording for row 1, line 1 on driving to: "I would recognise and be able to manage a severe hypo without much problem" and row 2, line 2 on driving to: "I would struggle to recognise and/or manage a severe hypo and would be a big problem for me". The wording for the lines on row 2 can be changed to "I understand the possible side effects from my diabetes medicines and not at all concerned" and "I understand the possible side effects from my diabetes medicines and very concerned". A new row can also be added to include the lines: "I am willing to change my diabetes medicines if I need too" and "I do not want to change my diabetes medicines".	Thank you for your comments. We have amended the statements following your comments. We have removed reference to driving from the visual analogue scale (the PDA text retains the words ' some [hypos] can cause people to feel dizzy or faint and, they might need help from someone else to treat the hypo. There are special rules for some drivers who have diabetes – talk to your diabetes team to see if they affect you.') After reviewing all consultation comments, the committee amended the first pair of statements to 'Having hypos would not be a problem for me'/ 'Having hypos would be a big problem for me'. They amended the second pair to 'I'm not concerned about possible side effects from diabetes medicines'/ 'I'm very concerned about possible side effects from diabetes medicines'. The committee decided not to add a new statement pair because they were concerned about increasing the length of this part of the PDA and also felt that, generally, intensifying treatment rather than changing medicines.
Diabetes UK	Guideline	010	001	'Lower' and 'Higher' HbA1c are vague. We suggest the inclusion of numerical values here which will help clinicians ensure safety and risk of hypoglycaemia and hyperglycaemia are being properly considered within their care planning discussion.	Thank you for your comments. The starting point is the targets given in recommendations 1.6.7 and 1.6.8. The aim of the PDA is to support an individualised discussion between the healthcare professional and person with

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				We are also concerned that this decision aid risks pushing people with type 2 diabetes towards less tight management of their condition. Statements like 'I do not want to take more medicines' and 'I do not want side effects from medicines' are likely to generate responses towards the higher HbA1c target – put simply, very few people want to take more medicines or to have side effects. The key to a person-centred approach is for the person with diabetes, carers (where relevant) and the clinician to explore options together providing information and signposting to overcome concerns where possible. The Diabetes UK Information Prescription referenced below provides further information to help increase knowledge and facilitate an options-based conversation. Reference: Diabetes UK Information Prescription_HbA1c.pdf	diabetes. The committee felt that putting specific target values in the PDA or visual analogue scale could be too restrictive and counter-productive to the aim of support shared decision making. They emphasised the need for dialogue that is tailored to the person's individual circumstances, preferences, goals and values. We agree with your comments about the need for healthcare professional and person with diabetes to explore options together. The figure is intended to support that discussion, not to replace it. The choices are not binary but the visual analogue scale enables the person to indicate the extent to which they agree with either statement. We agree that most people would wish to avoid side effects and not take unnecessary medicines. However, we hope that putting these considerations alongside others, such as life expectancy, will encourage discussions to support informed decision making and a better shared understanding of the issues at play. The Diabetes UK information referenced helps with information but does not relate specifically to making a decision about HbA1c targets.
Diabetes UK	Guideline	013	020	We feel the inclusion of 4 visual summaries fails to reflect clinical use of NICE guidelines. We note that NICE recently conducted a consultation asking clinicians about how they used guidelines. It is unclear what conclusions NICE has drawn from this consultation, but our understanding having spoken to clinicians working in diabetes is that 4 separate visual summaries are difficult to follow and unlikely to be useful. We recommend merging summaries 1, 2 and 3 into one document. For future proofing reasons, we also recommend removing visual summary 4 completely as this risks becoming out of date before the final update to NG28 is published.	Thank you for your comment. We have combined the visual summaries. The approach to pulling together guideline recommendations in a visual form is a proof of concept. We will be continually reviewing our processes and will be updating the table based on changes to recommendations and following feedback from stakeholders and users.
Diabetes UK	Guideline	014	029	Consider just using "heart failure" as the term "congestive heart failure" is out of date.	Thank you for your comment. The committee discussed the stakeholder comments about the use of the term 'congestive' heart failure. They agreed that it would be inappropriate to change this to say symptomatic chronic

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					heart failure with reduced ejection fraction because people with heart failure are a larger group of people than those with heart failure with reduced ejection fraction. In addition, the recommendations deliberately cover people with type 2 diabetes and heart failure to match the clinical and economic evidence. Based on stakeholder requests the committee decided to change congestive heart failure to chronic heart failure. This change was made because this term refers to the same population of people with heart failure as congestive heart failure does and it was thought that the wider medical society will understand this term better because it is in wider use currently.
Diabetes UK	Guideline	015	001	Consider including a definition of atherosclerotic disease here which may help clinicians notice under recognised high-risk cardiovascular disease states like peripheral arterial disease.	Thank you for your comment. The committee have now provided a definition of ASCVD in the Terms used in the guideline section. This includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, previous coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.
Diabetes UK	Guideline	015	010 - 012	We are pleased these recommendations are in line with some aspects of the ADA/EASD consensus guidelines but are concerned that updated recommendations on other, newer therapies like GLP-1s are not included in the scope of this update and is inconsistent with clinical practice. Therefore, we would strongly recommend that the 'Glucose-lowering medication in Type 2 diabetes: overall approach' on page 6 of the ADA/ EASD Consensus report, including GLP-1 alongside SGLT2i, be considered for adoption. References: http://care.diabetesjournals.org/content/diacare/early/2018/09/27/dci18-0033.full.pdf https://onlinelibrary.wiley.com/doi/full/10.1111/dme.13825	Thank you for your comment. The GLP-1s were included within the scope of this update but they proved not to be cost-effective at a class or individual level and the committee were therefore unable to recommend them for people with established cardiovascular disease or those with a higher risk of developing cardiovascular disease. The committee were aware of the ADA guidance, but their decisions were made according to the NICE guideline manual and took into account the evidence relevant to our review question. Although the NICE guidance may differ to the guidance provided by ADA, the committee were confident that their recommendations reflected the evidence they reviewed and their clinical judgement. It is of particular importance to note that the NICE guideline used an original economic model as the basis to recommend the most

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					clinically and cost-effective options while the ADA guidance did not systematically take cost-effectiveness into account.
Diabetes UK	Guideline	016	016	Rec 1.7.2 – We welcome this recommendation but feel that information about the side-effects of these treatments and risk of DKA should be more prominent and emphasised in guidelines, particularly for those on low-carb diets. It is vital that the healthcare professional initiating the use of these drugs has an education session with the person with diabetes and offers advice on who to contact if the person taking them is not feeling well. The need to provide the patient 'sick day guidance' needs to be made explicit in this guideline, including the need for the information to be provided in a language or suitable format (e.g. Easy Read) that fulfils the unique requirements of the individual. Advice on managing illness when you have diabetes can be found on our website, which includes information on medication including SGLT2i. References: https://diabetes-resources-production.s3.eu-west-1.amazonaws.com/resources-s3/public/2021-05/low-carb-diets-for-people-with-diabetes-position-statement-may-2021.pdf https://www.diabetes.org.uk/guide-to-diabetes/life-with-diabetes/illness	Thank you for your comment. Following stakeholder comments at consultation the committee have amended the wording of the recommendation about things to check before starting the SGLT2 inhibitor to focus on whether the person is at increased risk of diabetic ketoacidosis (DKA) if they take an SGLT2 inhibitor. They have included some examples that, in the committees view, could lead to increased risk, but this is not meant to be an exhaustive list. This is noted in the rationale that accompanies the recommendation. The committee agreed that prescribers should consult the summary of product characteristics for further information. The committee made an additional recommendation to highlight to the clinician that they should try to address any modifiable risk factors before starting SGLT2i treatment. The draft recommendation which included sick day rules was reviewed following stakeholder comments and the bullet point on sick day rules has now been removed as the committee agreed it would be inconsistent to present this information for one class of drugs but not any others. They expected that sick day rules and other safety related advice would be discussed with the individual with type 2 diabetes as part of the decision-making process regarding drug choice and wanted to keep the guidance as simple and clear as possible. The section of the guideline that covers patient education was not within the scope of this update and the committee are therefore unable to make the suggested amendments. However, there is an existing recommendation from 2009 that covers the need to ensure that patient education programmes meet the cultural, linguistic, cognitive and literacy needs of people in the local area.

Consultation on draft guideline - Stakeholder comments table
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Diabetes UK	Guideline	016	025	We would suggest adding that there is an expected eGFR decline and stabilisation following initiation of SGLT2i and no further need for closer monitoring of renal function.	Thank you for your comment. The committee discussed the stakeholder comments about the renal impact of SGLT2 inhibitors (SGLT2i). They agreed that the existing recommendation was unclear and potentially confusing because it gave no indication of the frequency or when the monitoring should take place. They also recognised that although SGT2i can have a negative effect on renal function this is usually a small reduction in function and not a reason to stop taking the SGLT2i. Taking these points into account the committee have now removed this draft recommendation.
Diabetes UK	Guideline	017	006	Low carbohydrate and ketogenic should be defined here as we are concerned that some of these terms may be misunderstood by some, non-specialist clinicians.	Thank you for your comment. We have added a definition of very low carb and ketogenic diet to the terms used in this guideline.
Diabetes UK	Guideline	017	010 – 011	We would again suggest making an explicit link to our 'Sick Day Rules' within the guidance here. Reference: https://www.diabetes.org.uk/guide-to-diabetes/life-with-diabetes/illness	Thank you for your comment. The draft recommendation which included sick day rules was reviewed following stakeholder comments and the bullet point on sick day rules has now been removed as the committee agreed it would be inconsistent to present this information for one class of drugs but not any others. They expected that sick day rules and other safety related advice would be discussed with the individual with type 2 diabetes as part of the decision-making process regarding drug choice and wanted to keep the guidance as simple and clear as possible. In addition, NICE does not routinely link to outside organisation resources unless they are formally endorsed by NICE. Please see the endorsement page on the NICE website for more details.
Diabetes UK	Guideline	017	012	Visual Summary 1 – We recommend adding "contradictions" to the 'Choosing Treatments' section as done on the guidelines on page 14, rec. 1.7.1. We would also strongly suggest adding a schedule for review for the 'Reviewing and Changing Treatments' section, considering the educational needs of the person with diabetes and offering emotional	Thank you for your comment. Contraindications has been added to the bullet. How often to carry out a review was not within scope of the guideline update. We have added a bullet on the need to check adherence to medicines and have cross referred to the NICE guideline on supporting medicines adherence.

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				support for individual circumstances affecting adherence to diabetes treatment regimen.	
Diabetes UK	Guideline	020	015 - 017	We are disappointed that consideration to mental well-being and psychological factors affecting adherence to medication regimens is not discussed in this section and would recommend this is added.	Thank you for your comment. Please note that this recommendation links to the NICE guideline on Medicines adherence as, as set out in your comment, the topic of adherence is multifactorial and too complex to be fully addressed within the current recommendations.
Diabetes UK	Guideline	022	019	Rec 1.7.21 - We disagree with this recommendation which should fully incorporate all the current treatment options that have evidence of effectiveness, offering more options to clinicians and their patients. It is important to note that atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death in people with type 2 diabetes. People with type 2 diabetes with clinical CVD not meeting individualized glycaemic targets while treated with metformin (or in whom metformin is contraindicated or not tolerated) should have an SGLT2 inhibitor or GLP-1 receptor agonist with proven benefit for cardiovascular risk reduction added to their treatment program. Among patients with type 2 diabetes who have established ASCVD, SGLT2 inhibitors or GLP-1 receptor agonists with proven cardiovascular benefit are recommended as part of glycaemic management. References: http://care.diabetesjournals.org/content/diacare/early/2018/09/27/dci18-0033.full.pdf American Diabetes Association. 9. Cardiovascular disease and risk management: Standards of Medical Care in Diabetes d2018. Diabetes Care 2018;41(Suppl. 1):S86–S10	Thank you for your comment. The committee have taken stakeholder comments into account and agreed to remove the recommendation about not using GLP1-mimetic therapy solely for cardiovascular risk reduction in people with type 2 diabetes. Upon reviewing the recommendation, the committee agreed that it was inappropriate to make a decision about treatment choice based solely on a single factor (cardiovascular risk) and that, as detailed in the recommendation on choosing drug treatments, multiple factors should be taken into account instead. Although there were a number of stakeholder comments asking for clarification of the treatment options for people with type 2 diabetes in whom SGLT2 inhibitors (SGLT2i) were contraindicated or not tolerated, there were no cardiovascular outcome trial style clinical trials identified that looked at the effectiveness of treatments for people at high cardiovascular (CV) risk in this population. The committee therefore used the evidence for effectiveness and cost effectiveness for other interventions from the same economic modelling scenarios as those looking at the cost-effectiveness of SGLT2i. The committee examined the cost-effectiveness evidence relating to GLP-1 mimetic treatment for people with type 2 diabetes and high cardiovascular risk. The committee reviewed the stakeholder comments regarding the use of GLP-1 mimetics and examined the updated economic evidence. In the NICE health economic

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					analyses, when looking at GLP-1 mimetics as a class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of £20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the intervention as an effective use of NHS resources will specifically take account of the following factors." and • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis." Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses,

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					and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors. In addition, the committee noted that there were differences in the clinical effectiveness of the 2 forms of semaglutide. Although the acquisition costs for injectable and oral semaglutide are similar they showed marked differences in cost-effectiveness in the economic analyses. This was caused by differences in the effect estimates for stroke, myocardial infarction and severe hypoglycaemia. From earlier discussions about the clinical evidence (see the discussion sections in the evidence review for more details) the committee had agreed that it was uncertain whether the observed differences in effect on all-cause mortality

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					compared to placebo between the 2 forms of semaglutide were real and they therefore decided not to place undue weight on them. They had also noted that this uncertainty and any other differences in effects between the drugs for other outcomes was probably due to wide 95% confidence intervals for many outcomes with these drugs, due to the smaller numbers of participants and events in the trials compared to other CVOTs. Due to the higher level of uncertainty surrounding the cost-effectiveness of the GLP-1 mimetics as a class compared to the SGLT2 inhibitors, the committee considered whether to recommend injectable semaglutide for people at high cardiovascular risk in whom an SGLT2 is contraindicated or not tolerated. However, taking into account the uncertainty in the cost-effectiveness and clinical effectiveness the committee decided against recommending injectable semaglutide for this population. The committee therefore agreed that they were unable to recommend injectable semaglutide for people with type 2 diabetes and high cardiovascular risk who were unable to take an SGLT2i. As a result, the committee noted that people with high CV risk who could not take the recommended dual therapy of metformin and SGLT2, because they are unable to take the SGLT2, would be offered metformin alone at treatment initiation. If they were also unable to take metformin then the clinician would select another treatment from the remaining options, namely sulfonylureas, DPP-4s or pioglitazone, depending on the individual's clinical circumstances and preferences. The committee decided against listing the options for people with type 2 diabetes who were at high CV risk and could not take an SGLT2i because they thought that this was an unnecessary level of detail given that they could not recommend a GLP-1 mimetic in place of the SGLT2i, that

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					the treatment options were therefore the same for these people as for the rest of the type 2 diabetes population and because, apart from for metformin, the guideline does not include details of which drug to take if a particular drug is contraindicated or not tolerated but rather expects the prescriber to use their clinical judgment.
Diabetes UK	Guideline	023	013	Including Visual Summary 1 here again is confusing. Can it be removed and hyperlinked instead for reference?	Thank you for your comment. This was intentional but the visual summaries have now been combined following feedback from users.
Diabetes UK	Guideline	024	General	Visual Summary 3 – We would suggest capitalising and ordering alphabetically Asian, Black and other ethnic minority groups (excluding white minorities) wherever used here in line with UK Govt's style guide. Reference: https://www.ethnicity-facts-figures.service.gov.uk/style-guide/writing-about-ethnicity	Thank you for your comment. It is currently NICE style to use 'Black, Asian and minority ethnic groups' but we have forwarded your query to the NICE style guide group for consideration and review.
Diabetes UK	Guideline	037	011 - 022	We feel this point is very important and should be made clearer earlier within the body of the guidance document.	Thank you for your comment. The committee have highlighted this by including recommendations about identifying and reducing the risks associated with DKA.
Diabetes UK	Guideline	038	005 - 006	If the monitoring schedule depends on individual clinical factors and baseline renal this should be made more explicit in the body of the guidance, earlier in the document.	Thank you for your comment. The committee discussed the stakeholder comments about the renal impact of SGLT2 inhibitors (SGLT2i). They agreed that the existing recommendation was unclear and potentially confusing because it gave no indication of the frequently or when the monitoring should take place. They also recognised that although SGT2i can have a negative effect on renal function this is usually a small reduction in function and not a reason to stop taking the SGLT2i. Taking these points into account the committee have now removed this draft recommendation.
Diabetes UK	Guideline	038	013 - 023	We strongly support this consideration and explanation by the committee and feel that the increased risk of DKA in people talking SGLT2i whilst also on a low-carbohydrate diet should be highlighted more in the guidelines.	Thank you for your comment. Please note that the recommendations on things to check before starting an SGLT2i, and on advice to adults with type 2 diabetes cover the discussion points raised in the rationale about the increased risk of DKA in people taking an SGLT2i.

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Diabetes UK	Guideline	042	008 - 015	We are very concerned that this decision has been made based on cost rather than good clinical practice and evidence. This approach fails to consider the full benefits of GLP-1 for people with diabetes and we feel that recommendations should be aligned with the ADA/EASD consensus guidelines. Reference: https://onlinelibrary.wiley.com/doi/full/10.1111/dme.13825	Thank you for your comment. The committee were aware of the ADA guidance, but their decisions were made according to the NICE guideline manual and took into account the evidence relevant to our review question. Although the NICE guidance may differ to the guidance provided by ADA, the committee were confident that their recommendations reflected the evidence they reviewed and their clinical judgement. It is of particular importance to note that the NICE guideline used an original economic model as the basis to recommend the most clinically and cost-effective options while the ADA guidance did not systematically take cost-effectiveness into account. When producing guidelines, NICE considers both effectiveness and cost-effectiveness for all of the recommendations it makes. As well as helping to ensure the recommendations made represent the best use of NHS resources (in particular, the opportunity costs of spending additional resources), this is also required by the legislation that originally established NICE (the Health and Social Care Act 2012), which states that when exercising its functions, NICE must have regard to "the broad balance between the benefits and costs of the provision of health services or of social care in England." NICE's principles further refine this by explicitly stating that "if possible, NICE considers value for money by calculating the incremental cost-effectiveness ratio" and "interventions with an ICER of less than £20,000 per QALY gained are generally considered to be cost effective." This guidance was developed in line with both these statutory requirements, and NICE's stated principles, methods and processes. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took

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					was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand.
Diabetes UK	Guideline	043	001 - 002	We welcome research recommendations to compare the effectiveness and cost effectiveness of GLP-1 and insulin and look forward to updated guidelines based on this but reiterate our concern that this has not already been considered in the current scope.	Thank you for your comment. Please note that following stakeholder comments at consultation this research recommendation has been removed. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand.
Diabetes UK	Guideline	056	020 - 021	Consider rewording this to add information about remission.	Thank you for your comment. The PDA is not a general information leaflet but is focussed on the decision about the person's target HbA1c. It reflects the guideline recommendations and the evidence reviewed. The topic of remission was not prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest

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					it should be included. Thus the committee did not review any evidence on this topic and were consequently unable to make the requested changes. The section of the guideline covering remission was not prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest existing recommendations needed amending.
Diabetes UK	Guideline	057	014 - 015	We believe that "losing weight without trying" should be added to the list of symptoms.	Thank you for your comment. The symptoms are examples only. We would not want people who wish to lose weight to run hyperglycaemic in an attempt to achieve this.
Diabetes UK	Guideline	057 - 058	033 / 001	We feel that given the possibility of the person taking the medication passing out this section should be more robust and we would suggest moving it to a separate section on mild and severe hypoglycaemia.	Thank you for your comment. We agree that education around hypos is very important but the committee did not think the PDA is the place for this because it is focussed on the decision about HbA1c targets not general information and education about diabetes. Extensive information would make the PDA too long and impractical for use: The PDA is intended as a tool to support discussions between the healthcare professional and the person with diabetes, and further information about hypos can be given if appropriate.
Diabetes UK	Guideline	Gener al	Gene ral	Diabetes UK welcomes new and additional guidance on drug treatments that will improve the clinical outcomes for people living with type 2 diabetes and increase treatment options. However, we remain disappointed by the limited scope of this guideline update which we consider a missed opportunity to ensure NICE guidelines remain in line with international clinical evidence, consensus and widespread clinical practice. The scope of this update has also shifted significantly over time but no clear explanation of why has been provided and there is a lack of clarity on the process for this update. For example, on the omission of GLP-1s from the scope. Additionally, drugs without cardiovascular benefits are being recommended ahead of GLP-1s and there is no recommendation of alternative agents if SGLT2s are contraindicated or not tolerated.	Thank you for your comment. The original scope of the update to the drug treatment sections of NG28 was to fully update the treatment section of the guideline as your comment notes. However, once work on the topic commenced it was determined that updating evidence reviews and health economics for such a wide scope, within the resources available to NICE for this topic, would take an unacceptably lengthy period. Taking such an approach for this guideline update would have further delayed publication of updated treatment recommendations in this rapidly changing area. In view of the timescales involved and the appetite from the committee and stakeholders for an update within an acceptable time period, we worked with our committee members to identify the priority areas for this update. The

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				Type 2 diabetes is a relentless condition to live with and diabetes-related complications including sight loss and kidney failure have a devastating impact on the lives of people living with type 2 diabetes every day. Blood glucose lowering drugs including SGLT2s and GLP-1s are evidenced to help reduce HbA1c levels in people living with type 2 diabetes for whom use of Metformin is not effective or appropriate. The increasingly widespread recognition of the effectiveness of these drugs is reflected in prescribing data which shows a significant increase in their use in recent years. Furthermore, the focus on cost-effectiveness of GLP-1s also fails to take into account wider changes in type 2 diabetes management, like remission, that have transformed the treatment landscape for many people with diabetes. Reference: https://bjd-abcd.com/index.php/bjd/article/view/711/909	committee members agreed that our initial focus should be on reviewing the evidence from trials looking at cardiovascular outcomes. This reflected the changing evidence base as a result of the significant investment in clinical trials to directly capture cardiovascular outcomes, feedback from stakeholders that assessing this evidence was a priority and the impact that this new evidence could have on recommendations for the treatment of people with diabetes. We therefore revised the scope to reflect this carried out the current piece of work. When producing guidelines, NICE considers both effectiveness and cost-effectiveness for all of the recommendations it makes. As well as helping to ensure the recommendations made represent the best use of NHS resources (in particular, the opportunity costs of spending additional resources), this is also required by the legislation that originally established NICE (the Health and Social Care Act 2012), which states that when exercising its functions, NICE must have regard to "the broad balance between the benefits and costs of the provision of health services or of social care in England." NICE's principles further refine this by explicitly stating that "if possible, NICE considers value for money by calculating the incremental cost-effectiveness ratio" and "interventions with an ICER of less than £20,000 per QALY gained are generally considered to be cost effective." This guidance was developed in line with both these statutory requirements, and NICE's stated principles, methods and processes. Although there were a number of stakeholder comments asking for clarification of the treatment options for people with type 2 diabetes in whom SGLT2 inhibitors (SGLT2i) were contraindicated or not tolerated, there were no cardiovascular outcome trial style clinical trials identified that looked at the effectiveness of treatments for people at high

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					cardiovascular (CV) risk in this population. The committee therefore used the evidence for effectiveness and cost effectiveness for other interventions from the same economic modelling scenarios as those looking at the cost-effectiveness of SGLT2i. The committee reviewed the stakeholder comments regarding the use of GLP-1 mimetics and examined the updated economic evidence relating to GLP-1 mimetic treatment for people with type 2 diabetes and high cardiovascular risk. In the NICE health economic analyses, when looking at GLP-1 mimetics as a class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2i, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of £20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the intervention as an effective use of NHS resources will specifically take account of the following factors." and • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of

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					NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis." Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of

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					confidence in those findings, compared again to the findings for SGLT2 inhibitors. In addition, the committee noted that there were differences in the clinical effectiveness of the 2 forms of semaglutide. Although the acquisition costs for injectable and oral semaglutide are similar they showed marked differences in cost-effectiveness in the economic analyses. This was caused by differences in the effect estimates for stroke, myocardial infarction and severe hypoglycaemia. From earlier discussions about the clinical evidence (see the discussion sections in the evidence review for more details) the committee had agreed that it was uncertain whether the observed differences in effect on all-cause mortality compared to placebo between the 2 forms of semaglutide were real and they therefore decided not to place undue weight on them. They had also noted that this uncertainty and any other differences in effects between the drugs for other outcomes was probably due to wide 95% confidence intervals for many outcomes with these drugs, due to the smaller numbers of participants and events in the trials compared to other CVOTs. The committee therefore agreed that they were unable to recommend injectable semaglutide for people with type 2 diabetes and high cardiovascular risk who were unable to take an SGLT2i. As a result, the committee noted that people with high CV risk who could not take the recommended dual therapy of metformin and SGLT2, because they are unable to take the SGLT2, would be offered metformin alone at treatment initiation. If they were also unable to take metformin then the clinician would select another treatment from the remaining options, namely sulfonylureas, DPP-4s or pioglitazone, depending on the individual's clinical circumstances and preferences. The committee decided against listing the options for people with

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					type 2 diabetes who were at high CV risk and could not take an SGLT2i because they thought that this was an unnecessary level of detail given that they could not recommend a GLP-1 mimetic in place of the SGLT2i, that the treatment options were therefore the same for these people as for the rest of the type 2 diabetes population and because, apart from for metformin, the guideline does not include details of which drug to take if a particular drug is contraindicated or not tolerated but rather expects the prescriber to use their clinical judgment. The committee wanted to keep the pathway as simple as possible and they agreed that it would not be possible to do this if alternative options were provided every time a drug was not contradicted or not tolerated. However, they agreed that it was appropriate to have recommendations for metformin being contradicted or not tolerated because this is the drug that the majority of people would take as first-line therapy. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand.
Diabetes UK	Guideline	General	General	As non-specialists will be mediating the use of these drugs in most cases, we are concerned that these guidelines will not be suitable for many without specialist diabetes knowledge.	Thank you for your comment and this information. We are unable to include other sources of evidence within our reviews or cross reference to other guidance unless they

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				We recommend the information in our joint position statement and recommendations with the Association of British Clinical Diabetologists (ABCD) for non-diabetes specialists on the use SGLT2i in people with type 2 diabetes (January 2021) on this matter be included in this guideline. We do not recommend signposting to this information but including it in the actual guidance. Clinicians and people with diabetes generally find it unhelpful to have guidelines with links to other external documents and it will be more practical to have the guidance and technology appraisals signposted to in one user-friendly document. Otherwise, we are concerned that this aspect of the guidelines risks being overlooked. This could lead to people with diabetes being given inaccurate information or denied access to this new group of drugs which can help them to achieve their targets and reduce their risk of devastating complications. Reference: https://www.rcpjournals.org/content/clinmedicine/21/3/204	have been endorsed by NICE. We will forward your request onto the NICE team responsible for this process.
East Suffolk & North Essex NHS Foundation Trust	Guideline	010	001	Getting side effects from diabetes medications doesnot necessarily imply should have a higher target HbA1c e.g. recurrent UTI with SGLT-2i should not indicate adopting a higher target HbA1c	Thank you for your comment. The PDA states clearly that not everyone will get side effects; that, if they do happen, they may not trouble the person; and that it is usually possible to change medicines to ones that suit the person better. We have amended the PDA to highlight that the person needs to consider the relative importance of all the factors in the VAS and also consider if other things that are important to them.
East Suffolk & North Essex NHS Foundation Trust	Guideline	010	001	If a patient comments "I do not want to take any more medications", it does not imply a higher target HbA1c should be adopted – rather appropriate counselling and structured education could mitigate these issues	Thank you for your comment. The PDA states clearly that not everyone will get side effects; that, if they do happen, they may not trouble the person; and that it is usually possible to change medicines to ones that suit the person better. We have amended the PDA to highlight that the person needs to consider the relative importance of all the

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					factors in the VAS and also consider if other things that are important to them.
East Suffolk & North Essex NHS Foundation Trust	Guideline	015	1.7.9	If SGLT-2i are to be considered first line treatment (if Metformin is not tolerated or contraindicated), then it should be as per existing eGFR cut offs (which can be different for various SGLT-2i as per latest EMC (SmPC) guidance. If SGLT2i cannot be used then due consideration for GLP-1Ra should be considered.	Thank you for your comment. It is expected that clinicians will refer to the SPCs or to the BNF to determine whether there are any contraindications for use or if dose adjustments need to made. The committee therefore declined to add this information to the recommendations as the agreed it should not be necessary. The table in visual summary 4 has been updated and has a column for dose adjustment to remind the clinician to check these. Although there were a number of stakeholder comments asking for clarification of the treatment options for people with type 2 diabetes in whom SGLT2 inhibitors (SGLT2i) were contraindicated or not tolerated, there were no cardiovascular outcome trial style clinical trials identified that looked at the effectiveness of treatments for people at high cardiovascular (CV) risk in this population. The committee therefore used the evidence for effectiveness and cost effectiveness for other interventions from the same economic modelling scenarios as those looking at the cost-effectiveness of SGLT2i. The committee examined the cost-effectiveness evidence relating to GLP-1 mimetic treatment for people with type 2 diabetes and high cardiovascular risk. In the NICE health economic analyses, when looking at GLP-1 mimetics as a class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable

					semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of £20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the intervention as an effective use of NHS resources will specifically take account of the following factors." and • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis." Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did

					reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors. The committee therefore agreed that they were unable to recommend injectable semaglutide for people with type 2 diabetes and high cardiovascular risk who were unable to take an SGLT2i. As a result, the committee noted that people with high CV risk who could not take the recommended dual therapy of metformin and SGLT2, because they are unable to take the SGLT2, would be offered metformin alone at treatment initiation. If they were also unable to take metformin then the clinician would select another treatment from the remaining options, namely sulfonylureas, DPP-4s or pioglitazone, depending on the individual's clinical circumstances and preferences. The committee decided against listing the options for people with type 2 diabetes who were at high CV risk and could not take an SGLT2i because they thought that this was an unnecessary level of detail given that they could not recommend a GLP-1 mimetic in place of the SGLT2i, that the treatment options were therefore the same for these people as for the rest of the type 2 diabetes population and because, apart from for metformin, the guideline does not include details of which drug to take if a particular drug is

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					contraindicated or not tolerated but rather expects the prescriber to use their clinical judgment. The committee wanted to keep the pathway as simple as possible and they agreed that it would not be possible to do this if alternative options were provided every time a drug was not contradicted or not tolerated. However, they agreed that it was appropriate to have recommendations for metformin being contradicted or not tolerated because this is the drug that the majority of people would take as first-line therapy.
East Suffolk & North Essex NHS Foundation Trust	Guideline	018	001	The presence of concomitant T2DM is by itself an established high-risk association for atherosclerotic cardiovascular disease (ASCVD). Categorisation of T2Dm patients at "not at high CVD risk"; high-risk CVD" and "Established CVD" is against current evidence base and runs a grave risk of not conferring adequate cardiovascular protection to these patients irrespective of primary or secondary prevention	Thank you for your comment. You are correct that having diabetes does increase your cardiovascular risk and a large proportion of people with type 2 diabetes are expected to fall into the category of being at high cardiovascular disease risk (or having cardiovascular disease). However, the committee agree that the cost-effective use of SGLT2 inhibitors in reducing the risk of premature mortality for those at high cardiovascular disease risk or with established cardiovascular disease is a positive step in the treatment of this condition.
East Suffolk & North Essex NHS Foundation Trust	Guideline	018	001	Visual summary makes glaring omission of the mention of the GLP-1Ra class in association with ASCVD reduction. It does not take into account the strong evidence base supporting the use of GLP-1Ra based on LEADER, SUSTAIN-6, REWIND and PIONEER-4 studies	Thank you for your comment. GLP-1 mimetics are not a first line treatment option and are included in the visual summary for where further interventions are needed.
East Suffolk & North Essex NHS Foundation Trust	Guideline	034	004	"Comparing effectiveness and cost effectiveness of GLP-1 mimetics with insulin therapy in adults with type 2 diabetes" is a regressive statement and is not evidence based. Apart from significant reduction of ASCVD, the earlier adoption of GLP-1Ra is beta cell sparing and comparing this class with Insulin in T2DM will give the impression that they are substitutable leading to further clinical inertia and delayed intensification of glycaemic control in the UK (Ref: Khunti K et al: Diabetes Obes Metab. 2016 Apr;18(4):401-9. Doi: 10.1111/dom.12626. Epub 2016 Feb 9.)	Thank you for your comment. Please note that following a discussion of the stakeholder comments received at consultation this research recommendation has been removed.

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East Suffolk & North Essex NHS Foundation Trust	Guideline	038	024	The guideline recommends the early use of SGLT-2i in association with Metformin in T2DM with heart failure and ASCVD. However there are some glaring omissions in this section which will significantly affect therapeutic practice: 1. The guideline fails to mention what can be used in place of SGLT-2i if they are contradicted (e.g. eGFR <45 or intolerated) for the same concomitant complications. 2. Furthermore, according to current (as of 15/09/2021) EMC (SmPC) guidance; there is considerable heterogeneity within the SGLT-2i class as regards eGFR cut offs and specific indications related to heart failure (reduce or preserved ejection fraction) and presence of chronic kidney disease or not Finally, there is no mention of the evidence base regarding improved renal outcomes by the use of SGLT-2i class (Renal composite end-points – 50% improvement of eGFR; halving of uACR/uPCR or delay in the onset of renal replacement therapy). This is based on several trials including CREDENCE, DAPA-CKD and EMPEROR-PRESERVED. The importance of early detection and management of Diabetes nephropathy has been completely ignored	Thank you for your comment. 1. Thank you for your comment. Although there were a number of stakeholder comments asking for clarification of the treatment options for people with type 2 diabetes in whom SGLT2 inhibitors (SGLT2i) were contraindicated or not tolerated, there were no cardiovascular outcome trial style clinical trials identified that looked at the effectiveness of treatments for people at high cardiovascular (CV) risk in this population. The committee therefore used the evidence for effectiveness and cost effectiveness for other interventions from the same economic modelling scenarios as those looking at the cost- effectiveness of SGLT2i. The committee examined the cost-effectiveness evidence relating to GLP-1 mimetic treatment for people with type 2 diabetes and high cardiovascular risk. In the NICE health economic analyses, when looking at GLP-1 mimetics as a class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of £20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the

					intervention as an effective use of NHS resources will specifically take account of the following factors." and • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis." Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-

					effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors. In addition, the committee noted that there were differences in the clinical effectiveness of the 2 forms of semaglutide. Although the acquisition costs for injectable and oral semaglutide are similar they showed marked differences in cost-effectiveness in the economic analyses. This was caused by differences in the effect estimates for stroke, myocardial infarction and severe hypoglycaemia. From earlier discussions about the clinical evidence (see the discussion sections in the evidence review for more details) the committee had agreed that it was uncertain whether the observed differences in effect on all-cause mortality compared to placebo between the 2 forms of semaglutide were real and they therefore decided not to place undue weight on them. They had also noted that this uncertainty and any other differences in effects between the drugs for other outcomes was probably due to wide 95% confidence intervals for many outcomes with these drugs, due to the smaller numbers of participants and events in the trials compared to other CVOTs. The committee therefore agreed that they were unable to recommend injectable semaglutide for people with type 2 diabetes and high cardiovascular risk who were unable to take an SGLT2i. As a result, the committee noted that people with high CV risk who could not take metformin with an SGLT2i would be offered metformin alone at treatment initiation. If they were also unable to take metformin then the clinician would select another treatment from the remaining options, namely sulfonylureas, DPP-4s or pioglitazone, depending on the individual's clinical circumstances and preferences. The committee decided against listing the options for people with type 2 diabetes who were at high CV

					risk and could not take an SGLT2i because they thought that this was an unnecessary level of detail given that they could not recommend a GLP-1 mimetic in place of the SGLT2i, that the treatment options were therefore the same for these people as for the rest of the type 2 diabetes population and because apart from for metformin, the guideline does not include details of which drug to take if a particular drug is contraindicated or not tolerated but rather expects the prescriber to use their clinical judgment. The committee wanted to keep the pathway as simple as possible and they agreed that it would not be possible to do this if alternative options were provided every time a drug was not contradicted or not tolerated. However, they agreed that it was appropriate to have recommendations for metformin being contradicted or not tolerated because this is the drug that the majority of people would take as first-line therapy. 2. For first line treatment we are not recommending off-label use of the SGLT2 inhibitors (SGLT2i) because all currently available SGLT2i have a marketing authorisation for glycaemic control in adults with type 2 diabetes. Some SGLT2i (dapagliflozin and empagliflozin) have a marketing authorisation which includes symptomatic chronic heart failure with reduced ejection fraction alone, but we are not making recommendations for people who have heart failure with reduced ejection fraction who do not have type 2 diabetes. Symptomatic chronic heart failure with reduced ejection fraction is a subgroup of heart failure, which is one of the populations covered by the recommendations for people who also have type 2 diabetes. The committee did not limit the recommendations to adults with type 2 diabetes and symptomatic chronic heart failure with reduced ejection fraction because they intended the recommendation to cover the broader heart failure population, which was defined based on the participants in the cardiovascular outcome trials.

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					In the recommendations for using SGLT2i for initial treatment in addition to metformin or in place of metformin if it is contraindicated / not tolerated, the SGLT2i is being used to provide glycaemic control and cardiovascular benefit. It is only if the use of an SGLT2i is retained despite not providing any glycaemic control that this would potentially be an off-label use. NICE expects that prescribers will use the drugs within the marketing authorisation over off-label use of a licensed medicine where appropriate. Please see additional information on prescribing medicines and off-label or unlicensed use. Finally, the on choosing drug treatments also states that the persons individual clinical circumstances and lists comorbidities as one such factor (this would include renal function and heart failure). 3. The renal benefits of using SGLT2 inhibitors in people with type 2 diabetes and CKD have been assessed in a separate piece of work that has recently been out for stakeholder consultation and was published in November 2021. The final recommendations on renal and cardiovascular benefits will be brought together in a single updated guideline document when this current work on cardiovascular benefits is published in 2022.
East Suffolk & North Essex NHS Foundation Trust	Guideline	043	001	The committee suggests a research recommendation to compare the effectiveness and cost effectiveness of GLP-1 mimetics and insulin. This cannot be a current recommendation since many studies have already been performed with many molecules in the past 5 years (e.g. Castellana M et al: GLP-1 receptor agonist added to insulin versus basal-plus or basal-bolus insulin therapy in type 2 diabetes: A systematic review and meta-analysis. Diabetes Metab Res Rev. 2019 Jan;35(1):e3082. doi: 10.1002/dmrr.3082. Epub 2018 Oct 18.)	Thank you for your comment. Please note that following stakeholder comments received at consultation this research recommendation has been removed.
East Suffolk & North Essex NHS	Guideline	043	018	The statement "*The recommendation not to offer GLP-1 mimetic therapy solely for cardiovascular risk reduction may lead to fewer people with high cardiovascular risk taking these drugs at earlier stages of the treatment*	Thank you for your comment. The committee have taken stakeholder comments into account and agreed to remove the recommendation about not using GLP1-mimetic therapy

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Foundation Trust				*pathway*" – this is based on what evidence and appears conjectural? Furthermore, we would like to know how the committee has come to this decision the guideline has portrayed the GLP-1 class as a glycaemic drug and obesity when the doses used specifically for obesity are much different?	solely for cardiovascular risk reduction in people with type 2 diabetes. Upon reviewing the recommendation, the committee agreed that it was inappropriate to make a decision about treatment choice based solely on a single factor (cardiovascular risk) and that, as detailed in the recommendation on choosing drug treatments, multiple factors should be taken into account instead. The scope of this update only included evidence for cardiovascular (CV) benefit of drug treatments used in the management of type 2 diabetes (see the Evidence review document for details). The only identified CV outcome trial evidence for Liraglutide (the only current GLP-1 with a licensed indication as an adjunct in weight management and type 2 diabetes) was from the LEADER trial which used a dose up to 1.8 mg per day. Higher doses of Liraglutide up to 3 mg per day can be prescribed as an adjunct in weight management but no cardiovascular outcome trial evidence was found for the higher daily dose, which also does not currently have a licensed indication for type 2 diabetes management, and so no recommendation for use of a higher dose could be made by the committee.
East Suffolk & North Essex NHS Foundation Trust	Guideline	044	011	It is ironic to find that a 2021/22 NICE guideline is using epidemiological data from 2013 when there is much more recent data to cite	Thank you for your comment. We have now updated this section with information from the 2021 Diabetes audit.
East Suffolk & North Essex NHS Foundation Trust	Guideline	045	014	It is surprising that the Reasons for the 2021 update make no mention on the ground-breaking therapeutic advances related to management of heart failure and CKD in diabetes	Thank you for your comment. The text focuses on the cardiovascular outcome trials and cardiovascular benefits because this evidence was the reason the current update was carried out. The renal protective effects of SGLT2s were looked at in a separate piece of work that will publish before the current work. It is therefore not included in the reasons for this 2021 update.

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East Suffolk & North Essex NHS Foundation Trust	Guideline	General	General	The guideline makes no mention of the use of Insulin biosimilars in the management of T2Dm despite their cost-effectives as compared to established insulin brand types	Thank you for your comment. The section of the guideline covering insulin-based treatments was not prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest existing recommendations needed amending. Howevert we have been able to add recommendations covering the points you have raised to this section. These were drafted as part of the diabetes type 1 update on this topic but were judged to be equally relevant to this guideline.
East Suffolk & North Essex NHS Foundation Trust	Guideline	General	General	Admittedly, the evidence base for pharmacological management of T2Dm has significantly evolved in recent times and also is constantly changing with new additions to existing licenses. This means that any guideline might need to be relooked at much earlier than the current NICE interval of 6 years. Due the same reasons, this guideline should also dedicate a "future evidence" section citing upcoming therapies line Finerenone (FIDELIO-CKD) and dual GLP-1 agonism (Tirzepatide – SURPASS) and tri-GLP agonism as future directions of therapy. (but yet to be approved)	Thank you for your comment. The NICE surveillance team carry out a standard check every 5 years. However, they also maintain an event tracker containing information on key events, such as ongoing studies, that are judged to be relevant to the guideline content. This aims to allow NICE to react quickly to changes in the evidence base, by initiating a check of the guideline as soon as the event has occurred. This NICE guideline does not currently contain a section covering upcoming therapies that have yet to be approved. This is unlikely to change in the future because such information would rapidly be out of date unless updated regularly, which would be resource intensive taking the size of the evidence base and number of potential therapies for type 2 diabetes into account, and this is not a priority topic for inclusion in a guideline.
East Suffolk & North Essex NHS Foundation Trust	Guideline	General	General	The unanimous opinion from all colleagues locally that the current guideline due to the above reasons is not acceptable and does not provide best possible diabetes care to T2DM subjects. We feel that unless the committee makes radical changes to update and recognise the evidences, we will continue to follow the ADA/EASD 2019 guidance which is more realistic, updated and holistic as compared to this guideline.	Thank you for your comment. The committee were aware of the ADA guidance, but their decisions were made according to the NICE guideline manual and took into account the evidence relevant to our review question. Although the NICE guidance may differ to the guidance provided by ADA, the committee were confident that their recommendations reflected the evidence they reviewed and their clinical judgement. It is of particular importance to note that the NICE guideline used an original economic model as the basis to recommend the most clinically and cost-effective

					options while the ADA guidance did not systematically take cost-effectiveness into account. When producing guidelines, NICE considers both effectiveness and cost-effectiveness for all of the recommendations it makes. As well as helping to ensure the recommendations made represent the best use of NHS resources (in particular, the opportunity costs of spending additional resources), this is also required by the legislation that originally established NICE (the Health and Social Care Act 2012), which states that when exercising its functions, NICE must have regard to "the broad balance between the benefits and costs of the provision of health services or of social care in England." NICE's principles further refine this by explicitly stating that "if possible, NICE considers value for money by calculating the incremental cost-effectiveness ratio" and "interventions with an ICER of less than £20,000 per QALY gained are generally considered to be cost effective." This guidance was developed in line with both these statutory requirements, and NICE's stated principles, methods and processes. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand. In the meantime, the new recommendations for people with

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					high CV risk, which have been amended based on stakeholder comments, will stand.
East Suffolk & North Essex NHS Foundation Trust	Guideline	General	General	Specific DPP-IV inhibitors like Saxagliptin, Alogliptin and Vildagliptin have been shown to aggravate heart failure and this important recommendation has no mention on a treatment guideline specifically meant for T2DM management	Thank you for your comment. The committee agreed that expanding the safety recommendations to cover all the points suggested by stakeholders was unfeasible and was inappropriate because the guideline is the not intended to cover all the safety advice that should be taken into account when prescribing drug treatments and some of the suggested safety events were quite rare. In order to keep the guideline as simple and easy to follow as possible, the committee rewrote the safety recommendations to focus on some key points relating to the safety of SGLT2 inhibitors because they are not widely used in practice yet in some areas, and in particular may be unfamiliar to many clinicians in primary care, and the new recommendations will greatly increase the number of people who are eligible to take them. They removed some of the safety information that was in the consultation version of the guideline where it was not specific to SGLT2s, was not thought to be useful by stakeholders or was thought to be widely known. The committee agreed that prescribers are expected to consult MHRA alerts, the BNF and summary of product characteristics (SPC) for more comprehensive safety information. This is highlighted in the recommendation on choosing drug treatments which includes safety as one of the factors to take into account. This would include the DPP-4 and the cautions around use in heart failure for Alogliptin, Saxagliptin and Vildagliptin. This recommendation also states that prescribers should discuss the risks and benefits of a drug considering comorbidities (such as heart failure), contraindications and safety.
East Suffolk & North Essex NHS Foundation Trust	Guideline	General	General	It is disappointing to note that committee has not given any recognition to the ADA/EASD 2019 guidelines for the management of T2Dm wherein – after Metformin – they have algorithmically divided patients into With and without ASCVD/CKD/Heart failure based on current evidence. Such simplistic evidence based approach is clearly missing in this guideline and	Thank you for your comment. Please note that the NICE guideline does make recommendations for people with established ASCVD and heart failure. The renal benefits of using SGLT2 inhibitors in people with type 2 diabetes and CKD have been assessed in a separate piece of work that

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				similarly fails to recognised the current evidence base supporting the early use of GLP-1Ra or with subjects with ASCVD	has recently been out for stakeholder consultation and was published in November 2021. The final recommendations on renal and cardiovascular benefits will be brought together in a single updated guideline document when this current work on cardiovascular benefits is published in 2022. The committee were aware of the ADA guidance, but their decisions were made according to the NICE guideline manual and took into account the evidence relevant to our review question. Although the NICE guidance may differ to the guidance provided by ADA, the committee were confident that their recommendations reflected the evidence they reviewed and their clinical judgement. It is of particular importance to note that the NICE guideline used an original economic model as the basis to recommend the most clinically and cost-effective options while the ADA guidance did not systematically take cost-effectiveness into account. When producing guidelines, NICE considers both effectiveness and cost-effectiveness for all of the recommendations it makes. As well as helping to ensure the recommendations made represent the best use of NHS resources (in particular, the opportunity costs of spending additional resources), this is also required by the legislation that originally established NICE (the Health and Social Care Act 2012), which states that when exercising its functions, NICE must have regard to "the broad balance between the benefits and costs of the provision of health services or of social care in England." NICE's principles further refine this by explicitly stating that "if possible, NICE considers value for money by calculating the incremental cost-effectiveness ratio" and "interventions with an ICER of less than £20,000 per QALY gained are generally considered to be cost effective." This guidance was developed in line with both

					these statutory requirements, and NICE's stated principles, methods and processes. The committee reviewed the stakeholder comments regarding the use of GLP-1 mimetics and examined the updated economic evidence relating to GLP-1 mimetic treatment for people with type 2 diabetes and high cardiovascular risk. In the NICE health economic analyses, when looking at GLP-1 mimetics as a class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of £20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the intervention as an effective use of NHS resources will specifically take account of the following factors." and • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular,

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					advisory bodies will be more cautious about recommending a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis." Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors.

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					In addition, the committee noted that there were differences in the clinical effectiveness of the 2 forms of semaglutide. Although the acquisition costs for injectable and oral semaglutide are similar they showed marked differences in cost-effectiveness in the economic analyses. This was caused by differences in the effect estimates for stroke, myocardial infarction and severe hypoglycaemia. From earlier discussions about the clinical evidence (see the discussion sections in the evidence review for more details) the committee had agreed that it was uncertain whether the observed differences in effect on all-cause mortality compared to placebo between the 2 forms of semaglutide were real and they therefore decided not to place undue weight on them. They had also noted that this uncertainty and any other differences in effects between the drugs for other outcomes was probably due to wide 95% confidence intervals for many outcomes with these drugs, due to the smaller numbers of participants and events in the trials compared to other CVOTs. Due to the higher level of uncertainty surrounding the cost-effectiveness of the GLP-1 mimetics as a class compared to the SGLT2 inhibitors, the committee considered whether to recommend injectable semaglutide for people at high cardiovascular risk in whom an SGLT2 is contraindicated or not tolerated. However, taking into account the uncertainty in the cost-effectiveness and clinical effectiveness the committee decided against recommending injectable semaglutide for this population.
Eli Lilly and Company	Guideline	010		Figure 1 - Whilst we support the increased focus on tailoring care to the individual and in agreeing individualised targets, we are concerned that this tool is biased towards less rigorous and unguided targets which may not be optimal for the individual and lead to confusion in consultations. We suggest that the guideline development group considers expanding the figure using the approach found in the ADA consensus guidelines which includes other important characteristics such as disease duration,	Thank you for your comment. The figure relates to reasons for thinking about relaxing the HbA1c target mentioned in recommendation 1.6.9. The guideline did not consider any new evidence on this topic so it is not possible to include disease duration per se, but it does include life expectancy ('thinking about my age and my health overall') and multimorbidity ('health issues apart from my diabetes').

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				life expectancy and comorbidities which are also relevant to individualisation of glycaemic targets. (ADA Standards of Medical Care in Diabetes 2021, includes a figure on 'The Approach to Individualisation of Patient Targets' [Chapter 6, figure 6.2] centred around a target of 53mmol/mol).	
Eli Lilly and Company	Guideline	019 & 025	General	Visual summary 4 - The GLP-1 renal impairment column states, "Avoid or use with caution." This should be amended as many of the newer GLP-1 mimetics can be used without dose adjustment down to an eGFR of 15ml/min.	Thank you for your comment. This content has been updated for specific medicines rather than for medicine classes.
Eli Lilly and Company	Guideline	General	General	It is disappointing that for the GLP-1 mimetics, the scope of the guideline update was limited to an evaluation of whether the cardiovascular (CV) benefits were cost-effective *in isolation*, rather than taking a holistic clinical and patient-centred approach that accounted for all important considerations, including glucose lowering, weight loss, risk of hypoglycaemia and CV benefits. The latter approach was taken in the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) consensus report on the management of hyperglycaemia in type 2 diabetes, which is held in very high regard by the diabetes clinical community in the UK and widely referred to. The very limited scope of the NICE guideline update runs the risk of the NICE guidance being seen as less credible than the ADA/EASD consensus report, particularly as several new agents and higher doses of existing agents in the GLP-1 mimetic class have become available since 2015. A broader, more holistic and up-to-date review of the class and its positioning in the treatment algorithm would be ideal but would clearly be a major undertaking. In the interim, the broad benefits of the GLP-1 mimetic class, including substantial glucose lowering, substantial weight loss, low risk of hypoglycaemia, CV benefit, and availability of weekly agents, could be better reflected in the current NICE guidance by removal or relaxation of the restrictions around BMI and the current requirements for HbA1c and weight loss response at 6 months after initiation.	Thank you for your comment. Please note that the NICE health economic model did not look at CV benefit in isolation (please see section 1.1.9 Economic Model of Evidence review document for details). The committee agreed with the need to produce guidance to help promote personalised treatment. The original scope of this work covered additional groups of interest including people with renal impairment, people in specific ethnic groups, adults aged 65 years and older, as well as people in specific cardiovascular risk groups. It aimed to fully update the drug treatment sections of the NG28 guideline. However, once work on the topic commenced it was determined that updating evidence reviews and health economics for such a wide scope, within the resources available to NICE for this topic, would take an unacceptably lengthy period. Taking such an approach for this guideline update would have further delayed publication of updated treatment recommendations in this rapidly changing area. In view of the timescales involved and the appetite from the committee and stakeholders for an update within an acceptable time period, we worked with our committee members to identify the priority areas for this update. The committee members agreed that our initial focus should be on reviewing the evidence from trials looking at cardiovascular outcomes. This reflected the changing evidence base as a result of the significant investment in

					clinical trials to directly capture cardiovascular outcomes, feedback from stakeholders that assessing this evidence was a priority and the impact that this new evidence could have on recommendations for the treatment of people with diabetes. We therefore revised the scope to reflect this and carried out the current piece of work. The committee were aware of the ADA guidance, but their decisions were made according to the NICE guideline manual and took into account the evidence relevant to our review question. Although the NICE guidance may differ to the guidance provided by ADA, the committee were confident that their recommendations reflected the evidence they reviewed and their clinical judgement. It is of particular importance to note that the NICE guideline used an original economic model as the basis to recommend the most clinically and cost-effective options while the ADA guidance did not systematically take cost-effectiveness into account. When producing guidelines, NICE considers both effectiveness and cost-effectiveness for all of the recommendations it makes. As well as helping to ensure the recommendations made represent the best use of NHS resources (in particular, the opportunity costs of spending additional resources), this is also required by the legislation that originally established NICE (the Health and Social Care Act 2012), which states that when exercising its functions, NICE must have regard to "the broad balance between the benefits and costs of the provision of health services or of social care in England." NICE's principles further refine this by explicitly stating that "if possible, NICE considers value for money by calculating the incremental cost-effectiveness ratio" and "interventions with an ICER of less than £20,000 per QALY gained are generally considered to be cost effective." This guidance was developed in line with both these statutory requirements, and NICE's stated principles, methods and processes.

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					The committee agreed that the evidence from the cardiovascular outcome trials was most relevant to people with established cardiovascular disease and those at high risk of developing cardiovascular disease. They therefore limited their recommendations to these people. The GLP-1s were not cost-effective for these groups and no new non-cardiovascular outcome trial evidence regarding the benefits of GLP-1s was included in this review. Therefore, the committee were unable to amend or rewrite the 2015 criteria for GLP-1 use in this current update. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand. In the meantime, to make it easier for prescribers to select appropriate treatment options that match the needs of each individual we have developed a summary table listing relevant factors such as whether the drug is associated with weight loss or weight gain. It is hoped that this table, together with the recommendation about choosing drug treatments that covers tailoring drug choice to individual needs and circumstances, will support personalised care.
Individual 1	Guideline	033	004	What is the definition of dyelipidaemia eg Cholesterol > 6 or LDL >4?	Thank you for your comment. The committee agreed that it was not necessary for this term to be defined in the guideline

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					as it is commonly understood by healthcare professionals in clinical practice.
Individual 1	Guideline	033	005	Would be good to qualify IHD below the age of 60	Thank you for your comment. The committee agreed that it was not necessary for this term to be defined in the guideline as it is commonly understood by healthcare professionals in clinical practice.
Individual 1	Guideline	033	005	Would be good to qualify definition of obesity (eg BMI >30)	Thank you for your comment. The committee agreed that it was not necessary for this term to be defined in the guideline as it is commonly understood by healthcare professionals in clinical practice.
Individual 2	Guideline	016	General	Table 2 - 1.7.10; 1.7.18;1.7.19 - Although bullet 3 in 1.7.1 adds CV protection, there is no reference in sections 1.7.10, 1.7.18 or 1.7.19 to CV protection in relation to the use of SGLT2i for people with established CV risk or for consideration in people with high CV risk.	Thank you for your comment. Please note that the consultation version recommendation 1.7.10 is for people without established CV disease or at high risk. The consultation version recommendations 1.7.18 and 1.7.19 are for people who require additional treatment to control glycaemia (irrespective of their CV risk). People already on glycaemia lowering treatment at increased risk of CV disease or with established CV disease will have access to SGLT2i treatment as per consultation version recommendation 1.7.16.
Individual 2	Guideline	022	General	Table 2 - 1.7.22 - By definition diabetes is a medical problem associated with obesity so the caveat re specific psychological or other medical conditions is redundant.	Thank you for your comment. The recommendations covering triple therapy with GLP-1 were not updated as part of the current work. The committee are unable to make any changes to this recommendation because the evidence they looked at was judged only to be generalisable to people who were at high risk of developing cardiovascular disease or who had established cardiovascular disease. Please note that although obesity is associated, as you point out, with diabetes, a significant proportion of people who have type 2 diabetes have a normal weight or are overweight rather than obese (see Figure 3 of PHE adult ovbesity and type 2 diabetes). The causes of type 2 diabetes are multifactorial and include age, ethnicity, genetic and environmental factors.

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Individual 2	Guideline	General	General	I am not in a position to challenge health economic advice but I think that those at high CV risk who are unable to take an SGLT2i should be offered a GLP-1RA with proven CV benefit. It is disappointing that the CV benefit of GLP-1 is being ignored, particularly in people where SGLT2i is not an option.	Thank you for your comment. When producing guidelines, NICE considers both effectiveness and cost-effectiveness for all of the recommendations it makes. As well as helping to ensure the recommendations made represent the best use of NHS resources (in particular, the opportunity costs of spending additional resources), this is also required by the legislation that originally established NICE (the Health and Social Care Act 2012), which states that when exercising its functions, NICE must have regard to "the broad balance between the benefits and costs of the provision of health services or of social care in England." NICE's principles further refine this by explicitly stating that "if possible, NICE considers value for money by calculating the incremental cost-effectiveness ratio" and "interventions with an ICER of less than £20,000 per QALY gained are generally considered to be cost effective." This guidance was developed in line with both these statutory requirements, and NICE's stated principles, methods and processes. Although there were a number of stakeholder comments asking for clarification of the treatment options for people with type 2 diabetes in whom SGLT2 inhibitors (SGLT2i) were contraindicated or not tolerated, there were no cardiovascular outcome trial style clinical trials identified that looked at the effectiveness of treatments for people at high cardiovascular (CV) risk in this population. The committee therefore used the evidence for effectiveness and cost effectiveness for other interventions from the same economic modelling scenarios as those looking at the cost-effectiveness of SGLT2i.

					The committee reviewed the stakeholder comments regarding the use of GLP-1 mimetics and examined the updated economic evidence. In the NICE health economic analyses, when looking at GLP-1 mimetics as a class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of £20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the intervention as an effective use of NHS resources will specifically take account of the following factors." and • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis." Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable

					semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors. In addition, the committee noted that there were differences in the clinical effectiveness of the 2 forms of semaglutide. Although the acquisition costs for injectable and oral semaglutide are similar they showed marked differences in cost-effectiveness in the economic analyses. This was caused by differences in the effect estimates for stroke, myocardial infarction and severe hypoglycaemia. From earlier discussions about the clinical evidence (see the discussion sections in the evidence review for more details) the committee had agreed that it was uncertain whether the

					observed differences in effect on all-cause mortality compared to placebo between the 2 forms of semaglutide were real and they therefore decided not to place undue weight on them. They had also noted that this uncertainty and any other differences in effects between the drugs for other outcomes was probably due to wide 95% confidence intervals for many outcomes with these drugs, due to the smaller numbers of participants and events in the trials compared to other CVOTs. The committee therefore agreed that they were unable to recommend injectable semaglutide for people with type 2 diabetes and high cardiovascular risk who were unable to take and SGLT2i. As a result, the committee noted that people with high CV risk who could not take metformin with an SGLT2i would be offered metformin alone at treatment initiation. If they were also unable to take metformin then the clinician would select another treatment from the remaining options, namely sulfonylureas, DPP-4s or pioglitazone, depending on the individual's clinical circumstances and preferences. The committee decided against listing the options for people with type 2 diabetes who were at high CV risk and could not take an SGLT2i because they thought that this was an unnecessary level of detail given that they could not recommend a GLP-1 mimetic in place of the SGLT2i, that the treatment options were therefore the same for these people as for the rest of the type 2 diabetes population and because apart from for metformin, the guideline does not include details of which drug to take if a particular drug is contraindicated or not tolerated but rather expects the prescriber to use their clinical judgment. The committee wanted to keep the pathway as simple as possible, and they agreed that it would not be possible to do this if alternative options were provided every time a drug was not contradicted or not tolerated. However, they agreed that it was appropriate to have recommendations for metformin being contradicted or not tolerated because this is the drug that the majority of people would take as first-line therapy.

Consultation on draft guideline - Stakeholder comments table
01/09/2021 – 14/10/2021

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
Individual 2	Questions on comments form	General	General	Q1, 2 & 3 - Current local guidelines are based on ADA/EASD, with SGLT2i recommended for high/established CVD and for renal disease, with GLP-1RA as an alternative where SGLT2i not appropriate, this NICE update is disappointing in its limitations but will not present any new challenges or costs.	Thank you for your response.
Individual 2	Questions on comments form	General	General	Q4 - I support the plan to stand down 1.7.20. It is hopelessly out of date.	Thank you for your response. Based on stakeholder comments this recommendation has been retained.
Individual 2	Visual summary document	002	General	Box left lower corner - This has retained previous advice that SGLT2i should only be used if DPP-4i would otherwise be prescribed. This is confusing as in the algorithm itself CVD is an indication for SGLT-2 monotherapy. This requires clarification.	Thank you for your comment. The TAs are applicable for people who are not at a high risk of CVD. We have amended the visual summaries to make it clearer that the TAs are linked with the 'not at high CVD risk' pathway.
Individual 2	Visual summary document	003	General	GLP-1 treatments box - This box also contains the redundant caveat 'and specific psychological or other medical problems associated with obesity'. A BMI >35 and type 2 diabetes is sufficient to advise this therapy	Thank you for your comment. The visual summary reflects the recommendations in the drug treatment section of the guideline. The committee agreed that the wording in the GLP recommendation was still applicable.
Individual 2	Visual summary document	General	General	There is no mention of CKD in relation to SGLT-2i despite strong evidence for benefit.	Thank you for your comment. We have included information in the choosing medicines table on use of medicines in renal impairment. Furthermore, the renal benefits of using SGLT2 inhibitors in people with type 2 diabetes and CKD have been assessed in a separate piece of work that has recently been out for stakeholder consultation and was published in November 2021. The final recommendations on renal and cardiovascular benefits will be brought together in a single updated guideline document when this current work on cardiovascular benefits is published in 2022 and linked from the visual summaries.
Individual 2	Visual summary document	General	General	When there is increasing emphasis is on 'precision medicine' it is extremely disappointing that NICE ignores the lead taken by the ADA and EASD and does not provide advice focused on avoiding hypoglycaemia (a particular problem/risk in older people which needs to be highlighted) or on avoidance of weight gain. Prescribing a medication which leads to weight gain in someone with weight concerns leads to non-adherence and waste of resources.	Thank you for your comment. The committee agreed with the need to produce guidance to help promote personalised treatment. The original scope of this work covered additional groups of interest including people with renal impairment, people in specific ethnic groups, adults aged 65 years and older, as well as people in specific cardiovascular risk groups. It aimed to fully update the drug treatment sections of the NG28 guideline. However, once work on the topic

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				Treatment focused on weight loss is much more likely to be accepted in the overweight group. Busy clinicians want guidance about selecting the best treatment for the individual patient and by avoiding recommendations for specific groups this guidance misses an opportunity to assist HCP decision making.	commenced it was determined that updating evidence reviews and health economics for such a wide scope, within the resources available to NICE for this topic, would take an unacceptably lengthy period. Taking such an approach for this guideline update would have further delayed publication of updated treatment recommendations in this rapidly changing area. In view of the timescales involved and the appetite from the committee and stakeholders for an update within an acceptable time period, we worked with our committee members to identify the priority areas for this update. The committee members agreed that our initial focus should be on reviewing the evidence from trials looking at cardiovascular outcomes. This reflected the changing evidence base as a result of the significant investment in clinical trials to directly capture cardiovascular outcomes, feedback from stakeholders that assessing this evidence was a priority and the impact that this new evidence could have on recommendations for the treatment of people with diabetes. We therefore revised the scope to reflect this and carried out the current piece of work.
Individual 2	Visual summary document	General	General	SGLT2i - By not differentiating between SGLT2i with and without evidence of CV benefit, the guideline implies that ertugliflozin carries CV protection but there is no CVOT evidence for this. It is inappropriate to include it in medication to be used in people at high CV risk.	Thank you for your comment. The committee reviewed the stakeholder comments but decided to continue treating SGLT2 inhibitors (SGLT2i) as a class for the following reasons: • There was a degree of uncertainty around whether there were real differences in cardiovascular (CV) benefits between the SGLT2i based on the clinical trial evidence and results from the NMAs. ○ Firstly, for hospitalisation for heart failure, the SGLT2i empagliflozin, canagliflozin, and dapagliflozin produced a clinically meaningful reduction compared with placebo in the random effects NMA model. However, in the sensitivity analyses using a fixed effect model

					ertugliflozin also showed a clinically meaningful reduction compared to placebo, which reflects the original clinical trial data. The NMA results could not differentiate between the SGLT2i for this outcome. ○ Secondly, for the 3 point MACE outcome, only canagliflozin and empagliflozin produced a statistically significant reduction compared to placebo but the SGLT2i could not be differentiated from each other in the NMA. ○ Thirdly for all cause and CV mortality empagliflozin showed a clinically meaningful reduction compared to placebo and the other SGLT2i, but the remaining SGLT2i could not be differentiated from each other or placebo in the NMA. ○ Fourthly, for non-fatal MI and non-fatal stroke the NMAs could not differentiate between empagliflozin, canagliflozin, ertugliflozin and placebo. The data for dapagliflozin was reported differently and could not be included in the NMAs. From the clinical trial data dapagliflozin could not be differentiated from placebo for MI and was not meaningfully different from placebo for stroke. ○ Finally, only dapagliflozin showed a clinically meaningful improvement in severe hypoglycaemia compared to placebo but the remaining SGLT2i could not be differentiated from each other and placebo in the NMA. • There was also a degree of uncertainty around the cost-effectiveness of individual SGLT2i in the economic modelling. Although only dapagliflozin was cost-effective at a threshold of £20,000/quality-adjusted life year (QALY) across all model scenarios and CV risk groups it could not be differentiated from the other SGLT2i in the NMA apart from for the all-cause and CV mortality outcomes where it was clinically meaningfully

					worse than empagliflozin. The ranking of ICERs for the other SGLT2i varied across model scenarios and risk groups. The committee agreed that there was sufficient uncertainty in the economic modelling (caused in turn by uncertainty in the underlying clinical data) to mean that they were not sufficiently confident that these different ICERs represented true underlying differences in cost-effectiveness, as opposed to simply random variation in the results between different SGLT2 trials. • Taking the cost-effectiveness and clinical results into account the committee decided against only recommending dapagliflozin and instead made recommendations for the SGLT2i as a class. However, they recognised that there was a greater degree of uncertainty around the CV benefit associated with ertugliflozin because, depending on the choice of model used in the NMA, it did not consistently show a clinically meaningful reduction in hospitalisation for heart failure compared to placebo, unlike empagliflozin, canagliflozin and dapagliflozin. It was also not statistically significantly better than placebo for the 3-point MACE outcome unlike canagliflozin and empagliflozin. The committee therefore recommended SGLT2i with proven CV benefit because this wording would enable the prescribers to select a particular drug from within the SGLT2 class if they thought this was clinically justified based on the individual characteristics of their patient, whilst future proofing the recommendation should additional evidence or new SGLT2s be made available. As per the recommendation on choosing drug treatment, once the clinical circumstances and needs of the person with type 2 diabetes, including their need for CV protection, have been taken into account, if 2 drugs in the same class are suitable for that individual then the prescriber is still expected to choose the option with the lowest acquisition cost to help use NHS resources wisely.

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					Please see evidence review A for more a more detailed explanation of the analyses that were carried out and the committee's discussion of the results.
Individual 3	Guideline	General	General	As a specialist diabetes department and integrated diabetes service, we are concerned that this document is out of step with practice on the ground. Within our service, GLP-1 therapy is established 3rd line treatment due to its significant clinical benefits in establishing and maintaining target HbA1c, reducing insulin resistance and improving cardiovascular outcomes. Use of GLP-1 RA therapy overcomes the perennial issues of hypoglycaemia, blood glucose monitoring and poor concordance with oral medication. We feel that this document does not address the long-term cost benefits of reduced HbA1c and weight on co-morbidities and subsequent demands on healthcare. In addition, this document does not address the high cost of poor concordance with oral therapies. It is for these reasons that we would find it difficult to reverse our practice and deprive patients of the therapies that offer them the most benefit.	Thank you for your comment. The current update focused on the cardiovascular benefits of drug treatments for people with type 2 diabetes. The committee agreed that the evidence from the cardiovascular outcome trials was more applicable to people with type 2 diabetes and established cardiovascular disease or at high risk of developing cardiovascular disease. They therefore restricted their recommendations to these people and the existing recommendations about when to use GLP-1s for the whole type 2 diabetes population remain unchanged. The committee reviewed the stakeholder comments regarding the use of GLP-1 mimetics for people with type 2 diabetes and established cardiovascular disease or at high risk of developing cardiovascular disease and examined the updated economic evidence. In the NICE health economic analyses, when looking at GLP-1 mimetics as a class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of

					£20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the intervention as an effective use of NHS resources will specifically take account of the following factors." and • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis." Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within

					class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors. In addition, the committee noted that there were differences in the clinical effectiveness of the 2 forms of semaglutide. Although the acquisition costs for injectable and oral semaglutide are similar they showed marked differences in cost-effectiveness in the economic analyses. This was caused by differences in the effect estimates for stroke, myocardial infarction and severe hypoglycaemia. From earlier discussions about the clinical evidence (see the discussion sections in the evidence review for more details) the committee had agreed that it was uncertain whether the observed differences in effect on all-cause mortality compared to placebo between the 2 forms of semaglutide were real and they therefore decided not to place undue weight on them. They had also noted that this uncertainty and any other differences in effects between the drugs for other outcomes was probably due to wide 95% confidence intervals for many outcomes with these drugs, due to the smaller numbers of participants and events in the trials compared to other CVOTs. Due to the higher level of uncertainty surrounding the cost-effectiveness of the GLP-1 mimetics as a class compared to the SGLT2 inhibitors, the committee considered whether to recommend injectable semaglutide for people at high cardiovascular risk in whom an SGLT2 is contraindicated or not tolerated. However, taking into account the uncertainty in the cost-effectiveness and clinical effectiveness the

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					committee decided against recommending injectable semaglutide for this population.
King's College Hospital NHS Foundation Trust	Guideline	016	025	"Be aware that SGLT2 inhibitors can cause fluid volume depletion and have an adverse effect on renal function and this needs to be monitored" – is this fluid volume status and/or renal function? May require guidance for non-medical practitioners on how to assess fluid balance. "…taking into account individual clinical factors and baseline renal function." – we feel that a statement of review of existing (non-diabetic) drugs i.e. diuretics and antihypertensive agents, should be made. Also might need to clarify that stable, mild/moderate CKD is not a contraindication to SGLT2 inhibitor (each having slightly different licencing) but that additional glucose lowering treatment might be require e.g. at eGFR < 45 ml/min.	Thank you for your comment. The committee discussed the stakeholder comments about the renal impact of SGLT2 inhibitors (SGLT2i). They agreed that the existing recommendation was unclear and potentially confusing because it gave no indication of the frequently or when the monitoring should take place. They also recognised that although SGT2i can have a negative effect on renal function this is usually a small reduction in function and not a reason to stop taking the SGLT2i. Taking these points into account the committee have now removed this draft recommendation. The committee declined to add information to the patient advice recommendation about ensuring adequate hydration because they would need to define what this what this meant and the amount of liquid a person needed to consume to be adequately hydrated would vary between individuals, depending on their clinical circumstances. The committee declined to add extra information about the contraindications or lack of for CKD because they expected that the clinician would refer to the SPCs for this information. In addition, the renal benefits of using SGLT2 inhibitors in people with type 2 diabetes and CKD have been assessed in a separate piece of work that has recently been out for stakeholder consultation and was published in November 2021. The final recommendations on renal and cardiovascular benefits will be brought together in a single updated guideline document when this current work on cardiovascular benefits is published in 2022.
King's College Hospital NHS	Guideline	024	General	In the "switching or adding treatment" box, Empagliflozin TA366 should be TA336 (TA366 is for pembrolizumab in advanced melanoma not previously treated with ipilimumab)	Thank you for your comment. This has been corrected.

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Foundation Trust					
King's College Hospital NHS Foundation Trust	Guideline	024	General	For the "insulin therapy" box, empagliflozin TA336 ("1.3: empagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes")	Thank you for your comment. Empagliflozin has been added to the insulin therapy box.
King's College Hospital NHS Foundation Trust	Guideline	031	009	Shouldn't there be a reference to NICE's draft recommendations on treatment for adults with chronic kidney disease and type 2 diabetes (2021) [GID-NG10256)?	Thank you for your comment. The renal benefits of using SGLT2 inhibitors in people with type 2 diabetes and CKD have been assessed in a separate piece of work that has recently been out for stakeholder consultation and was published in November 2021. The final recommendations on renal and cardiovascular benefits will be brought together in a single updated guideline document when this current work on cardiovascular benefits is published in 2022. Please note that GID-NG10256 on Diabetic retinopathy is a separate piece of work being undertaken by NICE which is not expected to publish until April 2024, please see the guideline page for updates and more information.
King's College Hospital NHS Foundation Trust	Guideline	034	021	"SLGT2" should be replaced by "SGLT2"	Thank you for your comment. This has been corrected.
King's College Hospital NHS Foundation Trust	Guideline	004	007	We believe that weight should be explicitly taken into account.	Thank you for your comment. This section of the guideline on individualised care was not prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest existing recommendations needed amending. Please note that the recommendation on choosing drug treatments now makes specific reference to weight.
King's College	Guideline	010		Figure 1 - "Thinking about things like driving, having severe hypos would not be a problem / would be a big problem for me". We believe that if	Thank you for your comments. We have amended the wording in the PDA and highlighted that some medicines are

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
Hospital NHS Foundation Trust				patients are experiencing severe hypos, this is a problem (even if the patient thinks it is not!). Given that the majority of glucose lowering agents (apart from insulin and sulphonylureas) have a low hypo risk, we are concerned that this statement may also be misleading to patients if they are not advised about hypo risk of each drug class and may prevent patients from taking up future treatment, including insulin.	more likely to cause hypos than others. Information on the pros and cons of different medicines is included in the visual summary which can be used alongside the PDA and VAS.
King's College Hospital NHS Foundation Trust	Guideline	010		Figure 1 - "I'm not concerned about the chance of getting side effects from medicine" / "Getting side effects from medicines would be a big problem for me" "I'm willing to take more medicines if I need to" / "I do not want to take any more medicines" We are concerned that these statements may potentially release a health care professional's responsibility to the patient if more intensive / rescue treatment is required to keep patients safe, if patients report that they do not want to take more medicines or if they are not counselled appropriately about side effects	Thank you for your comments. People with capacity have the right to decline treatment, even if the healthcare professional thinks this is unwise. We hope that providing a tool to support discussions between the healthcare professional and person with diabetes will support informed decision making and a better shared understanding of concerns and the potential benefits and harms of a higher or lower target HbA1c.
King's College Hospital NHS Foundation Trust	Guideline	010		Figure 1 - "I do not have any health issues apart from diabetes" / "I have lots of health issues as well as my diabetes". This links unspecified biomedical outcomes to HbA1c targets, which may not be appropriate.	Thank you for your comment. Recommendation 1.6.9 says that one reason for considering relaxing the HbA1c target would be if the person has significant comorbidities. Please also see the NICE guideline on multimorbidity(NG56). The wording in the PDA was chosen to convey this in non-technical language. The PDA and visual analogue scale are intended as tools that can be used if appropriate to support discussion between the healthcare professional and person with diabetes, and promote informed shared decision making.
King's College Hospital NHS Foundation Trust	Guideline	010		Figure 1 - Although not linked to HbA1c target decision making directly, we believe that weight should be mentioned.	Thank you for your comment. The figure relates to reasons for thinking about relaxing the HbA1c target mentioned in recommendation 1.6.9. Weight is not among them and the guideline did not consider any new evidence on this topic so it is not possible to include weight as a consideration.
King's College Hospital NHS	Guideline	014	005	Weight and cardiovascular risk should be explicitly stated	Thank you for your comment. Following committee discussion of stakeholder comments the recommendation on choosing drug treatments has been amended to include consideration of weight (first bullet). The committee decided

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Foundation Trust					against adding cardiovascular risk because they agreed that this would be covered by the first bullet on the person's individual clinical circumstances and cardiovascular protection is already mentioned under the point about the effectiveness of the drug treatments (third bullet).
King's College Hospital NHS Foundation Trust	Guideline	016	003	It should also be clear that for those in groups 1.7.9, if SGLT2 inhibitor therapy is contraindicated or not tolerated, consider ….	Thank you for your comment. Although there were a number of stakeholder comments asking for clarification of the treatment options for people with type 2 diabetes in whom SGLT2 inhibitors (SGLT2i) were contraindicated or not tolerated, there were no cardiovascular outcome trial style clinical trials identified that looked at the effectiveness of treatments for people at high cardiovascular (CV) risk in this population. The committee therefore used the evidence for effectiveness and cost effectiveness for other interventions from the same economic modelling scenarios as those looking at the cost- effectiveness of SGLT2i. The committee agreed that they were unable to recommend GLP-1 RA for people with type 2 diabetes and high cardiovascular risk who were unable to take an SGLT2i as they were not cost effective as a class or as individual drugs. As a result, the committee noted that people with high CV risk who could not take the recommended dual therapy of metformin and SGLT2, because they are unable to take the SGLT2, would be offered metformin alone at treatment initiation. If they were also unable to take metformin then the clinician would select another treatment from the remaining options, namely sulfonylureas, DPP-4s or pioglitazone, depending on the individual's clinical circumstances and preferences. The committee decided against listing the options for people with type 2 diabetes who were at high CV risk and could not take an SGLT2i because they thought that this was an unnecessary level of detail given that they could not recommend a GLP-1 mimetic in place of the SGLT2i, that the treatment options were therefore the same for these people as for the rest of the type 2 diabetes population and

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					because, apart from for metformin, the guideline does not include details of which drug to take if a particular drug is contraindicated or not tolerated but rather expects the prescriber to use their clinical judgment. The committee wanted to keep the pathway as simple as possible, and they agreed that it would not be possible to do this if alternative options were provided every time a drug was not contradicted or not tolerated. However, they agreed that it was appropriate to have recommendations for metformin being contradicted or not tolerated because this is the drug that the majority of people would take as first-line therapy.
King's College Hospital NHS Foundation Trust	Guideline	016	005	Given that there is consideration of heart failure is very prominent in this update, it should be mentioned here that pioglitazone should be avoided if there is evidence of congestive heart failure, or at the very least a warning about fluid retention.	Thank you for your comment. The committee agreed to stand down the previous MHRA information on pioglitazone and removed any mention to MHRA alerts in relation to specific drugs because it is expected that prescribers will check the MHRA, SPCs and BNF for any drugs before they prescribe them. The need to think about safety and take comorbidities into account when choosing drugs is highlighted in the recommendation on choosing drug treatments.
King's College Hospital NHS Foundation Trust	Guideline	016	016	We welcome the earlier introduction of SGLT2 inhibitor therapy based on a cardiovascular endpoint target (as opposed to an HbA1c target), which is likely to increase prescribing of this class of drug, perhaps to health care professionals that are less familiar with this class of drug. However, we think there needs to be more information on risk assessment for diabetic ketoacidosis e.g. HbA1c > 10%, marked symptoms of hyperglycaemia requiring rescue therapy, unexplained weight loss – which may be a flag for low beta cell reserve / possibility of an alternative diagnosis to type 2 diabetes). There is already a description of which patients may be at risk in the discussion on page 38, lines 9-12 [frail, older adults (aged 65 or over) or people at increased risk of dehydration) – can this statement not be made explicit here in this section on page 16?	Thank you for your comment. Following stakeholder comments at consultation the committee have amended the wording of the recommendation about things to check before starting the SGLT2 inhibitor to focus on whether the person is at increased risk of diabetic ketoacidosis (DKA) if they take an SGLT2 inhibitor. They have included some examples that, in the committees view, could lead to increased risk, but this is not meant to be an exhaustive list. This is noted in the rationale that accompanies the recommendation. The committee agreed that prescribers should consult the summary of product characteristics for further information. The committee made an additional recommendation to highlight to the clinician that they should try to address any modifiable risk factors before starting SGLT2i treatment.

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King's College Hospital NHS Foundation Trust	Guideline	017	010	Could further information on "sick day rules" be introduced here e.g. https://www.england.nhs.uk/london/wp-content/uploads/sites/8/2020/04/3.-Covid-19-Type-2-Sick-Day-Rules-Crib-Sheet-06042020.pdf)	Thank you for your comment. The recommendation which included sick day rules was reviewed following stakeholder comments and the bullet point on sick day rules has now been removed as the committee agreed it would be inconsistent to present this information for one class of drugs but not any others. They expected that sick day rules and other safety related advice would be discussed with the individual with type 2 diabetes as part of the decision-making process regarding drug choice and wanted to keep the guidance as simple and clear as possible.We have therefore been unable to include the additional information you suggested.
King's College Hospital NHS Foundation Trust	Guideline	017	012	"Choosing treatments": under "the person's individual clinical circumstances and their preferences and needs" this should include weight and pregnancy planning.	Thank you for your comment. 'Weight' has been added to bullet 1 in the prescribing guidance in the visual summary and a link to the pregnancy in diabetes guideline has been added to this section.
King's College Hospital NHS Foundation Trust	Guideline	017	012	"Choosing treatments": under "the medicine's safety and tolerability", we feel this should explicitly state hypo risk	Thank you for your comment. Risk of hypoglycaemia is covered by the 'medicine's safety and tolerability' and it is included in the choosing treatment visual summary table.
King's College Hospital NHS Foundation Trust	Guideline	017	012	"Rescue therapy". This should include a statement about considering switching to an alternative treatment (if ineffective for sulfonylurea – i.e. use insulin) or when blood glucose control has been achieved, to avoid long term use of these agents with considerable hypo risk and weight gain where possible.	Thank you for your comment. The section on rescue therapy was out of scope for this update. We have now included the statement that treatment should be reviewed once blood glucose control has been achieved.
King's College Hospital NHS Foundation Trust	Guideline	018	001	In the figure, if patients have high-risk or established CVD, and metformin is not tolerated or contraindicated, patients go down the consider / offer SGLT2 inhibitor alone. There needs to be an arrow after this to the left hand box with DPP-4 inhibitor / pioglitazone / sulphonylurea if SGLT2 inhibitor is contraindicated or not tolerated. Ideally, given the clinical evidence, this should be a GLP1 mimetic – in this scenario, GLP-1	Thank you for your comment. The committee decided against listing the options for people with type 2 diabetes who were at high CV risk and could not take an SGLT2i because they thought that this was an unnecessary level of detail given that they could not recommend a GLP-1 mimetic in place of the SGLT2i, that the treatment options were

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				mimetic would be being considered for *both* glucose lowering and cardiovascular risk reduction (not solely on the latter).	therefore the same for these people as for the rest of the type 2 diabetes population and because, apart from for metformin, the guideline does not include details of which drug to take if a particular drug is contraindicated or not tolerated but rather expects the prescriber to use their clinical judgment. The committee wanted to keep the pathway as simple as possible and they agreed that it would not be possible to do this if alternative options were provided every time a drug was not contradicted or not tolerated. However, they agreed that it was appropriate to have recommendations for metformin being contradicted or not tolerated because this is the drug that the majority of people would take as first-line therapy. GLP-1 mimetics are not a first line treatment option and are included in the visual summary for where further interventions are needed.
King's College Hospital NHS Foundation Trust	Guideline	018	002	"SLGT2" should be changed to "SGLT2" in the box in the bottom left corner	Thank you for your comment. The typo has been amended.
King's College Hospital NHS Foundation Trust	Guideline	019	001	For DPP-4 inhibitor and GLP-1 mimetic, pancreatitis should be listed as a contraindication.	Thank you for your comment. According to the BNF (November 2021), pancreatitis is listed as a caution. The committee agreed that it was useful to have contraindications in the table but prescribers should consult the BNF and SPCs for cautions.
King's College Hospital NHS Foundation Trust	Guideline	019	001	There is "no warnings" for GLP-1 mimetic use in hepatic impairment. This is not true of liraglutide (avoid in severe hepatic impairment) or semaglutide (caution in severe hepatic impairment) according to their respective SPC	Thank you for your comment. This content has now been updated for specific medicines rather than for medicine classes.
King's College	Guideline	019	001	The last line in the dashed box at the bottom should be "SGLT2" not "SLGT2"	Thank you for your comment. The typo has been amended.

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Hospital NHS Foundation Trust					
King's College Hospital NHS Foundation Trust	Guideline	020	002	Consideration of switching from a rescue therapy (insulin / sulphonylurea) to an alternative agent when blood glucose control has been achieved should be included, to avoid long term use of these agents with considerable hypo risk and weight gain where possible.	Thank you for your comment. The recommendation covering rescue therapy was not prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest existing recommendations needed amending.
King's College Hospital NHS Foundation Trust	Guideline	020	006	Should include a comment about pregnancy	Thank you for your comment. Please note that the recommendation on choosing treatments includes a cross reference to the NICE guideline on Diabetes in pregnancy. The actions in this recommendation are also relevant at the stage when drug treatment is being reviewed and a cross reference to this recommendation is included rather than duplicating the information here.
King's College Hospital NHS Foundation Trust	Guideline	020	015	"whether switching rather than adding drugs could be effective" – we assume this is effective at lowering glucose levels into target? It should be made clear, because if SGLT2 inhibitors have been chosen for their cardiovascular risk reduction properties, it may be pertinent to continue with this even if there has not been a reduction in HbA1c since its initiation (as recommended on page 40, line 6).	Thank you for your comment. The point about 'whether switching rather than adding drugs could be effective' referred to lowering glucose levels in the draft recommendations. After reviewing stakeholder comments committee have amended the recommendation on reviewing drug treatments to take account of the less apparent or measurable benefits such as cardiovascular and renal protection.
King's College Hospital NHS Foundation Trust	Guideline	022	019	We understand there are cost implications that will have directed the recommendation here that GLP-1 mimetic therapy should not be offered solely for cardiovascular risk reduction. However, given that this section is about treatment escalation if glucose targets have not been reached, is it not feasible to consider this class of treatment for glucose lowering purposes in those with high or established cardiovascular risk? The current guideline recommendation would mean that relatively few patients would be eligible for GLP-1 mimetic therapy, having to wait until three oral agents either fail to achieve glucose target or are not tolerated, by which point many will then require insulin due to insufficient endogenous insulin production, meaning that the incretin effect of GLP-1 mimetics would be	Thank you for your comment. The committee have taken stakeholder comments into account and agreed to remove the recommendation about not using GLP1-mimetic therapy solely for cardiovascular risk reduction in people with type 2 diabetes Upon reviewing the recommendation, the committee agreed that it was inappropriate to make a decision about treatment choice based solely on a single factor (cardiovascular risk) and that, as detailed in the recommendation on choosing drug treatments, multiple factors should be taken into account instead.

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				lower, than if started at an earlier stage of the disease. In the next section (line 24) where GLP-1 mimetics are recommended in the presence of obesity associated medical problems, cardiovascular disease should be recognised as being one such condition (as it is in the guidance on page 33, line 4).	The committee reviewed the stakeholder comments regarding the use of GLP-1 mimetics and examined the updated economic evidence relating to GLP-1 mimetic treatment for people with type 2 diabetes and high cardiovascular risk. In the NICE health economic analyses, when looking at GLP-1 mimetics as a class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of £20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the intervention as an effective use of NHS resources will specifically take account of the following factors." and • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis."

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					Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors. In addition, the committee noted that there were differences in the clinical effectiveness of the 2 forms of semaglutide. Although the acquisition costs for injectable and oral semaglutide are similar they showed marked differences in cost-effectiveness in the economic analyses. This was

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					caused by differences in the effect estimates for stroke, myocardial infarction and severe hypoglycaemia. From earlier discussions about the clinical evidence (see the discussion sections in the evidence review for more details) the committee had agreed that it was uncertain whether the observed differences in effect on all-cause mortality compared to placebo between the 2 forms of semaglutide were real and they therefore decided not to place undue weight on them. They had also noted that this uncertainty and any other differences in effects between the drugs for other outcomes was probably due to wide 95% confidence intervals for many outcomes with these drugs, due to the smaller numbers of participants and events in the trials compared to other CVOTs. The committee therefore agreed that they were unable to recommend injectable semaglutide for people with type 2 diabetes and high cardiovascular risk who were unable to take an SGLT2i. As a result, the committee noted that people with high CV risk who could not take the recommended dual therapy of metformin and SGLT2, because they are unable to take the SGLT2, would be offered metformin alone at treatment initiation. If they were also unable to take metformin then the clinician would select another treatment from the remaining options, namely sulfonylureas, DPP-4s or pioglitazone, depending on the individual's clinical circumstances and preferences. The committee decided against listing the options for people with type 2 diabetes who were at high CV risk and could not take an SGLT2i because they thought that this was an unnecessary level of detail given that they could not recommend a GLP-1 mimetic in place of the SGLT2i, that the treatment options were therefore the same for these people as for the rest of the type 2 diabetes population and because, apart from for metformin, the guideline does not include details of which drug to take if a particular drug is

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					contraindicated or not tolerated but rather expects the prescriber to use their clinical judgment.
King's College Hospital NHS Foundation Trust	Guideline	023	013	"Choosing treatments": under "the person's individual clinical circumstances and their preferences and needs" this should include weight and pregnancy planning.	Thank you for your comment. 'Weight' has been added to bullet 1 in the prescribing guidance in the visual summary and a link to the pregnancy in diabetes guideline has been added to this section.
King's College Hospital NHS Foundation Trust	Guideline	023	013	"Choosing treatments": under "the medicine's safety and tolerability", we feel this should explicitly state hypo risk	Thank you for your comment. Risk of hypoglycaemia is covered by the 'medicine's safety and tolerability' and it is included in the choosing treatment visual summary table.
King's College Hospital NHS Foundation Trust	Guideline	023	013	"Rescue therapy". This should include a statement about considering switching to an alternative treatment (if ineffective for sulfonylurea – i.e. use insulin) or when blood glucose control has been achieved, to avoid long term use of these agents with considerable hypo risk and weight gain where possible.	Thank you for your comment. Switching medicines in rescue therapy was not in scope for this guideline update. As in the guideline, we have included the statement on reviewing treatment once blood glucose has been controlled.
King's College Hospital NHS Foundation Trust	Guideline	025	General	For DPP-4 inhibitor and GLP-1 mimetic, pancreatitis should be listed as a contraindication.	Thank you for your comment. According to the BNF (November 2021), pancreatitis is listed as a caution. The committee agreed that it was useful to have contraindications in the table but prescribers should consult the BNF and SPCs for cautions.
King's College Hospital NHS Foundation Trust	Guideline	025	General	There is "no warnings" for GLP-1 mimetic use in hepatic impairment. This is not true of liraglutide (avoid in severe hepatic impairment) or semaglutide (caution in severe hepatic impairment) according to their respective SPC	Thank you for your comment. This content has been updated for specific medicines rather than for medicine classes.
King's College Hospital	Guideline	025	General	The last line in the dashed box at the bottom should be "SGLT2" not "SLGT2"	Thank you for your comment. The typo has been corrected.

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NHS Foundation Trust					
King's College Hospital NHS Foundation Trust	Guideline	028	019	Somewhere in this section on insulin, should be reference to guidelines on diabetes before and during pregnancy.	Thank you for your comment. The section of the guideline covering insulin-based treatments was not prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest existing recommendations needed amending. The committee did however include a cross reference to the NICE guideline on diabetes in pregnancy as part of recommendation on choosing drug treatments. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand.
King's College Hospital NHS Foundation Trust	Guideline	041	008	"SLGT2" should be replaced by "SGLT2"	Thank you for your comment. This has been corrected.
Leeds Teaching Hospital	Guideline	006	007	1.3 We are concerned that this section of the guidance has not been updated to include remission. We appreciate that this is not a section highlighted for comment however with NHS England supporting the roll-	Thank you for your comment. The section of the guideline covering dietary advice and bariatric surgery was not prioritised at the scoping stage as no evidence was identified

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NHS Foundation Trust and NHS Leeds CCG				out of remission programs we wanted to highlight our concern that this is not going to be supported by any recommendations from NICE.	in the surveillance review to suggest existing recommendations needed amending. The surveillance team at NICE monitor whether guidelines are up to date. The surveillance process includes reacting to events at any time after guideline publication (for example, publication of a key study) as well as a standard check every 5 years. Stakeholders can help with this process by letting us know which parts of the guideline stakeholders believe out-of-date and why during scope consultations. As these are evidence-based guidelines it is useful if stakeholders can provide links to important evidence sources that they believe would necessitate an update of a particular area of the guideline. We can then pass these references onto the NICE surveillance team for evaluation and a decision about whether an update is justified.
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	008	004	1.5.1 We are concerned that antiplatelet therapy has not been reviewed. Given the burden of cardiovascular disease on morbidity and mortality in people living with diabetes we had hoped this review would have looked at the new evidence and updated the recommendations accordingly.	Thank you for your comment. The section of the guideline covering antiplatelet therapy was not prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest existing recommendations needed amending. The surveillance team at NICE monitor whether guidelines are up to date. The surveillance process includes reacting to events at any time after guideline publication (for example, publication of a key study) as well as a standard check every 5 years. Stakeholders can help with this process by letting us know which parts of the guideline stakeholders believe out-of-date and why during scope consultations. As these are evidence-based guidelines it is useful if stakeholders can provide links to important evidence sources that they believe would necessitate an update of a particular area of the guideline. We can then pass these references onto the NICE surveillance team for evaluation and a decision about whether an update is justified.

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Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	009	006	We are concerned that Appendix A is not fit for purpose – in our opinion its length is unlikely to work in a clinical setting. It would not be suitable for those with low literacy or those with language barriers. Previous NICE guidance had a summary for patients on benefits vs risks of the different agents for glucose lowering. Could this document have a brief table summarising risks versus benefits for each agent? First sentence in the document states' if you have type 2 diabetes, you will have higher levels of glucose (sugar) in your blood.' This assumes that all people with T2DM have high glucose levels which is not the case. Should the words 'you will' be changed to 'you may'? Fifth bullet point down states 'taking a statin to manage your cholesterol if it is high'. The term 'high' is subjective. Could this statement be changed to be more reflective of the way we manage cardiovascular risk for example 'taking a statin' if relevant, to manage your cholesterol and reduce your cardiovascular risk. In addition, we now have a number of medications to reduce cardiovascular risk/cholesterol, not only statins. Last paragraph states that 'the lower you want to keep your blood glucose level, the more medicines you are likely to take. This also means that you are more likely to get side effects'. This statement could be seen as negative – it could be read that you will get side effects the more medicines you take, which is not necessarily the case. This could impact on both acceptance of additional medications and adherence of existing medications. Please can the language be used in this statement be reviewed?	Thank you for your comments. Both PDA and visual analogue scale (VAS) are tools that can be used if appropriate, neither is mandatory. During the clinical encounter the discussion can focus on the VAS. If the healthcare professional and person with diabetes do not want to go through the PDA during the consultation, it can be provided to support shared decision making either before or after the consultation, in line with the NICE guideline on shared decision making (NG197). The Flesch-Kincaid reading ease score suggests it will be understandable by people with a reading age of 11-13. This is in line with the NICE PDA standards. Information on the different blood glucose lowering drugs is now included in the guideline visual summary which can be used alongside the PDA. We have amended the sentence about blood glucose levels in people with type 2 diabetes and the reference to lipid management following your comment. The risk of side effects increases with increased numbers of medicines. It is one factor among many that needs to be considered. The first sentence you quote has been amended to say 'Aiming for a lower blood glucose target may mean you have to take more medicines'. As in the consultation version, the PDA balances that statement that taking more medicines may increase the risk of side effects by saying 'But not everyone will get side effects and they may not trouble you if they do happen. It is usually possible to change your medicines to ones that suit you better.' The committee considers this is fair, balanced and accurate.

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Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	009	006	In addition, some people will have lower blood glucose levels through dietary interventions and minimal medications. The statement 'the lower you want to keep your blood glucose level, the more medicines you are likely to take' is not strictly true for all	Thank you for your comment. We have amended the PDA to say 'Aiming for a lower blood glucose target may mean you have to take more medicines'.
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	009	007	Rec 1.6.5 – we felt that inclusion of some numerical values might help benchmark what you mean by 'a lower HbA1c target' and a 'higher HbA1c target' In other guidelines such as the ADA Standards of Care despite them using similar terms, qualification was made in other parts of the guidance with numerical targets. This will help a clinician balance the risk of hypoglycaemia vs. risk of sub optimal blood glucose control. If not this could lead to variation in care as people interpret their own target HbA1c levels- see examples of local guidance in the following links which have adapted the ADA target HbA1c diagram and ended up with different numerical values: https://www.hey.nhs.uk/wp/wp-content/uploads/2018/05/TYPE-2-DIABETES-HbA1c-TARGETS-v4-March-2018.pdf and https://www.hounslowccg.nhs.uk/media/116623/Diabetes-Individualising-HbA1c.pdf	Thank you for your comments. The starting point is the targets given in recommendations 1.6.7 and 1.6.8. The aim of the PDA is to support an individualised discussion between the healthcare professional and person with diabetes. The committee felt that putting specific target values in the PDA or visual analogue scale could be too restrictive and counter-productive to the aim of support shared decision making. They emphasised the need for dialogue that is tailored to the person's individual circumstances, preferences, goals and values.
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	010		Figure 1 - We have concerns regarding this decision aid. Although we believe it is useful to highlight when to approach tighter glycaemic control with caution, we do feel that the questions being asked in this decision aid push everyone to less stringent control. We would ask this is reviewed. The two questions in particular that are an issue are 'I do not want to take any more medicines' 'I do not want side effects from medicines', We believe most people would probably say they feel they do not want any more medicines and that they do not want side effects.	Thank you for your comments. The figure is intended as a basis for discussion between the healthcare professional and the person with diabetes. Moreover, the choices are not binary but the visual analogue scale (VAS) enables the person to indicate the extent to which they agree with either statement. We agree that most people would wish to avoid side effects and not take unnecessary medicines. However, we hope that putting these considerations alongside others, such as life expectancy, will encourage discussions between the healthcare professional and person with diabetes to support informed decision making and a better shared understanding of the issues at play. We have amended the PDA to highlight that the person needs to consider the

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					relative importance of all the factors in the VAS and also consider if other things that are important to them.
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	013	020	We would recommend that visual summary 1,2 and 3 are all combined into one algorithm. Visual summary 4 should be removed as it is likely to be out of date quickly and we don't believe it is value adding above what people could find in the BNF.	Thank you for your comment. We have combined the visual summaries. The approach to pulling together guideline recommendations in a visual form is a proof of concept. We will be continually reviewing our processes and will be updating the table based on changes to recommendations and following feedback from stakeholders and users.
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	014	008	We are concerned throughout this guidance that renal protection is ignored. Should renal protection be added in here as well as cardiovascular protection (with reference to the appropriate guidance)? We understand that duplication avoidance is at play however holistic care demands that we consider these things as a collective.	Thank you for your comment. Following committee discussion of stakeholder comments the recommendation on choosing drug treatments has been amended to include consideration of cardiovascular and renal protection (third bullet). The renal benefits of using SGLT2 inhibitors in people with type 2 diabetes and CKD have been assessed in a separate piece of work that has recently been out for stakeholder consultation and was published in November 2021. The final recommendations on renal and cardiovascular benefits will be brought together in a single updated guideline document when this current work on cardiovascular benefits is published in 2022.
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	014	013 - 014	We are concerned that the recommended 'lowest acquisition cost' SGLT2 is ertugliflozin with no compelling CV data	Thank you for your comment. We agree that the decision to prescribe a particular drug should not include consideration of treatment acquisition costs alone and it is for this reason that recommendation 1.7. 1 covers multiple factors to take into account when choosing drug treatments. These include the individual's clinical needs as well as their needs and preferences, monitoring licensing and safety issues. The point about lowest acquisition cost is intentionally the last bullet point and is only relevant if 2 drugs within the same class are appropriate having taken all the earlier points into account. This point not meant to be taken in isolation. The contents of this recommendation and the recommendation

					on reviewing treatments are intended to support personalised care by ensuring that the choice of drug is tailored to individual needs and circumstances. The committee reviewed the stakeholder comments but decided to continue treating SGLT2 inhibitors (SGLT2i) as a class for the following reasons: • There was a degree of uncertainty around whether there were real differences in cardiovascular (CV) benefits between the SGLT2i based on the clinical trial evidence and results from the NMAs. o Firstly, for hospitalisation for heart failure, the SGLT2i empagliflozin, canagliflozin, and dapagliflozin produced a clinically meaningful reduction compared with placebo in the random effects NMA model. However, in the sensitivity analyses using a fixed effect model ertugliflozin also showed a clinically meaningful reduction compared to placebo, which reflects the original clinical trial data. The NMA results could not differentiate between the SGLT2i for this outcome. o Secondly, for the 3 point MACE outcome, only canagliflozin and empagliflozin produced a statistically significant reduction compared to placebo but the SGLT2i could not be differentiated from each other in the NMA. o Thirdly for all cause and CV mortality empagliflozin showed a clinically meaningful reduction compared to placebo and the other SGLT2i, but the remaining SGLT2i could not be differentiated from each other or placebo in the NMA. o Fourthly, for non-fatal MI and non-fatal stroke the NMAs could not differentiate between empagliflozin, canagliflozin, ertugliflozin and placebo. The data for dapagliflozin was reported differently and could not be included

					in the NMAs. From the clinical trial data dapagliflozin could not be differentiated from placebo for MI and was not meaningfully different from placebo for stroke. ○ Finally, only dapagliflozin showed a clinically meaningful improvement in severe hypoglycaemia compared to placebo but the remaining SGLT2i could not be differentiated from each other and placebo in the NMA. • There was also a degree of uncertainty around the cost-effectiveness of individual SGLT2i in the economic modelling. Although only dapagliflozin was cost-effective at a threshold of £20,000/quality-adjusted life year (QALY) across all model scenarios and CV risk groups it could not be differentiated from the other SGLT2i in the NMA apart from for the all-cause and CV mortality outcomes where it was clinically meaningfully worse than empagliflozin. The ranking of ICERs for the other SGLT2i varied across model scenarios and risk groups. The committee agreed that there was sufficient uncertainty in the economic modelling (caused in turn by uncertainty in the underlying clinical data) to mean that they were not sufficiently confident that these different ICERs represented true underlying differences in cost-effectiveness, as opposed to simply random variation in the results between different SGLT2 trials. • Taking the cost-effectiveness and clinical results into account the committee decided against only recommending dapagliflozin and instead made recommendations for the SGLT2i as a class. However, they recognised that there was a greater degree of uncertainty around the CV benefit associated with ertugliflozin because, depending on the choice of model used in the NMA, it did not consistently show a clinically meaningful reduction in hospitalisation for heart failure compared to placebo, unlike empagliflozin, canagliflozin and dapagliflozin. It was also not statistically significantly better than placebo for the 3-point MACE

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					outcome unlike canagliflozin and empagliflozin. The committee therefore recommended SGLT2i with proven CV benefit because this wording would enable the prescribers to select a particular drug from within the SGLT2 class if they thought this was clinically justified based on the individual characteristics of their patient, whilst future proofing the recommendation should additional evidence or new SGLT2s be made available. As per the recommendation on choosing drug treatment, once the clinical circumstances and needs of the person with type 2 diabetes, including their need for CV protection, have been taken into account, if 2 drugs in the same class are suitable for that individual then the prescriber is still expected to choose the option with the lowest acquisition cost to help use NHS resources wisely. Please see evidence review A for more a more detailed explanation of the analyses that were carried out and the committee's discussion of the results.
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	014	029	1.7.4 - the term 'congestive' heart failure is out of date. Consider just saying 'heart failure' or 'chronic heart failure as per NICE NG 106	Thank you for your comment. The committee discussed the stakeholder comments about the use of the term 'congestive' heart failure. They agreed that it would be inappropriate to change this to say symptomatic chronic heart failure with reduced ejection fraction because people with heart failure are a larger group of people than those with heart failure with reduced ejection fraction. In addition, the recommendations deliberately cover people with type 2 diabetes and heart failure to match the clinical and economic evidence. Based on stakeholder requests the committee decided to change congestive heart failure to chronic heart failure. This change was made because this term refers to the same population of people with heart failure as congestive heart failure does and it was thought that the wider medical society will understand this term better because it is in wider use currently.

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Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	015	001	1.7.4 - Please consider defining atherosclerotic disease. This may help people pick up under recognised high-risk cardiovascular disease states e.g. peripheral arterial disease	Thank you for your comment. The committee have now provided a definition of ASCVD in the Terms used in the guideline section. This definition includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, previous coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	015	010	1.7.5 - we would ask that the committee consider adding in that this should be done sequentially here (it appears further down and may be missed) and potentially to be very explicit about titrating metformin to maximum tolerated dose and to add in SGLT2 despite HbA1c/Blood glucose readings.	Thank you for your comment. Following stakeholder comments the committee have reworded this recommendation to emphasise the need introduce the SGLT2 inhibitor without delay once metformin is tolerated. This is aimed at reducing the risk of clinical inertia delaying the introduction of the SGLT2.
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	015	011	There is concern over such a large inclusion criterion for dual therapy and cost implications/ prioritisation of the highest risk people. We would ask if the committee could consider revisiting this and defining e.g. very high risk and high-risk categories to try to enable primary care to take a structured approach to review. The DECLARE TIMI and CANVAS criteria may help with this. You could also consider looking at the EASD/ESC guidelines which define high/very high risk.	Thank you for your comment. The committee noted that the evidence showed cost-effectiveness of the SGLT2 inhibitors in the high risk and established cardiovascular disease populations modelled by the NICE economic model (please see the Evidence review document). The committee declined to amend the recommendations to cover very high risk and high-risk categories because they agreed that both groups should have access to the SGLT2s based on the results of the clinical and economic modelling. NICE is undertaking a resource impact assessment of the draft recommendations in preparation for finalising the guideline update. This includes consideration of the sizes of the populations that would be covered by the SGLT2 inhibitor recommendations for people with established cardiovascular disease (CVD) and high risk of CVD. The committee have access to this document and do take resource impact into account when finalising the recommendations.

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					The committee agreed that the use of SGLT2 inhibitors for people with established CVD or those at high risk of developing CVD would be costly and could lead to the implementation challenges you have highlighted. However, they agreed that since these drugs are clinically and cost-effective for this population in terms of CV protective benefits it is worth recommending them and facilitating work to overcome implementation challenges by providing a resource impact assessment tool. This document will be made available on the guideline website to help local and national commissioning bodies with their decision making. In addition, SGLT2s are already being used in this population in some areas based on other national or international guidance and so the resource impact may be less than anticipated. In the economic model, high CV risk populations were defined by either looking at the baseline characteristics, or by looking at their history of CV disease. The EASD guideline does define a very high risk population, but one of the conditions defining this is the condition of other target organ damage which we we are unable to identify in our baseline population (except for the eGFR condition). We have however included a combined High CV risk population which combined both the primary and secondary high CV risk populations (defined in section 3.1 in the economic report).
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	016	010	1.7.11 – if Repaglinide is to be included still, we are concerned that the wording on this is confusing and would recommend that it is reworded to say 'Repaglinide is licenced as monotherapy or as dual therapy but only in combination with metformin'.	Thank you for your comment. Based upon stakeholder comments this recommendation regarding Repaglinide, is being stood down because stakeholder agreed that this treatment was not widely used in current practice.

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Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	016	016 - 019	The wider use of SGLT-2 inhibitors is supported, however, we would like to ensure that NICE highlights safety in this wide-ranging population of eligible people living with type 2 diabetes. We recognise the risk of DKA associated with SGLT-2 inhibitors, however, the committee appears to be focused on low carbohydrate and ketogenic diets only. Low reserve of insulin secreting cells, low BMI or ketosis-prone diabetes should be considered (i.e., significant clinical features of insulin deficiency where we would not use an SGLT-2 inhibitor). Is there any reason why some risk factors have been chosen over others? Is there scope to add a prescribing decision aid around the SGLT-2i specifically focusing on risks versus benefits to highlight cohorts where benefits outweigh risks?	Thank you for your comment. The committee were aware that the aim of very-low carbohydrate and ketogenic diets is to replace dietary carbohydrate with fat with the specific intention of inducing a ketotic state. In people with type 2 diabetes taking an SGLT2 inhibitor (SGLT2i) this may increase the risk of diabetic ketoacidosis (DKA). DKA is a rare, but serious, complication in type 2 diabetes. The committee highlighted this risk because the SGLT2 inhibitors are comparatively new drugs and, in the committees' view, clinical experience with them is low in primary care in some areas, but the new recommendations are expected to greatly increase their use in this setting. Additionally, the summary of product characteristics (SmPC) for SGLT2i advise caution in people with restricted food intake in relation to ketosis. However, taking stakeholder comments into account, the committee have revised the wording to better reflect the need to check whether the individual would be at an increased risk of DKA if they take an SGLT2i rather than causative effect of such diets. They also included mention of several risk factors for DKA as examples, including the use of very-low carbohydrate and ketogenic diets. The list is not meant to be exhaustive but to highlight some risk factors that the committee thought were particularly important for prescribers to be aware of. The committee made an additional recommendation to highlight to the clinician that they should try to address any modifiable risk factors before starting SGLT2i treatment. This guideline already has a series of visual summaries to help the clinician with their prescribing decisions and with following the recommendations. It also has a PDA around blood glucose targets. Unfortunately, we are unable to provide additional decision support aids.
Leeds Teaching Hospital	Guideline	016	020 - 023	The importance of checking for pregnancy or planning pregnancy is welcomed however this should not only be for SGLT-2 inhibitors alone, it	Thank you for your comment. The committee have included a link under the recommendation on choosing drug

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NHS Foundation Trust and NHS Leeds CCG				should be included as a separate point and a routine question for type 2 diabetes **and** when prescribing any medication.	treatments to refer to the NICE guideline on Diabetes in pregnancy.
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	016	025	We note the importance of specific side effects with SGLT-2 inhibitors however would recommend adding in side effects linked to the three MHRA alerts currently published for SGLT-2 inhibitors: risk of DKA, fournier's gangrene and amputations. These are currently hidden on page 28, row 19 as a generic statement. If listing a side effect such as fluid volume depletion, we would welcome the advice that the patient should be counselled to ensure adequate hydration whilst taking SGLT-2 inhibitors and further details on renal parameters that would indicate cessation of therapy for example	Thank you for your comment. The committee agreed that expanding the safety recommendations to cover all the points suggested by stakeholders was unfeasible and was inappropriate because the guideline is the not intended to cover all the safety advice that should be taken into account when prescribing drug treatments and some of the suggested safety events were quite rare. In order to keep the guideline as simple and easy to follow as possible, the committee rewrote the safety recommendations to focus on some key points relating to the safety of SGLT2 inhibitors because they are not widely used in practice yet in some areas, and in particular may be unfamiliar to many clinicians in primary care, and the new recommendations will greatly increase the number of people who are eligible to take them. They removed some of the safety information that was in the consultation version of the guideline where it was not specific to SGLT2s, was not thought to be useful by stakeholders or was thought to be widely known. The committee agreed that prescribers are expected to consult MHRA alerts, the BNF and summary of product characteristics (SPC) for more comprehensive safety information. This is highlighted in the recommendation on choosing drug treatments which includes safety as one of the factors to take into account. The committee discussed the stakeholder comments about the renal impact of SGLT2 inhibitors (SGLT2i). They agreed that the existing recommendation was unclear and potentially confusing because it gave no indication of the frequency or when the monitoring should take place. They also recognised that although SGT2i can have a negative

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					effect on renal function this is usually a small reduction in function and not a reason to stop taking the SGLT2i. Taking these points into account the committee have now removed this draft recommendation. The committee declined to add information to the patient advice recommendation about ensuring adequate hydration because they would need to define what this what this meant and the amount of liquid a person needed to consume to be adequately hydrated would vary between individuals, depending on their clinical circumstances.
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	016	027	1.7.13 - We would ask that you consider being explicit on monitoring. https://kdigo.org/wp-content/uploads/2020/10/KDIGO-2020-Diabetes-in-CKD-GL.pdf and https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf may help pull something cohesive together. Once explicit monitoring requirements are established, ensure these align with NICE SGLT2i in CKD guidance	Thank you for your comment. The committee discussed the stakeholder comments about the renal impact of SGLT2 inhibitors (SGLT2i. They agreed that the existing recommendation was unclear and potentially confusing because it gave no indication of the frequently or when the monitoring should take place. They also recognised that although SGT2i can have a negative effect on renal function this is usually a small reduction in function and not a reason to stop taking the SGLT2i. Taking these points into account the committee have now removed this draft recommendation.
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	017	001 – 003	1.7.13 - We are concerned over the amount of cross referencing. This has to be a usable document.	Thank you for your comment. These cross references have been removed and a single cross reference to the section on CKD is included at the start of the initial treatment section on the guideline instead.

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Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	017	006	1.7.14 - We are concerned that particularly in a primary care environment some of these terms may be misunderstood. Very low carb and ketogenic should be defined. There are additional lifestyle factors that could increase the risk of DKA e.g., drugs and alcohol. It would also be helpful to include the importance of hydration to prevent dehydration given the mechanism of action of these drugs.	Thank you for your comment. We have added a definition of very low carb and ketogenic diet to the terms used in this guideline. Following stakeholder comments at consultation the committee have amended the wording of **the** recommendation on things to check before starting the SGLT2 inhibitor to focus on whether the person is at increased risk of diabetic ketoacidosis (DKA) if they take an SGLT2 inhibitor. They have included some examples that, in the committee's view, could lead to increased risk, but this is not meant to be an exhaustive list. This is noted in the rationale that accompanies the recommendation.The committee agreed that prescribers should consult the summary of product characteristics for further information. The committee made an additional recommendation to highlight to the clinician that they should try to address any modifiable risk factors before starting SGLT2i treatment. The committee declined to add information to the patient advice recommendation about ensuring adequate hydration because they would need to define what this what this meant and the amount of liquid a person needed to consume to be adequately hydrated would vary between individuals, depending on their clinical circumstances.
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	017	008	1.7.14 - We would ask that the committee considers saying rather than 'to avoid DKA' perhaps 'to reduce risk of DKA' we feel this is more appropriate given the evidence	Thank you for your comment. The committee have amended the draft recommendation to 'Advise adults with type 2 diabetes who are taking an SGLT2 inhibitor about the need to minimise their risk of DKA by not starting a very low carbohydrate or ketogenic diet without discussing it with their healthcare professional, because they may need to suspend SGLT2 inhibitor treatment.'
Leeds Teaching Hospital	Guideline	017	010	We welcome the addition of sick day rules for SGLT-2 inhibitors. Could these be expanded e.g. to include metformin, when to re-start, additional	Thank you for your comment. The recommendation which included sick day rules was reviewed following stakeholder comments and the bullet point on sick day rules has now

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NHS Foundation Trust and NHS Leeds CCG				information regarding stopping for surgery – see 3.-Covid-19-Type-2-Sick-Day-Rules-Crib-Sheet-06042020.pdf (england.nhs.uk)	been removed as the committee agreed it would be inconsistent to present this information for one class of drugs but not any others. They expected that sick day rules and other safety related advice would be discussed with the individual with type 2 diabetes as part of the decision-making process regarding drug choice and wanted to keep the guidance as simple and clear as possible. We have therefore been unable to include the additional information you suggested.
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	017	012	Visual Summary 1 – we are concerned that any consideration of renal benefit has been excluded. We feel strongly that renal should be included in this document so people can start thinking holistically. First bullet point discusses person's individual clinical circumstances, preference and needs. Could bullet point 4 be incorporated given that the persons cardiovascular risk and status would be a clinical circumstance. If so, the first bullet point could read 'the person's individual clinical circumstances (including cardiovascular disease [CVD] risk and status) and their preferences and needs Should the last bullet point 'check adherence to diet and lifestyle' be the first bullet point given diet and lifestyle is the cornerstone of T2DM management We would suggest that the bullet point starting with 'stop medicines that have not worked or not tolerated' state 'check adherence and stop medicines that have not worked or are not tolerated'. If medicines have not worked as people are not taking them, we need to review medication adherence rather than stopping the medication and taking it out of future options due to being ineffective. We would then suggest the bullet point below starting with Optimise…. Given that adherence has already been covered in the bullet point above. We are also concerned about the comment 'think about switching…' as we need to be careful to highlight that benefit may be beyond glycaemia.	Thank you for your comment. The visual summaries have now been grouped together and a link to the CKD recommendations has been added to the visual summary. Thank you for your comment. The committee have reworded the recommendation on reviewing drug treatments following stakeholder consultation to make their intentions clearer. However, it decided not to amend the order of the bullets as the entire recommendation should be read before beginning to act on the points included in it. We have updated the bullets so they are more aligned with the guideline recommendations and have moved diet and lifestyle advice to the top as a separate box.
Leeds Teaching Hospital NHS Foundation	Guideline	018	001	We are concerned that this is not a usable algorithm at this time. We feel strongly that one algorithm should be produced for treatment. We felt that it may look like 1st line treatment is DPP4 etc due to placement of title. Colours are poor for visibility. Re-enforcing lifestyle, diet and the need for structured education would benefit from being included at each stage. The	Thank you for your comment. We opted to keep the visual summaries for first line treatment and follow on treatment separate as they would never apply to the same patient at the same time. We felt that this would keep the visual summaries more simple and easier to follow. We have

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Trust and NHS Leeds CCG				sequential adding of sglt2s may be missed. There is a line at the top which says to assess renal function as part of your initial assessment and then it is ignored through the rest of the algorithm. Bottom left hand side box, SLGT2 needs to be changed to SGLT2 Bottom left hand side box states The Guideline update recommends SGLT2i use in wider population than technology appraisals published before August 2021. Does this statement mean that all previous TA's are now superseded? However the guideline links to the TA's. This could be made clearer. If this guideline accepts wider use, should the original TA's be superseded?	added a box on diet and lifestyle advice to visual 1. The statement on assessing renal function applies to both treatment initiation and follow on treatment, we have added additional information on cautions in renal impairment to the table. We have amended the typo. The TAs still apply to people who do not meet the guideline recommendations - those who are not at high risk of CVD. We have updated the visual summary so the TAs are more clearly linked with the 'not at high risk' pathway.
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	019	001	Visual summary 4 comes before 3	Thank you for your comment. This was intentional but the visual summaries have now been combined into either first line treatment or treatment options when further interventions are needed.
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	019	001	Visual summary 4 – we are concerned this algorithm will be out of date very quickly and there is nothing here that cannot be found in the BNF and SPC as needed. There also inaccuracies and given people may use this as their sole resource of information, this is concerning. The table may be more useful if it incorporates a traffic light system, perhaps as a quick reference/overview e.g. dose and we would welcome a section being added to this table to highlight key side effects - this is partly been added for the MHRA alerts for SGLT-2i however not consistent for all e.g. MHRA alert is missing - GLP-1 receptor agonists: reports of diabetic ketoacidosis when concomitant insulin was rapidly reduced or discontinued - GOV.UK (www.gov.uk). Side effects such as risk of worsening retinopathy for those on insulin and existing retinopathy when starting semaglutide are key prescribing points to consider. Having some information that is missing or incorrect is a concern as some prescribers may use this table as a sole resource In renal impairment the DPP4 linagliptin needs no dose adjustment for renal impairment and a number of GLP-1 agonists can be used down to	Thank you for your comment. The approach to pulling together guideline recommendations in a visual form is a proof of concept. We will be continually reviewing our processes and will be updating the table based on changes to recommendations and following feedback from stakeholders and users. MHRA warnings have been removed as we would expect prescribers to consult the MHRA, BNF, and SPCs before prescribing. This contraindication, renal and hepatic content in the table has been updated for specific medicines rather than for medicine classes.

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				eGFR 15ml/min. Please elaborate how the combination with insulin impairs hypoglycaemic response; was this meant to say that individuals are at more at risk of hypoglycaemia in the presence of renal impairment? SGLT2 needs more specifics on hepatic impairment Consider adding that with sulphonylureas, short acting agents in this class would be preferred in renal impairment. What differentiated hypo risk for SUs as moderate vs. insulin high risk? Sulphonylureas can have severe hypoglycaemia and this can be of long duration and can require hospitalisation. A more useful visual summary that takes into account cardiovascular and renal effects for each drug class would be more useful such as that produced by ADA, S101 https://care.diabetesjournals.org/content/diacare/suppl/2019/12/20/43.Supplement_1.DC1/Standards_of_Care_2020.pdf **Contraindications** - For all drugs listed in the table, looking at the SPC's and BNF often the only contra-indication is hypersensitivity to the ingredients only. In reality we know that there are clinical contra-indications and some have been listed, however, others haven't e.g. pancreatitis is missing from GLP-1 analogues and DPP-4 inhibitors. Would it be appropriate to title this section contra-indications and cautions for use and add in further information? Information on use in pregnancy and breast feeding are also missing from this table. We would ask that this section is updated and made more comprehensive. Having some information that is missing or incorrect is a concern as some prescribers may use this table as a sole resource **Renal Impairment** – in addition to the inaccuracies already discussed above compatibility in dialysis or end stage renal disease is missing for all. We would ask that this table is updated in line with the licensing documents. Having some information that is missing or incorrect is a concern as some prescribers may use this table as a sole resource. Sulfonylureas – under this section, it states to avoid where possible if severe. A number of the summary of product characteristic documents (www.medicines.org.uk) state that they are contra-indicated in severe renal impairment, rather than 'avoid where possible' e.g. glimepiride Glimepiride 1 mg Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) and gliclazide - Diamicron 80mg Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)	

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				Please can this section be reviewed. Having some information that is missing or incorrect is a concern as some prescribers may use this table as a sole resource. Metformin- please could this section be updated with the dose adjustments that need to be made when eGFR is between 30-45ml/min which are outlined in the SPC - Glucophage 500 mg film coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) Please can this section be reviewed. Having some information that is missing or incorrect is a concern as some prescribers may use this table as a sole resource. **Hepatic Impairment** DPP-4 inhibitors – the information in the table is misleading as there are differences between the DDP-4 inhibitors. For example linagliptin states no dose adjustments needed, however, clinical experience is lacking in hepatic impairment - Trajenta 5 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk), sitagliptin states no dose adjustment mild-moderate and in severe, care to be exercised as studies on severe hepatic impairment are lacking JANUVIA 100mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk). Vildagliptin states not to be used in hepatic impairment - Galvus 50 mg Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk). Please can this section be reviewed. Having some information that is missing or incorrect is a concern as some prescribers may use this table as a sole resource GLP-1 analogues – this section states that there are no warnings on use of GLP-1 analogues in hepatic impairment. Please can this section be updated as this statement is not correct – for example for liraglutide, no dose adjustment is required for mild to moderate impairment, however, it is not recommended for severe impairment - Victoza 6 mg/ml solution for injection in pre-filled pen - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk), semaglutide – no dose adjustment in mild to moderate hepatic impairment, limited experience in severe therefore caution in use - Ozempic 1 mg solution for injection in pre-filled pen - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk), dulaglutide – no dose adjustment - TRULICITY 1.5 mg solution for	

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				injection in pre-filled pen - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) Please can this section be reviewed. Having some information that is missing or incorrect is a concern as some prescribers may use this table as a sole resource. Sulfonylureas – under this section, it states to avoid if severe. A number of the summary of product characteristic documents (www.medicines.org.uk) state that they are contra-indicated in severe hepatic impairment, rather than 'avoid where possible' e.g. glimepiride Glimepiride 1 mg Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) and gliclazide - Diamicron 80mg Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) Please can this section be reviewed. Having some information that is missing or incorrect is a concern as some prescribers may use this table as a sole resource Metformin – the glucophage SPC states that metformin is contra-indicated in hepatic insufficiency - Glucophage 500 mg film coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk). SGLT-2i – the document states that caution is needed in severe hepatic impairment. The advice in the SPCs differ for example in dapagliflozin, it states it can be used with dose adjustments - Forxiga 10 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk). However in empagliflozin and canagliflozin it states not recommended Jardiance 10 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk), Invokana 100 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) Please can this section be reviewed. Having some information that is missing or incorrect is a concern. Some prescribers may use this table as a sole resource SGLT-2i – we welcome that the MHRA warnings on DKA and genital infections are noted here. The MHRA warning on lower limb amputations - SGLT2 inhibitors: updated advice on increased risk of lower-limb amputation (mainly toes) - GOV.UK (www.gov.uk) is not listed however is still a live MRA alert. We recognise that there is conflicting evidence around this. By omitting the MHRA alert, are NICE stating that this is no longer a concern and clinicians and patients do not need to discuss?	

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Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	020	001	Reviewing drug treatments – at each review of T2DM, adherence to lifestyle and diet interventions should be assessed given that these interventions work synergistically with medications. We would ask that lifestyle and diet are added into the sections e.g., in line 6, could it state 'how to optimise their current treatment regimen (including non-pharmacological management)	Thank you for your comment. The committee added a reference to revisiting advice about diet and lifestyle to the reviewing recommendation in response to your request. The committee agreed that it is important to revisit advice about diet and lifestyle because part of this discussion is to ensure the person is supported with both non-pharmacological and pharmacological interventions to improve their current health and prognosis.
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	020	005	We would suggest that the bullet point starting with 'stopping medicines that have not worked or not tolerated' state 'check adherence and stop medicines that have not worked or are not tolerated'. If medicines have not worked as people are not taking them, we need to review medication adherence rather than stopping the medication and taking it out of future options due to being ineffective. We would then suggest removing 'adherence to existing medication' in the bullet point below given that adherence has already been covered in the bullet point above	Thank you for your comment. The committee have reworded the recommendation on reviewing drug treatments following stakeholder consultation to bring the points about optimising current treatment regimens, including checking adherence, to the top. They decided against making your suggested changes as they agreed that checking adherence was a key component to facilitate optimising the current regimen. The point about stopping medicines is now directly below this one.
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	021	017	1.7.18 we are concerned that 'monotherapy' is not the correct word when most people will be on dual therapy if following the guidance by this point	Thank you for your comment. Although people with established cardiovascular disease or a high risk of developing cardiovascular disease will probably be taking dual therapy by this stage, some people will still be assessed as lower risk and be taking monotherapy (or may have declined dual therapy). The recommendation on adding further treatment applies to this population. There is another draft recommendation that covers additional treatment options for people who already on more than one drug.
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	021	019	1.7.18 We are concerned about the introduction of a new term 'individually agreed threshold'. We are concerned that this is not a term that makes sense in the context of this guideline given that earlier in the guideline you have set a threshold of 58mmol/mol for escalation from monotherapy. No guidance has been given on what this threshold is in relation to individualised targets.	Thank you for your comment. The term 'individually agreed threshold' has been retained from the 2015 version of this guideline. The section of the guideline covering targets was not within the scope of this update and the committee are therefore unable to change this terminology. However, the new update does contain a PDA to help with setting personalised targets.

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Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	022	019	1.7.21 The evidence shows vascular protection with GLP-1RA therapy and therefore the statement 1.7.21 can be misleading. While we do not advocate GLP-1RA use solely for vascular protection, agents in this class should be considered in those with inadequate glycaemic control and high cardiovascular risk in the absence of contraindications.	Thank you for your comment. The committee have taken stakeholder comments into account and agreed to remove the recommendation about not using GLP1-mimetic therapy solely for cardiovascular risk reduction in people with type 2 diabetes. Upon reviewing the recommendation, the committee agreed that it was inappropriate to make a decision about treatment choice based solely on a single factor (cardiovascular risk) and that, as detailed in the recommendation on choosing drug treatments, multiple factors should be taken into account instead. The committee reviewed the stakeholder comments regarding the use of GLP-1 mimetics and examined the updated economic evidence relating to GLP-1 mimetic treatment for people with type 2 diabetes and high cardiovascular risk. In the NICE health economic analyses, when looking at GLP-1 mimetics as a class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of £20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the

					intervention as an effective use of NHS resources will specifically take account of the following factors." and • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis." Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-

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					effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors. In addition, the committee noted that there were differences in the clinical effectiveness of the 2 forms of semaglutide. Although the acquisition costs for injectable and oral semaglutide are similar they showed marked differences in cost-effectiveness in the economic analyses. This was caused by differences in the effect estimates for stroke, myocardial infarction and severe hypoglycaemia. From earlier discussions about the clinical evidence (see the discussion sections in the evidence review for more details) the committee had agreed that it was uncertain whether the observed differences in effect on all-cause mortality compared to placebo between the 2 forms of semaglutide were real and they therefore decided not to place undue weight on them. They had also noted that this uncertainty and any other differences in effects between the drugs for other outcomes was probably due to wide 95% confidence intervals for many outcomes with these drugs, due to the smaller numbers of participants and events in the trials compared to other CVOTs. Due to the higher level of uncertainty surrounding the cost-effectiveness of the GLP-1 mimetics as a class compared to the SGLT2 inhibitors, the committee considered whether to recommend injectable semaglutide for people at high cardiovascular risk in whom an SGLT2 is contraindicated or not tolerated. However, taking into account the uncertainty in the cost-effectiveness and clinical effectiveness the committee decided against recommending injectable semaglutide for this population.

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Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	023	013	We are concerned that visual summary 1 has been included again. Is this supposed to be in the document twice?	Thank you for your comment. This was intentional but the visual summaries have now been combined following feedback from users.
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	024	General	We are concerned that you do seem to have included the circumstance of 'straight to insulin' in your algorithm	Thank you for your comment. Rescue therapy for symptomatic hyperglycaemia is included on the first page of the visual summary and we have added it to the top of the first line treatment visual and treatment options if further interventions are needed visual.
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	024	General	It should be highlighted that in some circumstances SGLT2 may be continued even when their glucose lowering effect is marginal e.g. HF, CKD.	Thank you for your comment. The following wording has been added to the reviewing treatment recommendation: 'stopping medicines that have had no impact on glycaemic control or weight, unless there is an additional clinical benefit, such as cardiovascular or renal protection, from continued treatment (see the note below on off-label use)'.
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	024	General	Visual summary 3. We are concerned that this is not fit for purpose at this time. No differentiation is made to medications that have CV risk vs. CV safe. Repeating the list of Tas for SGLT2s for dual and triple therapy is cumbersome and adds to confusion. Also why are two of the Tas listed in the insulin box? If the patient is not at high CVD risk and on metformin only, you would move on to the disease progression flow chart. It is not clear which combinations NICE are recommending without clicking into each of the TA documents. In the previous algorithm, the language used for SGLT-2i is 'offer' and 'consider'. In the metformin monotherapy scenario for those not at high CVD risk, the language reverts back to a TA and uses the words 'may be an option'. For this cohort, are NICE stating that we should be using a DPP-4i, pioglitazone or sulfonylurea over a	Thank you for your comment. The approach to pulling together guideline recommendations in a visual form is a proof of concept. We will be continually reviewing our processes and will be updating the visual summaries based on changes to recommendations and following feedback from stakeholders and users. Dapagliflozin TA288 does include insulin and has been linked in this section. Empagliflozin has now also been listed as an option with insulin.

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				SGLT-2i and follow the TA's for SGLT-2i? The flow charts could be clearer. The algorithm is less clear on use of triple oral therapies and beyond. The disease progression flow chart may be better set out as a flow chart cascading downwards rather than sideways. **It would be more helpful if options were detailed as first, second and third line options/intensification as per previous guidance**. Insulin is mentioned as an option to 'consider' when dual therapy has not controlled HbA1c. What about as third or fourth line? The algorithm suggests insulin should only be considered when dual therapy has not achieved the persons individualised target. Please can insulin be detailed in the algorithm as per the narrative on pages 26-28 The bottom box states 'switch or add treatments from different drug classes up to triple therapy (dual therapy if metformin contra-indicated). Is the guidance stating that quadruple therapy (triple oral plus GLP-1 analogue) is not recommended? If so, please state this Bottom box states The Guideline update recommends SGLT2i use in wider population than technology appraisals published before August 2021. Does this statement mean that all previous TA's are now superseded? However the guideline links to the TA's. This is confusing. Could this be made clearer? If this guideline accept wider use, should the original TA's not be superseded? Technology Appraisal for empagliflozin for dual therapy and triple therapy should read (and link to) TA336 and not 366. The different SGLT-2i are listed in different orders, should this be consistent i.e. alphabetically, in order of TA number, or other? Dapagliflozin TA 418 does not include insulin. Empagliflozin (TA 336) does include insulin, however, is not listed as an option here. Please can this section be reviewed to ensure the correct options are listed The term 'antidiabetic' drugs is used. Given the NHS England language matters document, please could this language be reviewed.	The visual summary reflects the guideline recommendations in that people would be offered a DPP4, pioglitazone, or a sulfonylurea second line. The TAs are included as they are options for some people. We have opted to link to the Tas rather than write out the TA recommendations to keep the summary clear and to one side of A4. We are not recommending that DPP4s, pioglitazone, and sulfonylureas are used in preference to SGLT2s. Where the TA recommendations apply, these should be considered as part of shared decision making alongside the other options. The purpose of the visual summaries is to summarise the recommendations in the drug treatment section of the guideline. If prescribers opted to try three oral medicines before insulin and it did not work, insulin would still be an option. The GLP mimetic recommendation states that triple therapy, including a GLP-mimetic should be used and this has been reflected in the visual summary. The word 'antidiabetic' has been removed from the visual summaries.

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				Given the evidence for cardiovascular risk reduction, should these agents not be classified as third line for those with existing CVD and those at high risk of CVD?	
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	027	025	1.7.28 consider adding something in about insulin biosimilars or most cost effective choices	Thank you for your comment. The section of the guideline covering insulin-based treatments was not prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest existing recommendations needed amending. However, we have been able to add recommendations covering the points you have raised to this section. These were drafted as part of the diabetes type 1 update on this topic but were judged to be equally relevant to this guideline.
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	029	002	We are concerned that the section on gastroparesis covers an extremely niche area of practice and that this section may be out of date with its drug recommendations. If we are going to look at all connecting co-morbidities should we be including other complications e.g. peripheral neuropathy, dental care etc.	Thank you for your comment. The section of the guideline covering managing was not prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest existing recommendations needed amending.
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	033	001	We are concerned about the use of the word 'clinical judgement' but then it appears to be well defined. Does this need further judgement?	Thank you for your comment. The committee have agreed that this did not require further explanation as it is, as stated in the comment, well defined.
Leeds Teaching Hospital NHS Foundation Trust and	Guideline	034	009	What do you mean by long term outcomes?	Thank you for your comment. The research recommendation covering long-term outcomes associated with blood glucose lowering agents has been reviewed by the committee and has been stood down. The committee believe that the longer-term outcomes (cardiovascular benefits) have been established by the CV outcome trials included in this update.

Consultation on draft guideline - Stakeholder comments table
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Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	034	013	We would like the committee to consider if meglitinides should feature in a research recommendation when they are so infrequently used in practice.	Thank you for your comment. The recommendation covering long-term outcomes associated with blood glucose lowering agents has been reviewed by the committee and has been stood down. The committee believe that the longer-term outcomes (cardiovascular benefits) have been established by the CV outcome trials included in this update. Additionally, the committee were aware that meglitinides are now infrequently used (when compared to 2015 when the research recommendation was initially made).
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	037	015 - 017	We also felt that the possibility of wrong diagnosis should be first on the list of things to explore if someone has presented with a DKA on these medications.	Thank you for your comment. While the committee agree that misdiagnosis might occur the scope of the guideline is for adults with confirmed diagnosis of type 2 diabetes.
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	038	005	We feel that the monitoring needs clear guidance. We are concerned that primary care will not know how to make this decision. L/S BP needs to be added in addition to renal function especially if they are co-commitment diuretics.	Thank you for your comment. The committee discussed the stakeholder comments about the renal impact of SGLT2 inhibitors (SGLT2i). They agreed that the existing recommendation was unclear and potentially confusing because it gave no indication of the frequently or when the monitoring should take place. They also recognised that although SGT2i can have a negative effect on renal function this is usually a small reduction in function and not a reason to stop taking the SGLT2i. Taking these points into account the committee have now removed this draft recommendation.
Leeds Teaching Hospital NHS Foundation Trust and	Guideline	042	008 - 015	1. We are very concerned that the full metabolic benefits of GLP-1 therapy has not been captured, given the narrow focus on part of their effect. 2. There is a great need for a full review of GLP-1 mimetics, which would capture glycaemic and other metabolic benefits.	Thank you for your comment. 1. You are correct that the model does not contain every outcome that could potentially be of interest for modelling adults with type 2 diabetes. However, the committee agreed these were the most important outcomes for assessing the additional cardiovascular and other benefits associated with

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NHS Leeds CCG				3. We would appreciate the committee also ensuring there is no confusion given some of these medications can be used for weight loss alone e.g. saxenda and ensure any technology appraisals align. 4. The guidance doesn't address the needs of those with diabetes (including when HbA1c at/near target) and severe obesity and who are in tier 3 obesity service and heading towards consideration for bariatric surgery. Access to GLP-1 treatment, including the higher doses of GLP-1 should probably be more readily available i.e. not having to have fulfilled the criteria of "triple therapy with metformin + 2 others ineffective, not tolerated or contra-indicated" …. Where for example if these individuals had pre-diabetes they would be eligible (i.e. NICE guidance for Saxenda). 5. In the ADA/EASD consensus statement they have a pathway for those with a compelling need for weight reduction.	drug treatment for type 2 diabetes, for the majority of the type 2 diabetes population. The committee agreed the cardiovascular outcome trials were the most appropriate data source to assess cardiovascular benefits of these drugs, being powered to specifically detect differences in hard outcomes, rather than only surrogate outcomes. The committee noted these studies were not representative of the full population of people with type 2 diabetes but agreed this was a lesser limitation than the need to extrapolate from surrogate endpoints to cardiovascular outcomes, particularly given the findings from those studies suggesting these surrogate extrapolations are often not very robust. They also agreed that taking data on weight and hypoglycaemic events from these cardiovascular outcome trials was the most appropriate approach, in order to match the data used for cardiovascular event rates. For hypoglycaemic events, the approach taken is broadly in line with that taken in many other evaluations in diabetes, attaching costs and quality of life outcomes to the incidence of severe hypoglycaemic events, as these are the ones that make the most difference to a person's life. For changes in weight, it was noted it was important not to double count the impact of changes, as the effects on cardiovascular outcomes should already be captured in the outcomes of those trials. It was therefore agreed that the most appropriate approach was to only include the direct quality of life gains associated with reductions in weight, with the other benefits captured through the cardiovascular event data. The committee noted that if anything the approach taken in the guideline may overestimate the benefits of weight reduction, as some of the estimated quality of life gains may be the result of avoided cardiovascular events, but it was agreed to be the best data source available. There are of course other benefits that could have been considered as part of the modelling, including renal (or other microvascular) outcomes, or additional benefits directly

					related to improved glycaemic control, but the committee considered these to be of lower priority than those included in the model. They also noted that it would not be appropriate for any modelling approach to simply look at benefits on different outcomes from different trials or data sources, and assume those benefits are additive, and therefore increase the cost-effectiveness of drugs when included together. They noted that in many circumstances these benefits are not additive, and which benefits are likely to be realised may depend on the individual characteristics of the people included in studies. As an example, in the separate evaluation of SGLT2 inhibitors for people with CKD and type 2 diabetes, SGLT2 inhibitors were found to significantly improve renal outcomes, but this is a population in which a large benefit would not be expected for glycaemic control (hence why these agents were not originally licensed for use in people with impaired renal function). It should also be noted that it is not the case that only additional outcomes beneficial to drug therapy were excluded from the modelling. As an example, adverse events related to drug treatment (excluding hypoglycaemia) were not included as part of the analysis. As a number of the analyses in the guideline explicitly compare the addition of new treatments (for example, using 3 drugs versus 2) rather than simply switching drugs, it would be expected that inclusion of adverse events would decrease the cost-effectiveness for any additional treatments, as they would add to the adverse event burden. Therefore, whilst it is likely there would be differences found in the results of the cost-effectiveness analysis were a different set of outcomes to be included, it is not clear in which direction the results would change for any given agent, and whether they would become more or less cost-effective. 2. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took

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					was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand. 3. The scope of this update only included evidence for cardiovascular benefit of drug treatments used in the management of type 2 diabetes (see the Evidence review document for details). The only identified CV outcome trial evidence for Liraglutide was from the LEADER trial which used a dose up to 1.8 mg per day. Higher doses of Liraglutide up to 3 mg per day can be prescribed as an adjunct in weight management but no cardiovascular outcome trial evidence was found for the higher daily dose, which also does not currently have a licensed indication for type 2 diabetes management, and so no recommendation for use of a higher dose could be made by the committee. Appropriate cross-referencing to all applicable technology appraisals has been made in the guideline. 4. The NICE guideline has a separate section, which was out-of-scope for this update, on dietary advice and bariatric surgery (section 1.3 of the Guideline document). This contains a link to the NICE guideline on Obesity: identification, assessment and management which contains recommendations for use of Pharmacological interventions in obesity. 5. The committee were aware of the ADA guidance, but their decisions were made according to the NICE guideline

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					manual and took into account the evidence relevant to our review question. Although the NICE guidance may differ to the guidance provided by ADA, the committee were confident that their recommendations reflected the evidence they reviewed and their clinical judgement. It is of particular importance to note that the NICE guideline used an original economic model as the basis to recommend the most clinically and cost-effective options while the ADA guidance did not systematically take cost-effectiveness into account.
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	043	001 - 003	Was there no evidence for Insulin vs. GLP-1 already? If there is some evidence of comparisons, then why was economic modelling not possible? what cost would a GLP-1 have to be to come out cost effective?	Thank you for your comment. Please note that following stakeholder comments at consultation this research recommendation has been removed. The economic evaluation concentrated on comparing treatment reducing CV risks as reported by cardiovascular outcome trials. This is in line with the treatments considered in the evidence review, and insulin therapy alone was not one of these treatments. Furthermore, the economic analysis was designed to estimate the incremental cost per QALY gained at the list price of the drug, in line with NICE processes, and threshold analyses were not conducted to determine at which point any particular treatment would become cost-effective for a given parameter.
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Guideline	045	015 - 020	We believe that a full review should be completed ASAP. There are many elements of this guideline that are not up to date and are not appropriately tying together as a result.	NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new

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					recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand.
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Questions on comments form	General	General	Q1 - Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why. *For places following the Portsmouth super six model of care, most people living with type 2 diabetes will be managed in a primary care setting. This guideline for most purposes will therefore be a primary care guideline.*	Thank you for your response.
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Questions on comments form	General	General	Q2 - Would implementation of any of the draft recommendations have significant cost implications? *Yes. If populations eligible for SGLT2s are rigorously searched for and there is primary care staffing that will allow review and initiation this will be a large overspend.*	Thank you for your response.
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Questions on comments form	General	General	Q3 - What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or examples of good practice.) *The main challenge of this document is going to be the fact that it does not represent expert practice. There are already localities that have adopted the ADA/EASD guidelines either in totality or in part. With the guidelines being so far removed from these, particularly in relation to the GLP-1 agonists and the failure to update so many facets of the guideline where current thinking has progressed, we are going to be left in a situation where a postcode lottery to best care will develop. We need these guidelines to be updated in full and for them to reflect current thinking and practice. We are very concerned that this has not happened.*	Thank you for your response. The committee were aware of the ADA guidance, but their decisions were made according to the NICE guideline manual and took into account the evidence relevant to our review question. Although the NICE guidance may differ to the guidance provided by ADA, the committee were confident that their recommendations reflected the evidence they reviewed and their clinical judgement. It is of particular importance to note that the NICE guideline used an original economic model as the basis to recommend the most clinically and cost-effective options while the ADA guidance did not systematically take cost-effectiveness into account. The committee are comprised of diabetes experts and in their opinion the recommendations for SGLT2s for people with high CV risk or establishd CVD are in line with current best practice. They recognised that ideally if the SGLT2 inhibitors were contraindicated or not tolerated that GLP-1s

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					would be an alternative option for these people. However, these drugs were not cost-effrective as a class or individually for people in these CV risk groups and so the committe could not recommend them in this current update. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand.
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Questions on comments form	General	General	Q4 - Should the recommendation for treatment options for people with type 2 diabetes in whom metformin is contraindicated / not tolerated after treatment initiation be retained or stood down? We propose retaining the recommendations for treatment initiation for these people but standing down recommendation 1.7.20 covering later treatment options. Do you agree or disagree and why? *We think in general that a logical flow to recommendations needs to be developed to make this a more usable document.*	Thank you for your response. We have tried to simplify the recommendations and order them to give a logical flow. However, we recognise that some people may find it easier to work from our visual summary document.
Leeds Teaching Hospital NHS Foundation Trust and	Questions on comments form	General	General	Q5 - What do you think about the positioning of the visuals alongside the recommendations they summarise? Please explain your response. *We did not feel the visual summaries needed to be in the main body of the text. Most people in primary care will only use the visual summary and refer to main text if clarification is needed.*	Thank you for your comment. Based on stakeholder responses, and to test the proof of concept of integrating guideline recommendations into a visual summary, we have kept the visual summaries alongside the recommendations and as a separate PDF.

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Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Questions on comments form	General	General	Q6 - Would the visual summaries in general help in your day-to-day practice? Please explain in your response how they would or would not help. *We did not find these visual summaries to be useful but an updated visual summary which covers everything on one side of A4 would be perfect and very useful for practice.*	Thank you for your comment. The approach to pulling together guideline recommendations in a visual form is a proof of concept. We will be continually reviewing our processes and will be updating the visual summaries based on changes to recommendations and following feedback from stakeholders and users. We realise that it would be useful to fit everything on one side of A4 but it was not possible to included all of the relevant information in a readable format. We have separated the visual summaries into 'first line treatment' and 'treatment options when further interventions are needed' to improve flow and readability.
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Questions on comments form	General	General	Q7 - We have also included a pdf version of all the visuals within a single document. Is this pdf needed as well as the visuals included in the guideline document? Please explain your response. *We would prefer to just have the pdf. See above*	Thank you for your comment. Based on stakeholder responses, and to test the proof of concept of integrating guideline recommendations into a visual summary, we have kept the visual summaries alongside the recommendations and as a separate PDF.
Leeds Teaching Hospital NHS Foundation Trust and NHS Leeds CCG	Questions on comments form	General	General	Q8 - Do you think the visual summaries could be improved or made more useful? Please explain your response. *Yes. We believe we have covered most of the issues with this in the main feedback. We would have expected to see something like the ADA/EASD algorithm.*	Thank you for your comment. The approach to pulling together guideline recommendations in a visual form is a proof of concept. We will be continually reviewing our processes and will be updating the visual summaries based on changes to recommendations and following feedback from stakeholders and users.
Medicines & Healthcare products Regulatory Agency (MHRA)	Late comments received after consultation closure	General	General	Oral Semaglutide 3mg, 7mg, 14mg (Rebelsus) have not been appraised in the draft guidance.	Thank you for your comment. However, please note that we included the available and relevant evidence to inform the update, oral semaglutide was trialled at a target daily dose of 14 mg/day in the PIONEER-6 CV outcomes trial (Husain et al 2019) which was an included study in the NICE evidence review and economic model. In the trial only 82% of those taking oral semaglutide achieved the target of 14 mg/day,

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					the remainder were on reduced doses of either 3 mg/day or 7 mg/day at End of Therapy (EOT) the split between the 2 lower doses is about approximately even (data from stacked bar chart in supplementary appendix to the trial paper). Of the remaining participants approximately 9% were taking 7 mg/day and 9% were taking 3 mg/day). Separate evidence on the effectiveness (CV benefit) of the intervention for the lower dose groups is not presented by the trial.
Medicines & Healthcare products Regulatory Agency (MHRA)	Late comments received after consultation closure	General	General	GLP-1 mimetic therapy (oral or subcutaneous) should be listed as a second line therapy to be aligned with approved SmPCs.	Thank you for your comment. In the NICE health economic analyses, when looking at GLP1 agonists as a class, the results from the probabilistic sensitivity analysis showed that GLP1 agonists had a very low probability of being cost-effective. Hence GLP1 agonists as a class were deemed not cost-effective and not considered, and the committee went on to considering the results specifically for injectable semaglutide. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of £20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the intervention as an effective use of NHS resources will specifically take account of the following factors." and • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending

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					a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis." Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors.
Medicines & Healthcare products	Late comments received	General	General	The recommendation "Do not offer GLP-1 mimetic therapy to adults with type 2 diabetes solely for cardiovascular risk reduction" is not aligned with international treatment guidance, i.e., the American Diabetes	Thank you for your comment. The committee were aware of the ADA guidance, but their decisions were made according to the NICE guideline manual and took into account the

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Regulatory Agency (MHRA)	after consultation closure			Association/the European Association for the Study of Diabetes consensus report.	evidence relevant to our review question. Although the NICE guidance may differ to the guidance provided by ADA, the committee were confident that their recommendations reflected the evidence they reviewed and their clinical judgement. It is of particular importance to note that the NICE guideline used an original economic model as the basis to recommend the most clinically and cost-effective options while the ADA guidance did not systematically take cost-effectiveness into account. However, the committee have taken stakeholder comments into account and agreed to remove the recommendation about not using GLP1-mimetic therapy solely for cardiovascular risk reduction in people with type 2 diabetes. Upon reviewing the recommendation, the committee agreed that it was inappropriate to make a decision about treatment choice based solely on a single factor (cardiovascular risk) and that, as detailed in the choosing drug treatments recommendation, multiple factors should be taken into account instead.
Medicines & Healthcare products Regulatory Agency (MHRA)	Late comments received after consultation closure	General	General	The potential lack of efficacy when eGFR<60ml/min in SGLT-2 inhibitors and associated potential side effects, i.e., urinary tract infections, osmotic diuresis induced orthostatic hypotention, fractures….are not addressed in detail.	Thank you for your comment. The committee agreed that expanding the safety recommendations to cover all the points suggested by stakeholders was unfeasible and was inappropriate because the guideline is the not intended to cover all the safety advice that should be taken into account when prescribing drug treatments and some of the suggested safety events were quite rare. In order to keep the guideline as simple and easy to follow as possible, the committee rewrote the safety recommendations to focus on some key points relating to the safety of SGLT2 inhibitors because they are not widely used in practice yet in some areas, and in particular may be unfamiliar to many clinicians

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					in primary care, and the new recommendations will greatly increase the number of people who are eligible to take them. They removed some of the safety information that was in the consultation version of the guideline where it was not specific to SGLT2s, was not thought to be useful by stakeholders or was thought to be widely known. The committee agreed that prescribers are expected to consult MHRA alerts, the BNF and summary of product characteristics (SPC) for more comprehensive safety information. This is highlighted in the choosing drug treatments recommendation which includes safety as one of the factors to take into account.. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. Taking these into account we have decided that a full update of this section of the guideline is warranted. However, this is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs.
Medicines & Healthcare products Regulatory Agency (MHRA)	Late comments received after consultation closure	General	General	There is a lack of emphasising the target HbA1c 7%; there is a bias towards avoiding insulin or sulfonylurea. These should be offered to patients whose initial HbA1c >10% or those who can maintain HbA1c < 6.5% safely themselves.	Thank you for your comment. Although the target HbA1c of 7.0% is covered in recommendation 1.6.7 and 1.6.8, please note these recommendations were not within the scope of this update. The current committee did not review any evidence on this topic. Similarly, the section on insulin therapy was out-of-scope for this update. The current committee did not review any evidence on this topic. The place in therapy of sulfonylurea drugs remains unchanged in this update from the previous 2015 update of the guideline.
Medicines & Healthcare products	Late comments received after	General	General	There is a lack of considering patient's preference; some patients may not be able to accommodate diuresis brought by SGLT-2 inhibitor because of their occupations; some may prefer weekly sc injections because of busy daily work demands.	Thank you for your comment. Please note that the recommendation on choosing drug treatments clearly states that a person's individual circumstances, preferences and needs should be considered. Safety issues including

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Regulatory Agency (MHRA)	consultation closure				tolerability and adverse events are a part of that decision making process, and the recommendation on reviewing treatments .
Merton Health GP Federation	Guideline	016	009	There is no mention about what if SGLT2 is not tolerated or recommended	Thank you for your comment. Although there were a number of stakeholder comments asking for clarification of the treatment options for people with type 2 diabetes in whom SGLT2 inhibitors (SGLT2i) were contraindicated or not tolerated, there were no cardiovascular outcome trial style clinical trials identified that looked at the effectiveness of treatments for people at high cardiovascular (CV) risk in this population. The committee therefore used the evidence for effectiveness and cost effectiveness for other interventions from the same economic modelling scenarios as those looking at the cost- effectiveness of SGLT2i. The committee agreed that they were unable to recommend GLP-1 RA for people with type 2 diabetes and high cardiovascular risk who were unable to take an SGLT2i as they were not cost effective as a class or as individual drugs. As a result, the committee noted that people with high CV risk who could not take the recommended dual therapy of metformin and SGLT2, because they are unable to take the SGLT2, would be offered metformin alone at treatment initiation. If they were also unable to take metformin then the clinician would select another treatment from the remaining options, namely sulfonylureas, DPP-4s or pioglitazone, depending on the individual's clinical circumstances and preferences. The committee decided against listing the options for people with type 2 diabetes who were at high CV risk and could not take an SGLT2i because they thought that this was an unnecessary level of detail given that they could not recommend a GLP-1 mimetic in place of the SGLT2i, that the treatment options were therefore the same for these people as for the rest of the type 2 diabetes population and because, apart from for metformin, the guideline does not include details of which drug to take if a particular drug is

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					contraindicated or not tolerated but rather expects the prescriber to use their clinical judgment. The committee wanted to keep the pathway as simple as possible and they agreed that it would not be possible to do this if alternative options were provided every time a drug was not contradicted or not tolerated. However, they agreed that it was appropriate to have recommendations for metformin being contradicted or not tolerated because this is the drug that the majority of people would take as first-line therapy.
Merton Health GP Federation	Guideline	017	012	No mention of CKD stages and issues related to prescribing medications	Thank you for your comment. A link has been added to the section in the guideline on CKD and more detail has been added on renal function to the choosing medicines table.
Merton Health GP Federation	Guideline	017 / 018 / 019 / 023 / 024 / 025	General	Visual summary - This guideline is aimed at primary care as Type 2 diabetes care mainly occurs in that setting and despite this the guidelines are far too complicated and confusing to allow GP and Nurses in primary care to make timely and appropriate therapeutic decision when faced with patients. The visual infographics are tedious and confusing with poor flow. The visual summary lacks patient centred decision making when it comes to weight and in situations where CV health is not the main issue. Need more clarity on weight and hypo issues on prescribing	Thank you for your comment. We have combined the visual summaries based on the treatment initiation and further treatment to improve flow and in response to stakeholder comments. We have also included information in the prescribing table on weight gain/loss, hypo risk, and form of the medicine to allow for improved shared decision making.
Merton Health GP Federation	Guideline	018	General	There is no commentary on why all patients with diabetes are at risk of CV issues, no mention on this page about CKD risks and issues and oral agent considerations. GLP-1 agents have not been mentioned on this page anywhere, although they have an important place in type 2 Diabetes care in patients with CV risk, it seems published data has not been reviewed for GLP-1 agents	Thank you for your comment. As with the recommendations, the visual summaries have stratified by not at a high risk of CVD, high risk of CVD, and established HF or ASCVD. Definitions have been added to the visual summaries. GLP-1 mimetics are not a first line treatment option therefore they are included in the visual for where further interventions are needed.
MSD UK Ltd	Evidence review A	025	General	Table 7 - The first footnote should read "Green et al. 201**5** (TECOS)". Green et al. 2013 described the rationale and design of the study but did not include study results.	Thank you for your comment. This has been corrected in line with your comment.
MSD UK Ltd	Evidence review A	039	031	We agree that the inclusion criteria for EMPA-REG and VERTIS-CV included patients with type 2 diabetes and established atherosclerotic cardiovascular disease (ASCVD), and that the populations are similar in both studies, however there were differences in the baseline	Thank you for your comment and agreement with recommending SGLT2 inhibitors (SGLT2i) as a class. However, in response to stakeholder comments the committee have slightly amended the wording of the draft

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				characteristics which may have contributed to the differences in outcomes in the SGLT2 inhibitor CVOTs. The statistical analysis plans also differed in the trials, and the order of primary endpoints in the pre-specified hierarchical testing differed. In some instances, the statistical significance values were marginally achieved (for example, the EMPA-REG study reported time to first MACE as HR (95% CI) 0.86 (0.74–0.99)),[1] meaning that downstream hierarchical testing can continue. Whilst we agree this is necessary to protect the statistical robustness of studies from a methodological perspective, these crude thresholds can mean that data is interpreted as either successful or unsuccessful only, and do not account for differences in study populations. The differences in baseline population risk of events are highlighted in a meta-analysis of the SGLT2 inhibitor CVOTs by McGuire et al, and in the absence of direct head to head comparison studies, this provides context to the difference in results observed in the individual CVOTs.[2] The following points demonstrate the placebo event rates for both EMPA-REG and VERTIS-CV studies to illustrate this point:[2] • For the overall major adverse cardiovascular events (MACE) outcomes the placebo event rate/1000 patient-years were 43.9 and 40.3 for EMPA-REG and VERTIS-CV, respectively. • For overall CV death, the placebo event rate/1000 patient-years was 20.2 and 19.0 for EMPA-REG and VERTIS-CV, respectively. • For overall hospitalisation for heart failure (HHF) the placebo event rate/1000 patient-years was 14.5 and 10.5 for EMPA-REG and VERTIS-CV respectively. Based on the above and in light of the fact that difference in effectiveness within the SGLT2 inhibitor class was not consistently observed across all cardiovascular outcomes in this review, we agree that the SGLT2 inhibitor agents should be treated as a class, rather than individual agents, when referring to the treatment of type 2 diabetes.	recommendations for people at high cardiovascular (CV) risk who can and cannot take metformin to refer to SGLT2i with proven CV benefit. They made this change to take into account that there was a greater degree of uncertainty around the CV benefit associated with ertugliflozin because, depending on the choice of model used in the NMA, it did not consistently show a clinically meaningful reduction in hospitalisation for heart failure compared to placebo, unlike empagliflozin, canagliflozin and dapagliflozin. It was also not statistically significantly better than placebo for the 3-point MACE outcome unlike canagliflozin and empagliflozin. However, in the NMAs ertugliflozin could not be differentiated from the other SGLT2i for hospitalisation for heart failure, non-fatal stroke, non-fatal myocardial infarction, or the 3 point MACE (see the evidence review and rationale in the updated guideline for more details). The committee recommended SGLT2i with proven CV benefit because this wording would enable the prescribers to select a particular drug from within the SGLT2i class if they thought this was clinically justified based on the individual characteristics of their patient, whilst future proofing the recommendation should additional evidence or new SGLT2i be made available.

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				1. Zinman B, et al. N Engl J Med 2015;373:2117-28. McGuire DK, et al. JAMA Cardiol. 2021;6(2):148-158.	
MSD UK Ltd	Evidence review A	045	010	We agree that the following worldview represents the needs of the majority of people living with type 2 diabetes: "There is inherent merit to achieving glycaemic control over and above its potential to prevent future cardiovascular and diabetic events. Because of this, evidence on treatment effects on cardiovascular events supplements evidence on measures of glycaemic control but does not take priority." The UKPDS study has demonstrated the effects of managing glycaemia on the reduction in microvascular complications in diabetes. These complications are costly to the patient, causing disability from loss of vision, foot ulceration/amputation, and chronic kidney disease and a reduction in quality of life. The cost to the health system to manage complications of type 2 diabetes contributes to the majority of health costs. A retrospective observational cohort study of type 2 diabetes patients in the UK who used secondary care services between 2010-2015 provides evidence for the burden of microvascular complications to the healthcare economy.[1] The study identified 26,629 patients with complete medical records. Healthcare resource utilisation (HCRU) and costs were obtained for patients with T2DM without microvascular complications, and for those with moderate or severe complications. Presence of microvascular complications at baseline were evident for 6021 (22.6%) with nephropathy, 824 (3.1%) with neuropathy and 5526 (20.8%) with retinopathy. The analysis estimated that an increase in annual HCRU costs associated with development or progression of severe nephropathy (through inpatient and outpatient interactions) was almost seven times the amount compared to a patient with no complications. The annual cost of severe nephropathy HCRU was £2765. The average HCRU costs associated with severe neuropathy per patient were £8700, over 13 times greater than for a type 2 diabetes patient with no diagnosis of neuropathy. The	Thank you for your comment and agreement on this issue.

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<tr><td></td><td></td><td></td><td></td><td>annual HCRU cost associated with severe retinopathy per patient was £984, which was reportedly higher compared to those for patients with no retinopathy reported.

The prevention of microvascular complications by improving glycaemic control to agreed targets is fundamental in reducing this costly burden for patients and health providers and should remain the priority worldview for a type 2 diabetes patient not deemed at high risk of cardiovascular events.

Chapman D, et al. Diabetes Ther (2019) 10:575–585</td><td></td></tr>
<tr><td>MSD UK Ltd</td><td>Evidence review A</td><td>052</td><td>010</td><td>The evidence review states that metformin + SU + SGLT2 inhibitors is more likely to be cost effective compared to metformin + SU + any other agent (provided that the SGLT2 inhibitors with the lowest acquisition cost is used). This evidence is based on current drug acquisition costs for all oral antihyperglycaemic agents. We want to highlight the upcoming loss of exclusivity for DPP-4 inhibitors; sitagliptin in September 2022 and vildagliptin during Quarter 3, 2022. This loss of exclusivity is likely to have a significant impact on this cost effectiveness calculation.

The UK is one of the Organisation for Economic Co-operation and Development (OECD) countries with the highest generic share of the total volume in the pharmaceutical market with generic share accounting for 85% of the total volume in 2016.[1] Therefore, it is reasonable to assume that significant cost savings will be achieved with the predicted high volume of generic medicine use, combined with the anticipated lower cost of generic versions after the loss of exclusivity for these agents.[2] When looking at simvastatin and atorvastatin as surrogates for the DPP-4 inhibitor genericisation, the predominant statins in the market, after loss of exclusivity the overall expenditure decreased dramatically as demonstrated in the following table:

Cost of different statins in England between 1998 and 2015 in sterling pounds:[3]

<table><tr><th></th><th></th><th>1998</th><th>2000</th><th>2003</th><th>20</th></tr></table></td><td>Thank you for your comment. The committee were aware of the position regarding the patent expiries for various DPP-4 inhibitors. It was agreed that it was not appropriate to model hypothetical future price reductions that may occur, due to uncertainties in the future prices that will be available. However, they agreed that should there be a substantial change in the price of DPP-4 inhibitors in the future, this would need to be reflected in future updates of the guidance. This issue has been passed to the NICE surveillance team, who are responsible for monitoring guidance and identifying when further updates may be necessary.</td></tr>
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<tr><td rowspan="2">Zocor</td><td>10mg</td><td>26.86</td><td>27</td><td>26.2</td><td>25.99</td><td>26.86</td><td>25.72</td><td>25.38</td></tr>
<tr><td>40mg</td><td>43</td><td>43.6</td><td>40.6</td><td>37.81</td><td>40.79</td><td>40.13</td><td>39.96</td></tr>
<tr><td rowspan="2">Generic simvastatin</td><td>10mg</td><td>-</td><td>-</td><td>22.49</td><td>2.43</td><td>1.15</td><td>1.02</td><td>1.02</td></tr>
<tr><td>40mg</td><td>-</td><td>-</td><td>36.01</td><td>5.2</td><td>1.74</td><td>1.4</td><td>1.32</td></tr>
<tr><td rowspan="2">Lipitor</td><td>10mg</td><td>28.37</td><td>26.72</td><td>25.1</td><td>24.32</td><td>22.9</td><td>16.48</td><td>18.44</td></tr>
<tr><td>40mg</td><td>70.67</td><td>71.67</td><td>41.9</td><td>37.52</td><td>31.74</td><td>29.47</td><td>34.89</td></tr>
<tr><td rowspan="2">Generic atorvastatin</td><td>10mg</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>4.13</td><td>1.46</td></tr>
<tr><td>40mg</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>7.21</td><td>1.85</td></tr>
</table>

Given the focus of this guideline on cost-effectiveness, for those patients on sitagliptin who continue to respond and are achieving their treatment targets it is important for them to continue therapy with the healthcare system achieving significant cost savings from September 2022 onwards, without workload intensification or utilising any additional workforce capacity. At the same time ensuring continuity of patient care and outcomes at the forefront.

1. OECD/EU, 'Health at a glance: Europe 2018: State of health in the EU cycle', OECD Publishing Paris (2018)
2. Vondeling, G.T., Cao, Q., Postma, M.J. et al. The Impact of Patent Expiry on Drug Prices: A Systematic Literature Review. Appl Health Econ Health Policy 16, 653–660 (2018).
3. Chapman, SR, Fitzpatrick, RW, Aladul, MI. Has cost inhibited the uptake of more potent statins in England?. Pharmacoepidemiol Drug Saf. 2017; 26: 984– 991</td><td></td></tr>
<tr><td>MSD UK Ltd</td><td>Evidence review A</td><td>058</td><td>025</td><td>Reference to Green et al 2013 should be added as follows:
Green, J. B., Bethel, M. A., Paul, S. K., Ring, A., Kaufman, K. D., Shapiro, D. R., Califf, R. M., & Holman, R. R. (2013). Rationale, design, and organization of a randomized, controlled Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) in patients with type 2 diabetes and established cardiovascular disease. American heart journal, 166(6), 983–989.e7.</td><td>Thank you for your comment. We are unable to reference this paper on page 58 line 25 as it does not contain outcome data for the TECOS trial. Section 1.1.13.1 Effectiveness lists the key paper used for data extraction (which for TECOS is Green et al 2015). However, we have added this reference to the all included studies reference list instead.</td></tr>
<tr><td>MSD UK Ltd</td><td>Evidence review A</td><td>079</td><td>001</td><td>We would like to suggest that the sentence in line 1 be revised as follows:
"No clinical decision thresholds were identified ~~thought his process of~~ by the committee".</td><td>Thank you for your comment. We have amended this sentence to "No clinical decision thresholds were identified through this process by the committee".</td></tr>
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Consultation on draft guideline - Stakeholder comments table
01/09/2021 – 14/10/2021

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MSD UK Ltd	Evidence review A	094	General	Row "other publications associated with this study included in review" - Reference to Green et al 2013 should be added as follows: Green, J. B., Bethel, M. A., Paul, S. K., Ring, A., Kaufman, K. D., Shapiro, D. R., Califf, R. M., & Holman, R. R. (2013). Rationale, design, and organization of a randomized, controlled Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) in patients with type 2 diabetes and established cardiovascular disease. American heart journal, 166(6), 983–989.e7.	Thank you for your comment. We have added this paper to the reference list as requested.
MSD UK Ltd	Evidence review A	162	009 - 011	We would like to suggest that the sentence in lines 9-11 be revised as follows: "The committee agreed that for the purposes of the evidence review analyses ~~that~~ certain interventions would be analysed at class level (DPP-4, insulins and sulfonylureas) and the remining interventions at an individual level (all SGLT2 and GLP-1 interventions)."	Thank you for your comment. We have reworded this sentence in line with your comment.
MSD UK Ltd	Evidence review A	184 - 185	General	Figure 11 Table 29 - HR [95%CI] of ertugliflozin vs placebo for hospitalisation for heart failure is 0.70 [0.54–0.90]. To aid readers' understanding, it should be clarified in the evidence review document whether the value reported in Figure 11 and Table 29 (0.70 [0.49, 1.00]) is due to different weighting applied to each of the studies in the random effects model.	Thank you for your comment. We have added extra sensitivity analyses (see figures 13 and 15 and tables 32 and 34 in the updated evidence review document) in which we used a fixed effect model which gives the original trial HR estimate (0.70, 95% CI 0.54 to 0.90). The interpretation of the models is discussed in section 1.1.11 and reports that in the sensitivity analyses where a fixed effect model was used ertugliflozin was associated with a reduction in hospitalisation for heart failure. This was not seen in the original analyses because this used a random effects model. .
MSD UK Ltd	Evidence review A	221	General	Table 49 - The publication reporting the study results (Green et al 201**5**) should be cited. Green et al. 2013 described the rationale and design of the study but did not include study results.	Thank you for your comment. We have amended the references in the table to Green et al 2015.
MSD UK Ltd	Guideline	016	026	We are concerned that the wording "adverse effect on renal function" is alarmist to a reader and based on the current evidence, is not consistent with the effect of SGLT2 inhibitors on renal function. It is well documented that there is an acute drop in eGFR following first administration of SGLT2 inhibitors which lasts approximately 6 weeks before returning towards baseline eGFR. The acute effect on eGFR decline is hypothesised to be due to haemodynamic effect on renal tubuloglomerular feedback, rather than damage to the structure of kidney.	Thank you for your comment. The committee discussed the stakeholder comments about the renal impact of SGLT2 inhibitors (SGLT2i). They agreed that the existing recommendation was unclear and potentially confusing because it gave no indication of the frequency or when the monitoring should take place. They also recognised that although SGT2i can have a negative effect on renal function this is usually a small reduction in function and not a reason to stop taking the SGLT2i. Taking these points into account

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				Using eGFR slope as a surrogate for chronic kidney disease (CKD) progression in clinical studies has been supported by National Kidney Foundation working groups. Studies which examine the "chronic eGFR slope" are used to omit the period when the known haemodynamic effects of SGLT2 inhibitors may confound the effect of SGLT2 inhibitors on longer-term kidney function decline. Chronic eGFR slope is commonly defined as from time point Week-6 to the end of study treatment.[1] The VERTIS-CV prespecified exploratory analysis investigated the effects of ertugliflozin on eGFR slope. Least squares (LS) mean differences between ertugliflozin and placebo for weekly or yearly eGFR slopes were assessed for the following periods:[1] 1) acute eGFR "dip" period: weekly slope from week 0 (baseline) to week 6; 2) post–eGFR "dip" readjustment period: yearly slope from week 6 to 52; 3) chronic slope: yearly slopes from week 6 to weeks 104, 156, 208, and 260; and 4) total yearly slope from week 0 (baseline) to weeks 52, 104, 156, 208, and 260. During the acute period (from week 0 to 6), least squares mean eGFR slopes (ml/min per 1.73 m^2 per week [95% CI]) were -0.07 (-0.16 to 0.03) and -0.54 (-0.61 to -0.48) for the placebo and ertugliflozin groups, respectively.[1] The placebo-adjusted LS mean difference in eGFR slope (ml/min per 1.73 m^2 per week [95% CI]) was -0.47 (-0.59 to -0.36) (P<0.001). During weeks 6–52, least squares mean eGFR slopes (ml/min per 1.73 m^2 per year [95% CI]) were -0.12 (-0.70 to 0.46) and 1.62 (1.21 to 2.02) for the placebo and ertugliflozin groups, respectively.[1] The placebo-adjusted LS mean difference in eGFR slope (ml/min per 1.73 m^2 per year [95% CI]) was 1.74 (1.03 to 2.45) (P<0.001). The placebo-adjusted LS mean chronic eGFR slopes (ml/min per 1.73 m^2 per year [95% CI]) were 1.43 (1.07 to 1.78), 1.19 (0.95 to 1.42), 1.03 (0.84	the committee have now removed this draft recommendation. Dapagliflozin (an SGLT2 inhibitor) has an additional licensed indication for CKD as well as type 2 diabetes. The committee assume that when making a decision about what to prescribe the clinician will take into account the licensed indications (see the recommendation on choosing drug treatments) and that if a licensed drug option is available, they will choose this over an unlicensed option, and that as part of this process they will also check the doses, cautions and contraindications in the BNF or summary of product characteristics (SPC).

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				to 1.22), and 1.02 (0.84 to 1.20), for the week 6 to weeks 104, 156, 208, and 260 periods, respectively, with all P values <0.001.[1] The placebo-adjusted LS mean chronic eGFR slopes (ml/min per 1.73 m^2 per year [95% CI]) were 0.89 (0.33 to 1.46), 1.13 (0.83 to 1.43), 1.06 (0.85 to 1.27), 0.96 (0.79 to 1.13), and 0.96 (0.80 to 1.11), for the week 0 to weeks 52, 104, 156, 208, and 260 periods, respectively, with all P values <0.003.[1] These results demonstrate the decline in eGFR over time for patients treated with ertugliflozin is attenuated compared to patients treated with placebo, with a consistent benefit from 2-5 years. This provides evidence for the kidney protective effects of SGLT2 inhibitors, which is contradictory to the wording used in the guideline. For prescribers who are less familiar to SGLT2 inhibitors, this wording may persuade them to choose an alternative therapy for a patient with chronic kidney disease (CKD) or at risk of developing CKD, despite the growing level of evidence the SGLT2 inhibitors have protective effects on the kidney. The recently published NICE guideline for CKD states the following:[2] 1.6.7 For adults with CKD and type 2 diabetes, offer an SGLT2 inhibitor, in addition to an ARB or an ACE inhibitor at an optimised dose if: ACR is more than 30 mg/mmol, and they meet the criteria in the marketing authorisation (including relevant eGFR thresholds). Monitor for volume depletion and eGFR decline. In August 2021, not all SGLT2 inhibitors were licensed for this indication. See NICE's information on prescribing medicines. [2021] The draft guideline for Type 2 diabetes in adults: management - SGLT2 inhibitors for chronic kidney disease (update), currently under consultation, states the following:[3]	

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				1.1.2 For adults with type 2 diabetes and CKD, offer an SGLT2 inhibitor, in addition to an ARB or an ACE inhibitor (titrated to the highest dose that they can tolerate), if: • ACR is over 30 mg/mmol and • they meet the criteria in the marketing authorisation (including relevant eGFR thresholds). Monitor for volume depletion and estimated glomerular filtration rate (eGFR) decline. The disparity between the type 2 diabetes NICE guidelines and the CKD NICE guidelines will create more confusion for prescribers. We recommend that the wording is changed to reflect the recommendations in the aforementioned guidelines. 1. Cherney, DZI, et al. CJASN 16: 1345–1354, 2021 2. Chronic kidney disease: assessment and management NICE guideline Published: 25 August 2021. Available at www.nice.org.uk/guidance/ng203 Type 2 diabetes in adults: management. SGLT2 inhibitors for adults with type 2 diabetes and chronic kidney disease. Available at: https://www.nice.org.uk/guidance/gid-ng10246/documents/draft-guideline	
MSD UK Ltd	Guideline	020	005	We are concerned with the wording "stopping medicines that have not worked", this statement is sweeping and does not consider the following points: • Reasons for not working e.g., medication compliance, non-adherence, or persistence. These should be explored with the patient before deciding to stop a medicine • Definition of not worked. This should be based on the agreed goal with the patient, which can be HbA1c target or effect on body weight for example. • Clinical impact of stopping therapy. There are numerous studies which describe the clinical outcomes following cessation of therapy. The inappropriate	Thank you for your comment. Please note that compliance/adherence is already included in a separate bullet of the recommendation on reviewing drug treatments under the heading of optimising their current regimen. Taking stakeholder feedback into account the committee have amended the recommendation on reviewing drug treatment. The committee clarified that they meant stopping medicines that have had no impact on glycaemic control or weigh unless they are expected to have less apparent or measurable benefits such as cardiovascular and renal protection. This change will hopefully reduce the likelihood of people stopping medication that may be of benefit to them.

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				stopping of therapy can lead to increases in HbA1c, increased healthcare utilisation and hospital admissions. This was demonstrated in a retrospective cohort study in the USA of type 2 diabetes adult patients prescribed dual oral antihyperglycaemic agents (OHAs).[1] The study investigated the effect of discontinuation of treatment on clinical outcomes (emergency department visits and all-cause hospitalisations, and glycaemic control) over a 36-month follow-up period. During follow-up, 11.8% and 8.4% of patients who discontinued one or both OHAs, respectively, had one or more hospitalizations vs. 7.6% of patients who were adherent and 8.9% of patients who were non-adherent. Among patients who discontinued one or both OHAs, 23.7% and 18.2%, respectively, had one or more emergency department visits during follow-up vs.15.6% of adherent patients and 18.8% of those who were non-adherent. However, there was no statistically significant difference in HbA1c control (defined as <7.0%) in patients who discontinued treatment vs patients who were adherent to therapy. The CompoSIT I study evaluated the impact of continuing the DPP4 inhibitor, sitagliptin, on glycaemic efficacy and hypoglycaemia when initiating and intensively titrating insulin glargine.[2] This was a multinational, randomised, double-blind, placebo controlled, parallel group, study enrolling 743 type 2 diabetes patients. Eligible patients were on a stable OHA regimen (≥12 weeks) of metformin (≥1500 mg/day) as part of dual or triple combination therapy with a DPP-4 inhibitor and/or sulphonylurea. The mean baseline HbA1c of patients enrolled in the study was 72.6mmol/mol (8.8%). The efficacy comparison of continuing sitagliptin vs withdrawing sitagliptin were measured using the two primary endpoints at a timepoint of 30-weeks: change from baseline HbA1c and documented hypoglycaemia event rate (blood glucose ≤70 mg/dL). The LS mean change from baseline in HbA1c were -20.5mmol/mol and −15.5 mmol/mol for continued sitagliptin and	Please note the committee also recommend considering switching therapies not just stopping, they were also aware of the clinical impact of ineffective therapies such as side effects and issues of polypharmacy particularly in older more frail adults.

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				placebo, respectively. The between-group difference in LS mean change from baseline in HbA1c at week 30 was −5.0 mmol/mol (95% CI –6.4, −3.7; −0.46% [95% CI –0.58, −0.34]; P < 0.001. The incidence of documented hypoglycaemia events per participant year was 1.55 and 2.12 for continuing and withdrawing respectively (event rate ratio 0.73 [95% CI 0.54,0.98] P=0.039). In COMPOSIT-I, the continued use of sitagliptin compared with discontinuation did not result in an increase in hypoglycaemia despite a statistically significant and clinically meaningful greater improvement in glycaemic control in patients initiating and intensively titrating basal insulin. The greater proportion of participants achieving an HbA1c target of <53 mmol/mol [<7.0%] and the greater proportion of participants achieving target HbA1c without hypoglycaemia episodes in the sitagliptin group provide additional data to demonstrate the clinically meaningful glycaemic benefits of continuing sitagliptin in this setting. This data adds to the evidence for the consideration to continue therapy in patients who are not meeting their HbA1c target. 1. Reynolds K, et al. Journal of Diabetes and Its Complications 30 (2016) 1443–1451 Roussel R, et al. Diabetes Obes Metab 2019 Apr;21(4):781-790.	
MSD UK Ltd	Guideline	024	General	Visual summary 3. Insulin therapy - There is evidence from the VERTIS-CV glycaemic sub studies for the efficacy and safety of ertugliflozin in combination with exogenous insulin. VERTIS-CV was a multicentre, randomized, double-blind, placebo-controlled, parallel-group, event-driven study in patients with type 2 diabetes mellitus (T2DM) and established atherosclerotic cardiovascular disease (ASCVD) that included a main cardiovascular (CV) outcomes study and 3 glycaemic sub-studies.[1] In relation to ertugliflozin in combination with insulin, one sub-study evaluated glycaemic and cardiometabolic efficacy and safety of ertugliflozin, added to insulin based	Thank you for your comment. The intent of the visual summaries is to pull together NICE guidance. The TAs for ertugliflozin do not mention its use in combination with insulin and that is why it has not been included here.

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				therapy, in patients with T2DM and ASCVD inadequately controlled by insulin in an 18-week sub-study of VERTIS CV.[2] The primary objectives were to assess the effect of ertugliflozin vs placebo at Week 18 on HbA1c and to evaluate ertugliflozin safety and tolerability.[2] Secondary objectives were assessment of the effect of ertugliflozin vs placebo at Week 18 on fasting plasma glucose, body weight, proportion of patients with HbA1c <7.0%, SBP, DBP, and insulin dose. Patients were randomly assigned (1:1:1) to oral, once daily ertugliflozin 5 mg, 15 mg, or placebo. The analysis included 1065 patients with T2DM and ASCVD. Changes to the background glucose-lowering treatment were not allowed except when patients met predefined glycaemic rescue thresholds or were experiencing clinically significant hypoglycaemia. Inclusion criteria as follows:[2] •Were aged ≥40 years with T2DM (HbA1c 7.0–10.5%, inclusive), with stable, established ASCVD involving the coronary, cerebrovascular, and/or peripheral arterial systems. •Were receiving insulin ≥20 units/day ± metformin ≥1500 mg/day. •Had a stable insulin dose for ≥8 weeks prior to screening and were required to maintain the same dose of insulin for the 18-week duration to enable the assessment of the glycaemic effects of ertugliflozin without the confounding effect of any change in the background insulin dose. •Those using prandial insulin alone were excluded. Overall, 979 (91.9%) patients completed the 18-week follow-up period on study medication.[2] At Week 18, ertugliflozin 5 mg and 15 mg significantly reduced HbA1c vs placebo, (placebo-adjusted LS means change: −0.58% [95% CI −0.71, −0.44] and −0.65% [95% CI −0.78, −0.51], respectively; P < 0.001 for both comparisons). Results were generally consistent across subgroup categories of baseline HbA1c, age, sex, race, ethnicity, and background metformin use. At Week 18, greater reductions from baseline in fasting plasma glucose, body weight, and systolic blood pressure were observed with ertugliflozin vs placebo[2] At Week 18 more patients who received ertugliflozin vs placebo had HbA1c <7.0%, odds ratio (OR) vs placebo at week 18 (95% CI) 2.6 (1.6,	

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				4.1) and 2.5 (1.6, 3.8), for the 5 and 15 mg doses respectively (P < 0.001 for both comparisons).[2] The proportion of patients who had received glycaemic rescue therapy was lower with ertugliflozin vs placebo. Difference in percentage estimate vs placebo at week 18 (95% CI) was −4.6 (−9.1, −0.3) and −5.9 (−10.2, −1.8) for the 5 and 15 mg doses respectively.[2] A small decrease in the mean daily insulin dose was observed with ertugliflozin 15 mg vs placebo. Change from baseline at week 18, mean (SD) for placebo, ertugliflozin 5 and 15 mg: −0.3 (11.5), −0.7 (10.1), −2.1 (10.2).[2] In women, the incidence of genital mycotic infections was higher with ertugliflozin 5 mg (3.4%; P = 0.05) and ertugliflozin 15 mg (3.6%; P = 0.04) compared with placebo (0.0%). The difference in genital mycotic infections was smaller in men; ertugliflozin 5 mg (1.7%) and 15 mg (2.7%) compared with placebo (0.8%). There were no serious adverse events (SAEs) of genital mycotic infections, and no patients discontinued study medication due to a genital mycotic infection. The incidence of urinary tract infection adverse events (AEs) was similar across treatment groups. The incidences of symptomatic, documented, and severe hypoglycaemia were similar across the treatment groups. The incidence of hypovolaemia was low (<2.5%) and similar across treatment groups. There were five patients with SAEs of hypovolaemia (ertugliflozin 5 mg: n = 1, ertugliflozin 15 mg: n = 1, placebo: n = 3) and one with an AE of hypovolaemia (ertugliflozin 15 mg) that led to discontinuation of study medication. This data is clinically relevant; it demonstrates in patients with T2DM and ASCVD receiving insulin ≥20 units/d, ertugliflozin provided clinically meaningful reductions from baseline in HbA1c and fasting plasma glucose at week 18 compared to placebo. These patients are typically difficult to manage in clinical practice (i.e., patients with long-standing T2DM and established ASCVD inadequately controlled on insulin therapy). The SGLT2 inhibitors are suitable agents to use in combination with insulin as the two classes of agents have complementary mechanisms of action on reducing blood glucose. In addition, SGLT2 inhibitors counterbalance the undesirable effect of weight gain with insulin therapy. These results are	

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				consistent with similar studies of SGLT2 inhibitors in combination with insulin and provides support for the SGLT2 inhibitor, ertugliflozin, in patients inadequately controlled on exogenous insulin. In addition to this data, the ertugliflozin SPC does not preclude the combination use of ertugliflozin and insulin, and recommends when used in combination with insulin, a lower dose of insulin may be required to reduce the risk of hypoglycaemia.[3] This reduction in insulin requirements has potential positive effects for the patient, in terms of limiting weight gain caused by exogenous insulin administration. 1. Protocol for: Cannon CP, et al. N Engl J Med 2020;383:1425-35. 2. Lingvay I, et al. Diabetes Obes Metab. 2021;23:1640–1651. Ertugliflozin Summary of Product Characteristics.	
MSD UK Ltd	Guideline	038	004	We are concerned that the wording "adverse effect on renal function" is alarmist to a reader and based on the current evidence, is not consistent with the effect of SGLT2 inhibitors on renal function. It is well documented that there is an acute drop in eGFR following first administration of SGLT2 inhibitors which lasts approximately 6 weeks before returning towards baseline eGFR. The acute effect on eGFR decline is hypothesised to be due to haemodynamic effect on renal tubuloglomerular feedback, rather than damage to the structure of kidney. Using eGFR slope as a surrogate for chronic kidney disease (CKD) progression in clinical studies has been supported by National Kidney Foundation working groups. Studies which examine the "chronic eGFR slope" are used to omit the period when the known haemodynamic effects of SGLT2 inhibitors may confound the effect of SGLT2 inhibitors on longer-term kidney function decline. Chronic eGFR slope is commonly defined as from time point Week-6 to the end of study treatment.[1] The VERTIS-CV prespecified exploratory analysis investigated the effects of ertugliflozin on eGFR slope. Least squares (LS) mean differences between ertugliflozin and placebo for weekly or yearly eGFR slopes were assessed for the following periods:[1]	Thank you for your comment. The committee discussed the stakeholder comments about the renal impact of SGLT2 inhibitors (SGLT2i). They agreed that the existing recommendation was unclear and potentially confusing because it gave no indication of the frequently or when the monitoring should take place. They also recognised that although SGT2i can have a negative effect on renal function this is usually a small reduction in function and not a reason to stop taking the SGLT2i. Taking these points into account the committee have now removed this draft recommendation.

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				1) acute eGFR "dip" period: weekly slope from week 0 (baseline) to week 6; 2) post–eGFR "dip" readjustment period: yearly slope from week 6 to 52; 3) chronic slope: yearly slopes from week 6 to weeks 104, 156, 208, and 260; and 4) total yearly slope from week 0 (baseline) to weeks 52, 104, 156, 208, and 260. During the acute period (from week 0 to 6), least squares mean eGFR slopes (ml/min per 1.73 m^2 per week [95% CI]) were -0.07 (-0.16 to 0.03) and -0.54 (-0.61 to -0.48) for the placebo and ertugliflozin groups, respectively.[1] The placebo-adjusted LS mean difference in eGFR slope (ml/min per 1.73 m^2 per week [95% CI]) was -0.47 (-0.59 to -0.36) (P<0.001). During weeks 6–52, least squares mean eGFR slopes (ml/min per 1.73 m^2 per year [95% CI]) were -0.12 (-0.70 to 0.46) and 1.62 (1.21 to 2.02) for the placebo and ertugliflozin groups, respectively.[1] The placebo-adjusted LS mean difference in eGFR slope (ml/min per 1.73 m^2 per year [95% CI]) was 1.74 (1.03 to 2.45) (P<0.001). The placebo-adjusted LS mean chronic eGFR slopes (ml/min per 1.73 m^2 per year [95% CI]) were 1.43 (1.07 to 1.78), 1.19 (0.95 to 1.42), 1.03 (0.84 to 1.22), and 1.02 (0.84 to 1.20), for the week 6 to weeks 104, 156, 208, and 260 periods, respectively, with all P values <0.001.[1] The placebo-adjusted LS mean chronic eGFR slopes (ml/min per 1.73 m^2 per year [95% CI]) were 0.89 (0.33 to 1.46), 1.13 (0.83 to 1.43), 1.06 (0.85 to 1.27), 0.96 (0.79 to 1.13), and 0.96 (0.80 to 1.11), for the week 0 to weeks 52, 104, 156, 208, and 260 periods, respectively, with all P values <0.003.[1] These results demonstrate the decline in eGFR over time for patients treated with ertugliflozin is attenuated compared to patients treated with placebo, with a consistent benefit from 2-5 years. This provides evidence	

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				for the kidney protective effects of SGLT2 inhibitors, which is contradictory to the wording used in the guideline. For prescribers who are less familiar to SGLT2 inhibitors, this wording may persuade them to choose an alternative therapy for a patient with chronic kidney disease (CKD) or at risk of developing CKD, despite the growing level of evidence the SGLT2 inhibitors have protective effects on the kidney. The recently published NICE guideline for CKD states the following:[2] 1.6.7 For adults with CKD and type 2 diabetes, offer an SGLT2 inhibitor, in addition to an ARB or an ACE inhibitor at an optimised dose if: ACR is more than 30 mg/mmol, and they meet the criteria in the marketing authorisation (including relevant eGFR thresholds). Monitor for volume depletion and eGFR decline. In August 2021, not all SGLT2 inhibitors were licensed for this indication. See NICE's information on prescribing medicines. [2021] The draft guideline for Type 2 diabetes in adults: management - SGLT2 inhibitors for chronic kidney disease (update), currently under consultation, states the following:[3] 1.1.2 For adults with type 2 diabetes and CKD, offer an SGLT2 inhibitor, in addition to an ARB or an ACE inhibitor (titrated to the highest dose that they can tolerate), if: • ACR is over 30 mg/mmol and • they meet the criteria in the marketing authorisation (including relevant eGFR thresholds). Monitor for volume depletion and estimated glomerular filtration rate (eGFR) decline. The disparity between the type 2 diabetes NICE guidelines and the CKD NICE guidelines will create more confusion for prescribers. We recommend that the wording is changed to reflect the recommendations in the aforementioned guidelines.	

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				1. Cherney, DZI, et al. CJASN 16: 1345–1354, 2021 2. Chronic kidney disease: assessment and management NICE guideline Published: 25 August 2021. Available at www.nice.org.uk/guidance/ng203 Type 2 diabetes in adults: management. SGLT2 inhibitors for adults with type 2 diabetes and chronic kidney disease. Available at: https://www.nice.org.uk/guidance/gid-ng10246/documents/draft-guideline	
Napp Pharmaceuticals Ltd.	Guideline	013	015 - 018	Napp are concerned by the decision of NICE to consider all drugs in a specific class as a group, rather than as individual agents. This approach does not reflect the core principles of evidence-based medicine, and is in opposition to the approach used by MHRA / EMA whereby each individual agent is considered on individually. Where a specific class of agents has demonstrated highly similar efficacy and safety data across all agents within that class, including in dedicated cardiovascular outcome trials, this approach may be rational and suitable – e.g. for the DPP-IVi class of agents. However, for those classes where efficacy and safety outcome data have proven to be heterogenous, this approach may lead to NICE providing treatment recommendations that are not supported by, or are even in contradiction of, the actual RCT evidence base for some specific agents. In this regard, Napp would particularly like to highlight the historical case of the biguanide class – where the agents metformin and phenformin were once considered comparable in safety and efficacy, but now have been conclusively demonstrated to produce very different safety outcomes, despite their high degree of molecular similarity. NICE's current approach is particularly concerning in the case of the SGLT2i class, where there is significant variance in RCT results between the various agents. Namely, the CardioVascular Outcome Trials (CVOTs) for the different agents have shown marked differences in cardiovascular safety amongst the class. For the agents empagliflozin and canagliflozin, statistically significant reductions in Major Adverse Cardiovascular Events (MACE) were demonstrated in both agents' respective CVOTs. Subsequently, though the dapagliflozin CVOT failed to show a statistically significant reduction in MACE, this trial did demonstrate significant reductions in other cardiovascular endpoints, and the cardiovascular	Thank you for your comment. Please note that although the recommendations may refer to a class of drugs (SGLT2 inhibitors for example) where the committee have agreed this appropriate, the SGLT2 inhibitors and GLP-1s were analysed as individual drugs and there was no a priori assumption that there was a class level of effect for these treatments. The only 2 classes which were grouped before analyses were performed were (as mentioned by the stakeholder) were the DPP-4s and sulfonylureas and this approach was based on committee consensus. Thank you for your comment. The committee reviewed the stakeholder comments but decided to continue treating SGLT2 inhibitors (SGLT2i) as a class for the following reasons: • There was a degree of uncertainty around whether there were real differences in cardiovascular (CV) benefits between the SGLT2i based on the clinical trial evidence and results from the NMAs. ○ Firstly, for hospitalisation for heart failure, the SGLT2i empagliflozin, canagliflozin, and dapagliflozin produced a clinically meaningful reduction compared with placebo in the random effects NMA model. However, in the sensitivity analyses using a fixed effect model ertugliflozin also showed a clinically meaningful reduction compared to placebo, which reflects the original clinical trial data. The NMA results

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				benefits of dapagliflozin have now been further elucidated in the DAPA-HF trial. All of this outcome data is in contrast to that of the ertugliflozin CVOT, which showed no benefit of this agent on MACE or any other cardiovascular outcome – other than a reduction in hospitalisation for heart failure, which was not considered a valid result due to the endpoint statistical testing hierarchy. The absence of any cardiovascular benefit for this agent is also evident in the licensed indication: • Cana-, Dapa-, and Empa- gliflozin are all indicated *"for the treatment of insufficiently controlled T2DM",* with specific reference in section 4.1 of the respective SmPCs to the effect of each of these agents on cardiovascular outcomes. • Whereas the indication of ertugliflozin is only to *"improve glycaemic control"*, with no mention made of any cardiovascular effects. This is directly comparable to the licensed indication for all other agents that have not demonstrated any cardiovascular benefits, e.g. the DPP-IVi class. The difference in wording of the ertugliflozin label vs the other gliflozins is subtle but meaningful – ertugliflozin is <u>not licensed</u> to be prescribed for cardiovascular benefit, as there is strong evidence that there is not any benefit. Therefore, by treating the entire SGLT2i class as whole, NICE are potentially endorsing not only prescribing of ertugliflozin that is not supported by any clinical evidence, but also off-label use of this agent, alongside the other three SGLT2i which are indicated for cardiovascular risk reduction in T2DM. This is even more problematic when viewed in context of the recommendation on page 14 line 13 that *"if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost"*: In addition to the more restrictive licence, the only other notable difference between ertugliflozin and the other agents in this class is that is has a lower acquisition cost. Therefore, the sum of these various recommendations is effectively that ertugliflozin will be the NICE	could not differentiate between the SGLT2i for this outcome. o Secondly, for the 3 point MACE outcome, only canagliflozin and empagliflozin produced a statistically significant reduction compared to placebo but the SGLT2i could not be differentiated from each other in the NMA. o Thirdly for all cause and CV mortality empagliflozin showed a clinically meaningful reduction compared to placebo and the other SGLT2i, but the remaining SGLT2i could not be differentiated from each other or placebo in the NMA. o Fourthly, for non-fatal MI and non-fatal stroke the NMAs could not differentiate between empagliflozin, canagliflozin, ertugliflozin and placebo. The data for dapagliflozin was reported differently and could not be included in the NMAs. From the clinical trial data dapagliflozin could not be differentiated from placebo for MI and was not meaningfully different from placebo for stroke. o Finally, only dapagliflozin showed a clinically meaningful improvement in severe hypoglycaemia compared to placebo but the remaining SGLT2i could not be differentiated from each other and placebo in the NMA. • There was also a degree of uncertainty around the cost-effectiveness of individual SGLT2i in the economic modelling. Although only dapagliflozin was cost-effective at a threshold of £20,000/quality-adjusted life year (QALY) across all model scenarios and CV risk groups it could not be differentiated from the other SGLT2i in the NMA apart from for the all-cause and CV mortality outcomes where it was clinically meaningfully worse than empagliflozin. The ranking of ICERs for the

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				recommended SGLT2i for patients with established (or high risk of) CVD, despite there being clear RCT evidence of no CVD benefit associated with this agent, and this recommendation being in contravention of the current ertugliflozin licensed indication.	other SGLT2i varied across model scenarios and risk groups. The committee agreed that there was sufficient uncertainty in the economic modelling (caused in turn by uncertainty in the underlying clinical data) to mean that they were not sufficiently confident that these different ICERs represented true underlying differences in cost-effectiveness, as opposed to simply random variation in the results between different SGLT2 trials. • Taking the cost-effectiveness and clinical results into account the committee decided against only recommending dapagliflozin and instead made recommendations for the SGLT2i as a class. However, they recognised that there was a greater degree of uncertainty around the CV benefit associated with ertugliflozin because, depending on the choice of model used in the NMA, it did not consistently show a clinically meaningful reduction in hospitalisation for heart failure compared to placebo, unlike empagliflozin, canagliflozin and dapagliflozin. It was also not statistically significantly better than placebo for the 3-point MACE outcome unlike canagliflozin and empagliflozin. The committee therefore recommended SGLT2i with proven CV benefit because this wording would enable the prescribers to select a particular drug from within the SGLT2 class if they thought this was clinically justified based on the individual characteristics of their patient, whilst future proofing the recommendation should additional evidence or new SGLT2s be made available. As per the recommendation on choosing drug treatment, once the clinical circumstances and needs of the person with type 2 diabetes, including their need for CV protection, have been taken into account, if 2 drugs in the same class are suitable for that individual then the prescriber is still expected to choose the option with the

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					lowest acquisition cost to help use NHS resources wisely. Please see evidence review A for more a more detailed explanation of the analyses that were carried out and the committee's discussion of the results.
Napp Pharmaceuticals Ltd.	Guideline	013	018	Text box - It is unclear what message this text box is trying to convey or what it is referring to. The link is only to the MHRA Drug Safety Update webpage in general, and not to any specific safety advice. If the statement is intended to imply that there is specific MHRA safety advice on use on concomitant use of pioglitazone and SGLT2i, then the statement is incorrect and should be removed. (In the past dapagliflozin was not licensed to be used in conjunction with pioglitazone, but this restriction has now been removed). If the statement is intended to simply imply that there is MHRA safety advice for both pioglitazone and for SGLT2 inhibitors (when the two are used independently), then this is true. However, in this case it is then unclear why only these agents are mentioned here – as MHRA safety advice also exists for DPP-IVi's, GLP-1 RA's, and insulin.	Thank you for your comment. In response to stakeholder consultation comments the committee have removed the text boxes containing the MHRA safety advice because they agreed that prescribers are expected to consult MHRA alerts, the BNF and summary of product characteristics (SPC) for safety information and that it was therefore unnecessary and potentially confusing to refer to MHRA alerts in the guideline.
Napp Pharmaceuticals Ltd.	Guideline	016	025	The statement that SGLT2i's *"have an adverse effect on renal function and this needs to be monitored*" is incorrect and must be removed or significantly revised. When SGLT2i agents were first introduced into clinical use, there was some concern that they could result in a higher rate of Acute Kidney Injury (AKI) due to their expected diuretic effect, however all trials of these agents have thus far demonstrated that the converse is in fact true – with a significantly reduced risk of AKI in patients receiving these agents. Furthermore, there are no other data showing any "adverse effect on renal function" with any SGLT2i - on the contrary there is compelling and high-quality evidence that both canagliflozin and dapagliflozin are extremely beneficial to T2DM patients with CKD/DKD, and both agents are now specifically licensed as renoprotective agents independent of their glycaemic benefits. There is also reasonable quality evidence that both empagliflozin and ertugliflozin are renoprotective, though this has not yet been demonstrated conclusively and neither are licensed as renoprotective agents.	Thank you for your comment. The committee discussed the stakeholder comments about the renal impact of SGLT2 inhibitors (SGLT2i). They agreed that the existing recommendation was unclear and potentially confusing because it gave no indication of the frequency or when the monitoring should take place. They also recognised that although SGT2i can have a negative effect on renal function this is usually a small reduction in function and not a reason to stop taking the SGLT2i. Taking these points into account the committee have now removed this draft recommendation.

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				The second half of this sentence ("*…and this needs to be monitored"*), is also unhelpful without any context or qualification as to what biomarkers of renal function should be monitored, why they should be monitored, or what threshold values should be cause for clinical concern. Initiation of SGLT2i therapy in patients with T2DM & CKD/DKD has been shown to (typically) result in a profound reduction in albuminuria, and a measurable (though relatively small) reversible decrease in eGFR. Given that a reduction in albuminuria would never be perceived as *"an adverse effect on renal function"*, Napp assume that this statement is intended to refer to the observed reversible decrease in eGFR. This unqualified statement is therefore likely be perceived by many readers as implying that "SGLT2i therapy should be discontinued if eGFR acutely declines after initiation". This would constitute inappropriate clinical advice, as rapid decline in eGFR after SGLT2i initiation is believed to be representative of a reversal of pathological glomerular hyperfiltration rather than loss of filtration capacity. There are no data to suggest that a large (but <30%) decrease in eGFR on SGLT2i initiation is associated with any acute or chronic adverse effect. On the contrary, there are now data suggesting that a larger initial decrease in eGFR on initiation of SGLT2i therapy is correlated with a lower subsequent long-term decrease in eGFR. A very good summary of these considerations can be found in this recently published article: https://cjasn.asnjournals.org/content/16/8/1278 Napp strongly suggest that either the recommendation to monitor eGFR after SGLT2i initiation is simply removed (which is in line with both current clinical opinion and SGLT2i product licences), or if NICE wish to retain this statement, then an explanation should be added as to what variance in eGFR can be considered normal *vs.* abnormal, and what clinical actions are appropriate in either scenario. Napp suggest a suitable starting point for drafting this guidance could be the section of this NICE CKS that describes management of serum creatinine and eGFR on initiation/titration of ACE inhibitors. Though this	

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				CKS refers to a different class of agents, the fundamental principles are highly analogous to the SGLT2i class: ACEi are well-known to cause an acute, reversible decline in eGFR on initiation/titration via direct intrarenal efferent vasodilation, which leads to reduced intraglomerular filtration pressure and a long-term renoprotective effect: https://pubmed.ncbi.nlm.nih.gov/8879974/. This is directly comparable to the acute, reversible, decline in eGFR; decrease in glomerular filtration pressure, and renoprotective effect seen with use of SGLT2i in T2DM & CKD (albeit that this effect occurs via afferent arteriole constriction): care.diabetesjournals.org/content/39/Supplement_2/S165. The recommendations made with respect to threshold creatinine and eGFR levels in the above mentioned CKS are specifically intended to aid the healthcare professional in distinguishing clinically between beneficial alterations in glomerular haemodynamics *vs* other distinct pathological processes, both of which manifest as acutely decreased eGFR. This guidance could therefore be useful in developing similar guidance for SGLT2i initiation in this population, or may even be considered to be broadly applicable across both drug classes in its current form.	
Napp Pharmaceuticals Ltd.	Guideline	018	General	Visual Summary 2 - Box containing the wording "Established CVD" - This box should say "Established CVD or **Heart Failure**" in order to be consistent with the guidance given in section 1.7.5	Thank you for your comment. We have amended this wording in line with the guideline.
Napp Pharmaceuticals Ltd.	Guideline	018	General	Visual Summary 2 - Box outlined with a dashed line - There is a transposition of L and G in SGLT2 in the last sentence.	Thank you for your comment. The typo has been amended.
Napp Pharmaceuticals Ltd.	Guideline	018	General	Visual Summary 2 - Box titled "Offer" under the established CVD section - Currently the layout in this box is somewhat ambiguous in that it could be misinterpreted as advising *"Offer metformin, or if there is GI disturbance offer metformin MR and an SGLT2 inhibitor*" Whereas the intended guidance is *"Offer metformin (or metformin MR if GI disturbance) and offer an SGLT2 inhibitor"*. A small change to the layout here should be sufficient to make the distinction clear.	Thank you for your comment. We have switched the pathways so the 'offer' recommendation comes before the 'consider' recommendation as the committee thought this was clearer.
Napp Pharmaceuticals Ltd.	Guideline	018	General	Visual Summary 2 - Napp do not believe it is appropriate to recommend treatment with ertugliflozin specifically for cardiovascular risk reduction, as this is not supported by the data or product label. Please see comment 1 above.	Thank you for your comment. The committee reviewed the stakeholder comments but decided to continue treating

					SGLT2 inhibitors (SGLT2i) as a class for the following reasons: • There was a degree of uncertainty around whether there were real differences in cardiovascular (CV) benefits between the SGLT2i based on the clinical trial evidence and results from the NMAs. o Firstly, for hospitalisation for heart failure, the SGLT2i empagliflozin, canagliflozin, and dapagliflozin produced a clinically meaningful reduction compared with placebo in the random effects NMA model. However, in the sensitivity analyses using a fixed effect model ertugliflozin also showed a clinically meaningful reduction compared to placebo, which reflects the original clinical trial data. The NMA results could not differentiate between the SGLT2i for this outcome. o Secondly, for the 3 point MACE outcome, only canagliflozin and empagliflozin produced a statistically significant reduction compared to placebo but the SGLT2i could not be differentiated from each other in the NMA. o Thirdly for all cause and CV mortality empagliflozin showed a clinically meaningful reduction compared to placebo and the other SGLT2i, but the remaining SGLT2i could not be differentiated from each other or placebo in the NMA. o Fourthly, for non-fatal MI and non-fatal stroke the NMAs could not differentiate between empagliflozin, canagliflozin, ertugliflozin and placebo. The data for dapagliflozin was reported differently and could not be included in the NMAs. From the clinical trial data dapagliflozin could not be differentiated from placebo for MI and was not meaningfully different from placebo for stroke.

					○ Finally, only dapagliflozin showed a clinically meaningful improvement in severe hypoglycaemia compared to placebo but the remaining SGLT2i could not be differentiated from each other and placebo in the NMA. • There was also a degree of uncertainty around the cost-effectiveness of individual SGLT2i in the economic modelling. Although only dapagliflozin was cost-effective at a threshold of £20,000/quality-adjusted life year (QALY) across all model scenarios and CV risk groups it could not be differentiated from the other SGLT2i in the NMA apart from for the all-cause and CV mortality outcomes where it was clinically meaningfully worse than empagliflozin. The ranking of ICERs for the other SGLT2i varied across model scenarios and risk groups. The committee agreed that there was sufficient uncertainty in the economic modelling (caused in turn by uncertainty in the underlying clinical data) to mean that they were not sufficiently confident that these different ICERs represented true underlying differences in cost-effectiveness, as opposed to simply random variation in the results between different SGLT2 trials. • Taking the cost-effectiveness and clinical results into account the committee decided against only recommending dapagliflozin and instead made recommendations for the SGLT2i as a class. However, they recognised that there was a greater degree of uncertainty around the CV benefit associated with ertugliflozin because, depending on the choice of model used in the NMA, it did not consistently show a clinically meaningful reduction in hospitalisation for heart failure compared to placebo, unlike empagliflozin, canagliflozin and dapagliflozin. It was also not statistically significantly better than placebo for the 3-point MACE outcome unlike canagliflozin and empagliflozin. The committee therefore recommended SGLT2i with proven CV benefit because this wording would enable the prescribers to select a particular drug from within the

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					SGLT2 class if they thought this was clinically justified based on the individual characteristics of their patient, whilst future proofing the recommendation should additional evidence or new SGLT2s be made available. As per the recommendation on choosing drug treatment, once the clinical circumstances and needs of the person with type 2 diabetes, including their need for CV protection, have been taken into account, if 2 drugs in the same class are suitable for that individual then the prescriber is still expected to choose the option with the lowest acquisition cost to help use NHS resources wisely. Please see evidence review A for more a more detailed explanation of the analyses that were carried out and the committee's discussion of the results.
Napp Pharmaceuticals Ltd.	Guideline	018	General	Visual Summary 2 - Large box on the far left titled "Consider" - We suggest just representing all four SGLT2i in this box with a single light grey shape containing the words "SGLT2 inhibitor ('flozin'), in the same style as this current appears in the High-risk CVD section. All four SGLT2i are equally as appropriate in this population, therefore there doesn't seem to be any benefit in naming each agent separately. References to TA390 and TA572 could be added as footnotes instead – this approach would considerably increase readability. However, if you do wish to retain all four SGLT2i mentioned individually by name in this box, please list them in alphabetical order.	Thank you for your comment. The SGLT2 inhibitors are now in alphabetical order. The committee agreed that listing and linking to all the relevant TAs was useful.
Napp Pharmaceuticals Ltd.	Guideline	019	General	Visual Summary 4 - Box outlined with a dashed line - There is a transposition of L and G in SGLT2 in the last sentence.	Thank you for your comment. This has been corrected.
Napp Pharmaceuticals Ltd.	Guideline	019	General	Visual Summary 4 - Renal and hepatic impairment columns - There are very large intra-class variations licensing for use in renal or hepatic impairment for several of the classes listed here. Therefore, trying to provide a single summary guidance statement across a whole class is unlikely to provide any useful information at best, and at worst could lead to unsafe recommendations. For example, just within the DPPIV-i class	Thank you for your comment. The content in the table has been updated for specific medicines rather than for medicine classes.

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				the renal impairment guidance varies from no dose adjustment at any level of renal impairment (linagliptin), to 75% dose reduction in severe renal impairment (sitagliptin). Napp suggest deletion of these two columns.	
Napp Pharmaceuticals Ltd.	Guideline	021	012	This comment relates to the entirety of the section of text entitled *"Treatment options if further interventions are needed".* Most of this section has been greyed out (i.e. not open for comment), but it appears that a large portion of this section is completely missing on the draft document sent out for consultation: The right-hand side of Visual Summary 3 outlines an algorithm for further intervention where there is a change in cardiovascular risk status, independent of the algorithm for further intervention relating to HbA1c control. The guidance for further intervention relating to HbA1c control is fully described in the text of this section, but there is no mention in the text of the recommended treatment approach for patients with a change in cardiovascular risk status. This is confusing as the visual summary and the text therefore seem to contradict one another?	Thank you for your comment. In the guideline the recommendation on what action to take if there is a change in cardiovascular (CV) risk are presented in a separate section above the section on 'Treatment options if further interventions' are needed, called 'reviewing drug treatments'. This recommendation covers in people who are already being treated for type 2 diabetes who have high CV risk or established CV disease and could benefit from having an SGLT2 in addition to or instead of one of their current drugs. It also covers people with type 2 diabetes who go onto develop either of these conditions. In the visual summary, these recommendations have been combined into a single diagram for simplicity.
Napp Pharmaceuticals Ltd.	Guideline	024	General	Visual Summary 3 - Box outlined with a dashed line - There is a transposition of L and G in SGLT2 in the last sentence.	Thank you for your comment. We have corrected the typo.
Napp Pharmaceuticals Ltd.	Guideline	024	General	Visual Summary 3 - Large box on the far left titled "Consider" - Please see comment 12 above – we suggest implementing the same change here for clarity.	Thank you for your comment. We have switched the pathways so the 'offer' recommendation comes before the 'consider' recommendation as the committee thought this was clearer.
Napp Pharmaceuticals Ltd.	Guideline	028	019 (text box)	The link is not to any specific MHRA safety advice on SGLT2i, it is just a link to the MHRA Drug Safety Update Homepage. It is also not clear which of the various MHRA historical safety advice relating to SGLT2i's it is referring to – many of the listings on the linked website are several years old and have been superseded by subsequent safety warnings, and/or have been fully incorporated into the relevant product labels rendering the separate safety alert redundant.	Thank you for your comment. Use of landing pages, rather than the specific SGLT2 inhibitor information webpage, is because external webpages often change these specific web addresses meaning that the links in the guideline would soon not work. Landing page web addresses are changed much less frequently and so are preferred. While we agree that older alerts and safety warnings might now be historical, the MHRA webpage would still be the place to find any new or updated safety information. However, in response to stakeholder consultation comments the committee have removed the text boxes containing the MHRA safety advice

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					because they agreed that prescribers are expected to consult MHRA alerts, the BNF and summary of product characteristics (SPC) for safety information and that it was therefore unnecessary and potentially confusing to refer to MHRA alerts in the guideline.
Napp Pharmaceuticals Ltd.	Guideline	037	011 – 022	Napp agree that the risk of DKA should be assessed in all patients starting treatment on an SGLT2i, as although rare this adverse event can be life-threatening. The committee only note here that it should be checked that the patient is not following a very-low carbohydrate or ketogenic diet in relation to this concern. Napp strongly recommend that the following patient characteristics should also be listed here as particular cause for concern in relation to risk of DKA: • History of any prior DKA (contraindication) • Excessive alcohol intake (contraindication) • Progression to insulin with 1 year of diagnosis (contraindication, as it indicated potential for misdiagnosis of another form of diabetes) • History of, or suspected high risk of, any eating disorder (caution) • BMI < 25 kg/m^2 (caution) For further information on this topic, a useful summary of the issue from the EMA PRAC is available here: https://www.ema.europa.eu/en/documents/referral/sglt2-inhibitors-article-20-procedure-assessment-report_en.pdf	Thank you for your comment. The recommendation on choosing drug treatment includes the need for the healthcare professionals to consider safety. Following stakeholder consultation, the committee have reworded the recommendation on what to check before starting an SGLT2 inhibitor. This now covers whether the person may be at increased risk of diabetic ketoacidosis (DKA) if they take an SGLT2 inhibitor and includes some examples of when a person might have a higher risk of DKA. This list includes a previous episode of DKA, they are unwell with intercurrent illness, or are following a very low carbohydrate or ketogenic diet, but is not intended to be exhaustive.
Napp Pharmaceuticals Ltd.	Guideline	038	001 - 007	Please refer to comment 3 above. The statement that "drug-induced renal damage could become widespread" with increased SGLT2i usage is not supported by any trial data, and has not been observed in any post-marketing pharmacovigilance analysis, despite extensive clinical use of these agents worldwide for nearly a decade.	Thank you for your comment. **T**he committee discussed the stakeholder comments about the renal impact of SGLT2 inhibitors (SGLT2i). They agreed that the existing recommendation was unclear and potentially confusing because it gave no indication of the frequently or when the monitoring should take place. They also recognised that although SGT2i can have a negative effect on renal function this is usually a small reduction in function and not a reason to stop taking the SGLT2i. Taking these points into account the committee have now removed this draft recommendation.

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Napp Pharmaceuticals Ltd.	Guideline	039	020 - 022	It is unclear why the committee believe that an increase in the use of SGLT2i will increase renal function testing. No additional renal function testing is recommended for patients receiving SGLT2i, and furthermore NICE already recommend that all T2DM patients receive regular renal function testing as part of the nine recommended care processes. In addition to this, the NHS National Diabetes Audit regularly highlights the problem of insufficient renal function testing across many areas of the country - leading to unnecessary progression and burden of CKD/DKD in T2DM patients. Any intervention or guideline that results in increased renal function testing is very much a positive development rather than an unnecessary cost.	Thank you for your comment. The committee discussed the stakeholder comments about the renal impact of SGLT2 inhibitors (SGLT2i). They agreed that the existing recommendation was unclear and potentially confusing because it gave no indication of the frequently or when the monitoring should take place. They also recognised that although SGT2i can have a negative effect on renal function this is usually a small reduction in function and not a reason to stop taking the SGLT2i. Taking these points into account the committee have now removed this draft recommendation.
Napp Pharmaceuticals Ltd.	Guideline	043	004	The statement that GLP-1 mimetics are weekly injections is not correct – some of the agents are weekly injections, but several of them are daily injections.	Thank you for your comment. We have amended the wording to 'may require fewer or less frequent injections".
Newcastle University (NCL)	Guideline	006	028	Add after 1.3.5 - Add new paragraph: 'Discuss the possibility of aiming to achieve long term remission of type 2 diabetes.' This is essential to reflect the research findings from 2011 onwards that type 2 diabetes should no longer be regarded as an inevitably progressive, lifelong condition. This is underscored by the recent publication of a joint statement from the American Diabetes Association, the European Association for the study of Diabetes and Diabetes UK on the exact definition of remission of type 2 diabetes (https://doi.org/10.2337/dci21-0034). To ignore international expert opinion on the potential for achieving remission of this disease appears illogical. Following elucidation of the reversible pathophysiology of the condition, The DiRECT RCT demonstrated feasibility of achieving remission merely by training nurses (or dietitians) in Primary Care (http://dx.doi.org/10.1016/S2213-8587(19)30068-3). The findings have been repeated in many countries, and in a strict RCT format in the Diadem-1 trial. The NHS pilot launch to determine the most cost effective way to deliver remission of type 2 diabetes is underway. In its current form, the Guideline is focussed on use of drugs. Good care for the individual with type 2 diabetes must include discussion of the possibility of achieving long term remission.	Thank you for your comment. The section of the guideline covering dietary advice and bariatric surgery was not prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest existing recommendations needed amending. However, we will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.

Type 2 diabetes in adults: management (update)

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NHS County Durham CCG	Guideline	010 - 011	020	Figure 1 - We feel that "consider relaxing the target Haba1c level... older... frail" page 11, line 20 is at odds with the rhetoric of figure 1 and the visual analogue scales suggesting this will be a truly personalised plan of patient's choice	Thank you for your comment. All NICE guidelines say, on their landing page, that when exercising their judgement, 'professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian'. In particular, the use in NICE guidelines of the word 'consider', rather than 'offer' or similar, indicates a particular need to take into account the individual needs, preferences, values and circumstances of the person. Figure 1 and the PDA are provided to support those discussions if the healthcare professional and person with diabetes wish to make use of them.
NHS County Durham CCG	Guideline	016	008	Please drop the link to previous Technology assessments as advice on the use of SGLT2 drugs in CKD in TA572/ TA390 does not reflect current practice and or draft guidance: GID-NG10246. It may also be a source of confusion – see next comment	Thank you for your comment. This guideline update (2021) has looked at the clinical and cost-effectiveness evidence for SGLT2 inhibitors in people with cardiovascular disease or at high risk of developing cardiovascular disease and recommends SLGT2 inhibitors in a wider population than the technology appraisals published before August 2021. However, the new recommendations only cover people with established cardiovascular disease or at high risk of cardiovascular disease. The technology appraisals TA390 and TA572 are still regarded as current NICE guidance, as such the recommendations and requirements are still in place for those people meeting the criteria for use.
NHS County Durham CCG	Guideline	017	001	We also commented on this in GID-NG10246. Between the two guidelines there is no clarity, and perhaps contradictory advice, as to how SGLT2s should be introduced for people who diabetes, CKD, and raised ACRs. Should they be used as first-line treatments (as with heart failure)? Should they only be added later but as the preferential drug for anyone with CKD? Should they be restricted to people with high ACRs and according	Thank you for your comment. The renal benefits of using SGLT2 inhibitors in people with type 2 diabetes and CKD was not within the scope of this work. The committee did not

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				to the stipulations in the confusing TA guidance (see comment above) which suggests they are not first choice 'second line drugs'. *This will be confusing for clinicians on the ground, and we recommend that this is corrected before publication*	review any evidence relating to this group and are unable to answer your questions on this topic. The renal benefits of using SGLT2 inhibitors in people with type 2 diabetes and CKD have been assessed in a separate piece of work that has recently been out for stakeholder consultation and was published in November 2021. The final recommendations on renal and cardiovascular benefits will be brought together in a single updated guideline document when this current work on cardiovascular benefits is published in 2022. A cross reference to the section on CKD where these recommendations sit is included at the start of the initial treatment section on the guideline which will hopefully make it clear that they are applicable from this stage in the treatment pathway onwards.
NHS South Sefton Clinical Commissioning Group	Guideline	010		Figure 1 as a whole may be difficult to understand for some people living with type 2 diabetes even if a healthcare professional talks this through with them. It is appreciated that the first statement which includes the consideration of "severe hypos" is being used as part of the discussion with the patient to help with target setting. Severe hypos would be a problem whether some one was driving or not and are reported to be associated with an increase in major cardiovascular events and death. Hypoglycaemia other than when severe also has recognised problems but if this statement is to be included would it be sufficient to consider whether a "hypo" would or would not be a problem, as it is not always possible to avoid hypos and in general, most people living with a diagnosis of diabetes do not like hypos and want to avoid them as much as possible. Question 5 :- putting visuals alongside recommendations they summarise is helpful as it avoids the need to scroll through to find the relevant visual at the end. Questions 6 & 7:- visual summaries in pdf format which can copied and laminated and used for reference could be helpful as they are then more likely to be used rather than being part of the Guidelines document.	Thank you for your comments and support for positioning of the visual analogue scale within the guideline. Both PDA and visual analogue scale (VAS) are tools that can be used if appropriate, neither is mandatory. The Flesch-Kincaid reading ease score suggests it will be understandable by people with a reading age of 11-13. This is in line with the NICE PDA standards. The committee emphasised the need for dialogue that is tailored to the person's individual circumstances, preferences, goals and values. We have amended the statements about hypos in the VAS and the PDA text.
NHS South Sefton Clinical	Guideline	011	021	Page 58 Lines 3 to 7 are potentially confusing in saying taking more medicines increases the risk of side effects and it appears to be delivering a negative message regarding medicines. Page 56 Lines 8 and 9 do	Thank you for your comment. The risk of side effects increases with increased numbers of medicines. It is one factor among many that needs to be considered. The PDA

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Commissioning Group				mention diet, lifestyle and a healthy weight can help to manage blood glucose which is good but could there be more emphasis about aiming to improve diet and life style whilst trying to achieve a healthy weight all of which can assist in lowering blood glucose levels.	says that if you take more medicines 'you are more likely to get side effects. but not everyone will get side effects and they may not trouble you if they do happen. It is usually possible to change your medicines to ones that suit you better.' The committee considers this is fair, balanced and accurate. The PDA states that diet and lifestyle measures can help the person manage their blood glucose and reduce their cardiovascular risk. The PDA is not a general information leaflet but is focussed on the decision about the person's target HbA1c.
NHS South Sefton Clinical Commissioning Group	Guideline	016	026	Rec. 1.7.13 It seems to imply that SGLT2 inhibitors have an adverse effect on renal function. Would it be correct to say that "SGLT2 inhibitors can cause fluid volume depletion which may have an adverse effect on renal function and this needs to be monitored, taking into account individual clinical factors and baseline renal function". It does not give advice about maintaining fluid intake or following advice given in the data sheet for the SGLT2 inhibitor which has been prescribed, which could be appropriate here or in Rec. 1.7.14. Advice is provided about SGLT2 inhibitors and pioglitazone on Page 13 Line 18 and again about SGLT2 inhibitors alone in a Box on Page 28 Line 19 and yet an SGLT2 inhibitor is not being considered until Page 15 Line 12. On Page 17 there is reference to SGLT2 inhibitors which are now being indicated for the treatment of Chronic Kidney Disease.	Thank you for your comment. The committee discussed the stakeholder comments about the renal impact of SGLT2 inhibitors (SGLT2i). They agreed that the existing recommendation was unclear and potentially confusing because it gave no indication of the frequency or when the monitoring should take place. They also recognised that although SGT2i can have a negative effect on renal function this is usually a small reduction in function and not a reason to stop taking the SGLT2i. Taking these points into account the committee have now removed this draft recommendation. The committee declined to add information to the patient advice recommendation about ensuring adequate hydration because they would need to define what this what this meant and the amount of liquid a person needed to consume to be adequately hydrated would vary between individuals, depending on their clinical circumstances.
NHS South Sefton Clinical Commissioning Group	Guideline	017	004	Rec. 1.7.14 does not give advice about maintaining fluid intake especially if unwell in addition to temporarily stopping the SGLT2 inhibitor.	Thank you for your comment. The committee declined to add information to the patient advice recommendation about ensuring adequate hydration because they would need to define what this what this meant and the amount of liquid a person needed to consume to be adequately hydrated would vary between individuals, depending on their clinical circumstances.

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NHS South Sefton Clinical Commissioning Group	Guideline	General	General	Page 15 Line 3 and Page 32 Line 27 QRisk 2 is being referred to when QRisk 3 is now being used.	Thank you for your comment. The committee deliberated over the definition of high risk of developing CV risk disease (high risk of future major adverse cardiovascular event such as an MI or stroke) to capture this population. They agreed that a QRISK2 score of >10% would be appropriate because this score takes into account most of the factors that were used to define this population in the economic model (and factors such as age, gender and ethnicity. They noted that QRISK2 is recommended for the assessment of CV risk in people with the 2 diabetes in the NICE guideline on NICE guideline on Cardiovascular disease: risk assessment and reduction, including lipid modification and is widely used and accepted in current general practice. Although other algorithms for assessing CVD risk exist, such as QRISK3, in the committee's experience they are not in widespread use currently, while QRISK2 is integrated into systems in use in primary care. Since a review of the evidence about the accuracy of such algorithms in comparison to each other and QRISK2 was not within the scope of this work, the committee agreed that QRISK2 was a pragmatic choice for assessing CV risk in people with type 2 diabetes.
NHS South Sefton Clinical Commissioning Group	Questions on comments form	General	General	Question 1:- Targeting patients with an increased CVD Risk will have the greatest impact on practice, with the prospect of improving outcomes for this group of patients. It could be a challenge to easily identify patients and implement initially in primary care and also in community or hospital diabetes clinics until appropriate searches are developed either to work in isolation or part of a risk stratification tool. Question 2:- There could be an increase in the cost for medication initially but if there is an improvement in CVD outcomes then this could more than offset the costs. Question 3:- Any easy way to identify the at risk patients would be helpful. Question 4:- The recommendation for treatment options for people with type 2 diabetes in whom metformin is contraindicated / not tolerated after treatment initiation should be retained as there will be clinicians who are new to treating patients with Type 2 Diabetes and will need somewhere to turn for advice if metformin is contraindicated/not tolerated.	Q1. Thank you for your response.The expectation is that people with type 2 diabetes who are at high of developing cardiovascular disease will be identified at their next medication review. This shouldn't add greatly to the workload of primary care clinicians as they are already expected to reassess individual circumstances at these reviews and adjust medications accordingly. Q2. Thank you for your response. NICE is undertaking a resource impact assessment of the draft recommendations in preparation for finalisation of the guideline update. This includes consideration of the sizes of the populations that would be covered by the SGLT2 inhibitor recommendations for people with established cardiovascular disease (CVD) and high risk of CVD. This document will be available on the

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				1.7.20 could be stood down but there would need to be a step for patients who are only able to take/tolerate dual therapy or even monotherapy for whatever reason.	type 2 diabetes topic homepage. However, although these costs are expected to be offset by downstream savings to the system as you point out in your comment, the resource impact assessment document has been unable to take this into account. This was because this information was not made available to the NICE resource impact team and therefore the resulting document does accurately reflect the financial benefits to the system of using these drugs. Q3. Thank you for your response. The committee have recomended using QRISK 2 to identify people with type 2 diabetes who are at risk of developing cardiovascular disease. They assure us that this is in widespread use in primary care. Q4. Thank you for your response. We have retained recommendation the recommendation for treatment options for people with type 2 diabetes in whom metformin is contraindicated / not tolerated after treatment initiation should be retained in line with your response.
North Lincolnshire and Goole NHS Foundation Trust	Guideline	018 / 060	General	**SGLT2i.** The positioning of SGLT2i therapies within the draft guideline is reasonable. However there is not homogeneity within the class. The VERTIS CV (Ertugliflozin) failed to match its rivals in producing benefits over placebo for a composite of CV death or hospitalization for heart failure (HHF), CV death alone, and a composite of renal death and decline. Furthermore VERTIS CV demonstrated a 20 – 60% increase in lower limb (predominantly toe) amputations but the draft guidance appears to suggest equivalence within the SGLT2i class.	Thank you for your comment. The committee reviewed the stakeholder comments but decided to continue treating SGLT2 inhibitors (SGLT2i) as a class for the following reasons: • There was a degree of uncertainty around whether there were real differences in cardiovascular (CV) benefits between the SGLT2i based on the clinical trial evidence and results from the NMAs. ○ Firstly, for hospitalisation for heart failure, the SGLT2i empagliflozin, canagliflozin, and dapagliflozin produced a clinically meaningful reduction compared with placebo in the random effects NMA model. However, in the sensitivity analyses using a fixed effect model ertugliflozin also showed a clinically meaningful reduction compared to placebo, which reflects

					the original clinical trial data. The NMA results could not differentiate between the SGLT2i for this outcome. o Secondly, for the 3 point MACE outcome, only canagliflozin and empagliflozin produced a statistically significant reduction compared to placebo but the SGLT2i could not be differentiated from each other in the NMA. o Thirdly for all cause and CV mortality empagliflozin showed a clinically meaningful reduction compared to placebo and the other SGLT2i, but the remaining SGLT2i could not be differentiated from each other or placebo in the NMA. o Fourthly, for non-fatal MI and non-fatal stroke the NMAs could not differentiate between empagliflozin, canagliflozin, ertugliflozin and placebo. The data for dapagliflozin was reported differently and could not be included in the NMAs. From the clinical trial data dapagliflozin could not be differentiated from placebo for MI and was not meaningfully different from placebo for stroke. o Finally, only dapagliflozin showed a clinically meaningful improvement in severe hypoglycaemia compared to placebo but the remaining SGLT2i could not be differentiated from each other and placebo in the NMA. • There was also a degree of uncertainty around the cost-effectiveness of individual SGLT2i in the economic modelling. Although only dapagliflozin was cost-effective at a threshold of £20,000/quality-adjusted life year (QALY) across all model scenarios and CV risk groups it could not be differentiated from the other SGLT2i in the NMA apart from for the all-cause and CV mortality outcomes where it was clinically meaningfully worse than empagliflozin. The ranking of ICERs for the other SGLT2i varied across model scenarios and risk

					groups. The committee agreed that there was sufficient uncertainty in the economic modelling (caused in turn by uncertainty in the underlying clinical data) to mean that they were not sufficiently confident that these different ICERs represented true underlying differences in cost-effectiveness, as opposed to simply random variation in the results between different SGLT2 trials. • Taking the cost-effectiveness and clinical results into account the committee decided against only recommending dapagliflozin and instead made recommendations for the SGLT2i as a class. However, they recognised that there was a greater degree of uncertainty around the CV benefit associated with ertugliflozin because, depending on the choice of model used in the NMA, it did not consistently show a clinically meaningful reduction in hospitalisation for heart failure compared to placebo, unlike empagliflozin, canagliflozin and dapagliflozin. It was also not statistically significantly better than placebo for the 3-point MACE outcome unlike canagliflozin and empagliflozin. The committee therefore recommended SGLT2i with proven CV benefit because this wording would enable the prescribers to select a particular drug from within the SGLT2 class if they thought this was clinically justified based on the individual characteristics of their patient, whilst future proofing the recommendation should additional evidence or new SGLT2s be made available. As per the recommendation on choosing drug treatment, once the clinical circumstances and needs of the person with type 2 diabetes, including their need for CV protection, have been taken into account, if 2 drugs in the same class are suitable for that individual then the prescriber is still expected to choose the option with the lowest acquisition cost to help use NHS resources wisely.

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					Please see evidence review A for more a more detailed explanation of the analyses that were carried out and the committee's discussion of the results.
North Lincolnshire and Goole NHS Foundation Trust	Guideline	022	019 +	1:7:21 - **GLP1 RA therapies.** The positioning of GLP1 RA within the guideline essentially continues to place them as fourth line after failure of triple oral glucose lowering therapy and this cannot be right. These therapies are HbA_{1c} lowering (some very significantly although glucose lowering efficacy varies within the class), weight reducing (some very significantly but varies), offering cardio-protection for some and also in individuals with no prior cardiovascular disease (Dulaglutide). They confer no hypoglycaemia risk over placebo and a small but clinically significant systolic blood pressure reduction. To continue to place GLP1 RA therapies as fourth line glucose lowering therapies, can not be right when evidence points to the fact that we should be using significantly more GLP therapy and earlier (Farmer R, 2021). Uptake of GLP1 therapy in the UK is very low and their usage for the reasons outlined above should be encouraged. The draft document indicates that a cost effectiveness analysis of GLP1 therapy was not conducted, only an analysis in respect of cardiovascular protection. If that cardiovascular cost analysis was conducted on the class as a whole, the cost benefit will be under-estimated as not all drugs within the GLP1 class show cardio-protection. I draw attention to the committee, work by Capehorn (*2021*) who conclude that: '*When clinical and cost outcomes were combined to assess cost-effectiveness, once-weekly Semaglutide 1 mg was associated with an ICER of GBP 4,439 per QALY gained versus Empagliflozin 25 mg over patient lifetimes*.' Outside of a cardiovascular cost effectiveness modelling for the GLP1 class as a whole, we suggest that modelling should be based on those GLP1 therapies with the highest HbA_{1c} lowering efficacy and coincidently providing cardiovascular risk reduction, these being: Liraglutide;	Thank you for your comment. The committee reviewed the stakeholder comments regarding the use of GLP-1 mimetics and examined the updated economic evidence relating to GLP-1 mimetic treatment for people with type 2 diabetes and high cardiovascular risk. In the NICE health economic analyses, when looking at GLP-1 mimetics as a class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of £20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the intervention as an effective use of NHS resources will specifically take account of the following factors." and • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular,

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				Dulaglutide; Semaglutide injectable and Semaglutide oral (HbA_{1c} lowering efficacy but not CV protection). Cost modelling should analyse all potential benefits of GLP1 therapy: HbA_{1c} lowering, potential for reduction in CV events, weight reducing and systolic blood pressure reducing. The draft document fails in any way to acknowledge the last 5 years or so of evidence related to GLP1 RA and their role in cardio-protection following the publication of LEADER (Liraglutide CVOT) in 2016 and subsequently REWIND, SUSTAIN 6 and PIONEER 6. The 6 month stopping rules persist with GLP1 RA's whereby the drug should be stopped if there is not an 11 mmol/mol reduction in HbA_{1c} and a 3% reduction in body weight. Many patients have significant HbA_{1c} reduction but not the 3% reduction in baseline body weight. Given the other advantages that GLP1 therapy may confer, it seems prudent to continue the therapy and this is in reality what happens. The ADA / EASD consensus statement make no mention of BMI criteria when starting GLP1 therapy, seeing instead the other significant benefits including cardio-protection.	advisory bodies will be more cautious about recommending a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis." Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of

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					confidence in those findings, compared again to the findings for SGLT2 inhibitors. In addition, the committee noted that there were differences in the clinical effectiveness of the 2 forms of semaglutide. Although the acquisition costs for injectable and oral semaglutide are similar they showed marked differences in cost-effectiveness in the economic analyses. This was caused by differences in the effect estimates for stroke, myocardial infarction and severe hypoglycaemia. From earlier discussions about the clinical evidence (see the discussion sections in the evidence review for more details) the committee had agreed that it was uncertain whether the observed differences in effect on all-cause mortality compared to placebo between the 2 forms of semaglutide were real and they therefore decided not to place undue weight on them. They had also noted that this uncertainty and any other differences in effects between the drugs for other outcomes was probably due to wide 95% confidence intervals for many outcomes with these drugs, due to the smaller numbers of participants and events in the trials compared to other CVOTs. Due to the higher level of uncertainty surrounding the cost-effectiveness of the GLP-1 mimetics as a class compared to the SGLT2 inhibitors, the committee considered whether to recommend injectable semaglutide for people at high cardiovascular risk in whom an SGLT2 is contraindicated or not tolerated. However, taking into account the uncertainty in the cost-effectiveness and clinical effectiveness the committee decided against recommending injectable semaglutide for this population.
North Lincolnshire and Goole NHS	Guideline	025 / 060	General	There is a statement in '*Visual Summary 4: Medicines Table' (page 25/60*) that GLP1 should be avoided or used with caution in renal disease. This is incorrect / misleading, when some (Liraglutide, Dulaglutide,	Thank you for your comment. We have now provided this information specific for individual medicines rather than medicine classes.

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Foundation Trust				Semaglutide injectable and oral) can be safely used down to an eGFR of 15 ml/min/1.73m^2.	
North Lincolnshire and Goole NHS Foundation Trust	Guideline	027 / 060	General	**Insulins.** It is unclear why NICE persists on a focus on NPH insulins and GLARGINE (Lantus) when an alternative basal insulin DEGLUDEC (Tresiba) is well established in the UK market and provides greater inter-subject predictability and price equivalence when greater glucose lowering efficacy is considered. Our own default basal insulin is DEGLUDEC, largely based on overwhelming patient feedback on predictability of fasting glucose readings. Variability studies exist (*Heise T, 2018*) and NICE is encouraged to consider these.	Thank you for your comment. The section of the guideline covering insulin-based treatment was not within the scope of this update. The committee did not review any evidence on this topic and were therefore unable to make the requested changes or consider the evidence in the reference you mention. The surveillance team at NICE monitor whether guidelines are up to date. The surveillance process includes reacting to events at any time after guideline publication (for example, publication of a key study) as well as a standard check every 5 years. Stakeholders can help with this process by letting us know which parts of the guideline stakeholders believe out-of-date and why during scope consultations. As these are evidence-based guidelines it is useful if stakeholders can provide links to important evidence sources that they believe would necessitate an update of a particular area of the guideline. We can then pass these references onto the NICE surveillance team for evaluation and a decision about whether an update is justified. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs..

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North Lincolnshire and Goole NHS Foundation Trust	Guideline	034 / 060		**Cost focus**. The Diabetes State of the Nation report (*Diabetes UK, 2015*) suggests that diabetes complication rates in England are rising. This is clearly by far the biggest expense in diabetes management, accounting for 70-80% of diabetes costs (*Hex, Bartlett 2012, Kanavos 2012*). So, more therapy and particularly more potent glucose lowering, cardio and reno-protective therapy should be encouraged and its use earlier. Diabetes costs account for around 9% of total UK Diabetes spend. When we consider growing complication costs, and factor in newer glucose lowering therapies with evidence of cardiovascular protection and / or renal protection, we believe the current proposed NICE guidance will fail to address rising diabetes (complication) costs going forward.	Thank you for your comment. The cost-effectiveness analysis has taken into account the cost of complications related to diabetes as outlined in section 2.3.3.2 in the health economic report. Differences in complication costs between treatments were accounted for by treatment effects outlined in section 2.3.2 in the health economic report. Hence the total cost component for each treatment as reported in the results section (and is used to calculate the cost-effectiveness of interventions) have taken into account the cost of complications.
North Lincolnshire and Goole NHS Foundation Trust	Guideline	General	General	**Existing glucose lowering guidance.** Our current NICE NG28 Type2 Diabetes guidance is clearly now very out-dated. However, we already have a very fit for purpose, evidenced based diabetes pathway: The ADA / EASD Consensus Statement (*Buse J et al., 2020*). This pathway is widely used in the UK and has formed the basis of many localised glucose lowering pathways including our own. The previous NICE Type 2 Diabetes Consultation Document (surveillance stage) of around 2 years ago (since shelved) was very much more in line with the ADA / EASD Consultation Statement. Why wasn't this enacted? The vast majority of clinicians in diabetes would have found this understandable and workable in clinical practice and so potentially benefiting patient outcomes. Failure to adopt guidance that aligns to the ADA / EASD will, in our view mean that practitioners will simply ignore the NICE Type 2 Diabetes guidance in favour of the former.	Thank you for your comment. The original scope of the update to the drug treatment sections of NG28 was to fully update the treatment section of the guideline as your comment notes. However, once work on the topic commenced it was determined that updating evidence reviews and health economics for such a wide scope, within the resources available to NICE for this topic, would take an unacceptably lengthy period. Taking such an approach for this guideline update would have further delayed publication of updated treatment recommendations in this rapidly changing area. In view of the timescales involved and the appetite from the committee and stakeholders for an update within an acceptable time period, we worked with our committee members to identify the priority areas for this update. The committee members agreed that our initial focus should be on reviewing the evidence from trials looking at cardiovascular outcomes. This reflected the changing evidence base as a result of the significant investment in clinical trials to directly capture cardiovascular outcomes, feedback from stakeholders that assessing this evidence was a priority and the impact that this new evidence could have on recommendations for the treatment of people with

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					diabetes. We therefore revised the scope to reflect this and carried out the current piece of work. The committee are aware of the ADA guidance, but their decisions were made according to the NICE guideline manual and took into account the evidence relevant to our review question. Although the NICE guidance may differ to the guidance provided by ADA, the committee were confident that their recommendations reflected the evidence they reviewed and their clinical judgement. It is of particular importance to note that the NICE guideline used an original economic model as the basis to recommend the most clinically and cost-effective options while the ADA guidance did not systematically take cost-effectiveness into account. When producing guidelines, NICE considers both effectiveness and cost-effectiveness for all of the recommendations it makes. As well as helping to ensure the recommendations made represent the best use of NHS resources (in particular, the opportunity costs of spending additional resources), this is also required by the legislation that originally established NICE (the Health and Social Care Act 2012), which states that when exercising its functions, NICE must have regard to "the broad balance between the benefits and costs of the provision of health services or of social care in England." NICE's principles further refine this by explicitly stating that "if possible, NICE considers value for money by calculating the incremental cost-effectiveness ratio" and "interventions with an ICER of less than £20,000 per QALY gained are generally considered to be cost effective." This guidance was developed in line with both these statutory requirements, and NICE's stated principles, methods and processes. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we

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					have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand.
North Lincolnshire and Goole NHS Foundation Trust	Guideline	General	General	a. **Hypoglycaemia and weight gain.** There is still disproportionate focus on older, potentially weight gaining, hypoglycaemia causing therapies. The draft guidance largely ignores potential harms of older therapies but also the secondary benefits of cardiovascular and renal benefits and lack of weight gain or weight loss, with newer therapy classes. The draft document includes a consultation tool whereby patient can score on a visual analogue scale their view and attitudes to medications and their side effects. We think this model is good and would work well in practice. The model includes a patient attitude scale in relation to '*thinking about things like driving, severe hypo's would or would not be a big problem for me*'.	Thank you for your comment and support of the PDA. a. You are correct that the model does not contain every outcome that could potentially be of interest for modelling adults with type 2 diabetes. However, the committee agreed these were the most important outcomes for assessing the additional cardiovascular and other benefits associated with drug treatment for type 2 diabetes, for the majority of the type 2 diabetes population. The committee agreed the cardiovascular outcome trials were the most appropriate data source to assess cardiovascular benefits of these drugs, being powered to specifically detect differences in hard outcomes, rather than only surrogate outcomes. The committee noted these studies were not representative of the full population of people with type 2 diabetes, but agreed this was a lesser limitation than the need to extrapolate from surrogate endpoints to cardiovascular outcomes, particularly given the findings from those studies suggesting these surrogate extrapolations are often not very robust. They also agreed that taking data on weight and hypoglycaemic events from these cardiovascular outcome

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					trials was the most appropriate approach, in order to match the data used for cardiovascular event rates. For hypoglycaemic events, the approach taken is broadly in line with that taken in many other evaluations in diabetes, attaching costs and quality of life outcomes to the incidence of severe hypoglycaemic events, as these are the ones that make the most difference to a person's life. For changes in weight, it was noted it was important not to double count the impact of changes, as the effects on cardiovascular outcomes should already be captured in the outcomes of those trials. It was therefore agreed that the most appropriate approach was to only include the direct quality of life gains associated with reductions in weight, with the other benefits captured through the cardiovascular event data. The committee noted that if anything the approach taken in the guideline may overestimate the benefits of weight reduction, as some of the estimated quality of life gains may be the result of avoided cardiovascular events, but it was agreed to be the best data source available. It should also be noted that it is not the case that only additional outcomes beneficial to drug therapy were excluded from the modelling. As an example, adverse events related to drug treatment (excluding hypoglycaemia) were not included as part of the analysis. As a number of the analyses in the guideline explicitly compare the addition of new treatments (for example, using 3 drugs versus 2) rather than simply switching drugs, it would be expected that inclusion of adverse events would decrease the cost-effectiveness for any additional treatments, as they would add to the adverse event burden. Therefore, whilst it is likely there would be differences found in the results of the cost-effectiveness analysis were a different set of outcomes to be included, it is not clear in which direction the results would

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					change for any given agent, and whether they would become more or less cost-effective. The renal benefits of using SGLT2 inhibitors in people with type 2 diabetes and CKD have been assessed in a separate piece of work that has been out for stakeholder consultation and was published in November 2021. The final recommendations on renal and cardiovascular benefits will be brought together in a single updated guideline document when this current work on cardiovascular benefits is published in 2022. The CKD recommendations are situated in the section on CKD in the type 2 diabetes guideline with a cross reference from the drug treatment section. The original scope of the update to the drug treatment sections of NG28 was to fully update the treatment section of the guideline as your comment notes. However, once work on the topic commenced it was determined that updating evidence reviews and health economics for such a wide scope, within the resources available to NICE for this topic, would take an unacceptably lengthy period. Taking such an approach for this guideline update would have further delayed publication of updated treatment recommendations in this rapidly changing area. In view of the timescales involved and the appetite from the committee and stakeholders for an update within an acceptable time period, we worked with our committee members to identify the priority areas for this update. The committee members agreed that our initial focus should be on reviewing the evidence from trials looking at cardiovascular outcomes. This reflected the changing evidence base as a result of the significant investment in clinical trials to directly capture cardiovascular outcomes, feedback from stakeholders that assessing this evidence was a priority and the impact that this new evidence could

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					have on recommendations for the treatment of people with diabetes. We therefore revised the scope to reflect this and carried out the current piece of work. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand. b. The guideline updates the previous version of NG28 considering the cardiovascular outcomes trials evidence. The evidence from other formats of trials was not updated. The current update has resulted in new recommendations for SGLT2 inhibitors people with type 2 diabetes who have with established cardiovascular disease or who are a high risk of cardiovascular disease. The committee do not think SU are prominent but do remain an option for some people. The committee retained the existing 2015 NG28 recommendations for treatment options, including for sulfonylureas, for those at lower CV risk or if further interventions are required. The committee have ensured that the recommendation on factors to take into account when choosing drug treatments

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				b. We know that severe hypo's is feared by patients, will affect their driving licence and their safety in respect of driving and machine operating and may contribute to falls in the elderly and frail. Patients also become treatment averse if they fear hypo's and may well reduce medication and / or over-eat to compensate. Why then are hypo-causing oral agents (Sulphonylureas) given so much prominence in this draft document?	includes taking safety and the persons needs and preferences into account when choosing a drug treatment, and the reviewing treatment recommendation includes consideration of adverse effects. In addition, the new visual summary includes additional information for the prescriber to help them tailor the choice of therapy to individual needs.
North Wood Group Practice	Guideline	002	General	Patient decision aid - Fifth bullet point down states 'taking a statin to manage your cholesterol if it is high'. The term 'high' is subjective. Could this statement be changed to be more reflective of the way we manage cardiovascular risk for example 'taking a statin' if relevant, to manage your cholesterol and reduce your cardiovascular risk. In addition, we now have a number of medications to reduce cardiovascular risk/cholesterol, not only statins.	Thank you for your comment, we have amended the text to say 'and for some people … taking a statin or other medicine to manage your cholesterol.' The conext of the section is about reducing cardiovascular risk.

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North Wood Group Practice	Guideline	002	General	Patient decision aid - Last paragraph states that 'the lower you want to keep your blood glucose level, the more medicines you are likely to take. This also means that you are more likely to get side effects'. This statement could be seen as negative – it could be read that you will get side effects the more medicines you take, which is not necessarily the case. This could impact on both acceptance of additional medications and adherence of existing medications. Please can the language be used in this statement be reviewed? In addition, some people will have lower blood glucose levels through dietary interventions and minimal medications. The statement 'the lower you want to keep your blood glucose level, the more medicines you are likely to take' is not strictly true for all	Thank you for your comment. The consultation draft of the PDA went on to say that 'not everyone will get side effects and they may not trouble you if they do happen. It is usually possible to change your medicines to ones that suit you better'. The committee feel that this is a fair and balanced statement. Regarding your second point we have amended the PDA. That paragraph now says 'Aiming for a lower blood glucose target may mean you have to take more medicines. Taking more medicines may also mean you are more likely to get side effects. But not everyone will get side effects and they may not trouble you if they do happen. It is usually possible to change your medicines to ones that suit you better.'
North Wood Group Practice	Guideline	015	003	Reference to using QRISK2 to asses CVD risk – some reference in NICE to using QRISK3 as superseding QRISK2 (Scenario: CVD risk 10% or more | Management | CVD risk assessment and management | CKS | NICE) and surveillance-report-2018-cardiovascular-disease-risk-assessment-and-reduction-including-lipid-modification-2014-nice-guideline-cg181-pdf-6123288665797	Thank you for your comment The committee deliberated over the definition of high risk of developing CV risk disease (high risk of future major adverse cardiovascular event such as an MI or stroke) to capture this population. They agreed that a QRISK2 score of >10% would be appropriate because this score takes into account most of the factors that were used to define this population in the economic model (and factors such as age, gender and ethnicity. They noted that QRISK2 is recommended for the assessment of CV risk in people with the 2 diabetes in the NICE guideline on NICE guideline on Cardiovascular disease: risk assessment and reduction, including lipid modification and is widely used and accepted in current general practice. Although other algorithms for assessing CVD risk exist, such as QRISK3, they are not in widespread use currently. Since a review of the evidence about the accuracy of such algorithms in comparison to each other and QRISK2 was not within the scope of this work, the committee agreed that QRISK2 was a pragmatic choice for assessing CV risk in people with type 2 diabetes.
North Wood Group Practice	Guideline	016	016 - 019	We welcome the wider use of SGLT-2inhibitors given the evidence however use in a much wider population than current practice has risks that need to be managed. Ensuring the safe use of medicines needs to be	Thank you for your comment. The committee were aware that the aim of very-low carbohydrate and ketogenic diets is to replace dietary carbohydrate with fat with the specific

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				paramount. We recognise the risk of DKA associated with SGLT-2 inhibitors however there are other risk factors for DKA other than a low carbohydrate diet or ketogenic diet such as low reserve of insulin secreting cells, low BMI or ketone prone type 2 diabetes, significant clinical features of insulin deficiency where we would not use an SGLT-2 inhibitor. Is there any reason why some risk factors have been chosen over others? Is there scope to add a prescribing decision aid around the SGLT-2i specifically focusing on risks versus benefits to highlight cohorts where benefits outweigh risks and vice versa	intention of inducing a ketotic state. In people with type 2 diabetes taking an SGLT2 inhibitor (SGLT2i) this may increase the risk of diabetic ketoacidosis (DKA). DKA is a rare, but serious, complication in type 2 diabetes. The committee highlighted this risk because the SGLT2 inhibitors are comparatively new drugs and, in the committees' view, clinical experience with them is low in primary care in some areas, but the new recommendations are expected to greatly increase their use in this setting. Additionally, the summary of product characteristics (SmPC) for SGLT2i advise caution in people with restricted food intake in relation to ketosis. However, taking stakeholder comments into account, the committee have revised the wording to better reflect the need to check whether the individual would be at an increased risk of DKA if they take an SGLT2i rather than causative effect of such diets. They also included mention of several risk factors for DKA as examples, including the use of very-low carbohydrate and ketogenic diets. The list is not meant to be exhaustive but to highlight some risk factors that the committee thought were particularly important for prescribers to be aware of. The committee made an additional recommendation to highlight to the clinician that they should try to address any modifiable risk factors before starting SGLT2i treatment. This guideline already has a series of visual summaries to help the clinician with their prescribing decisions and with following the recommendations. It also has a PDA around blood glucose targets. Unfortunately, we are unable to provide additional decision support aids.
North Wood Group Practice	Guideline	016	020 - 023	The importance of checking for pregnancy or planning pregnancy is welcomed however this should not only be for SGLT-2 inhibitors alone, it should be included as a separate point and a routine question for type 2 diabetes **and** when prescribing any medication.	Thank you for your comment. The committee have included a link under the recommendation on choosing drug treatments to refer to the NICE guideline on Diabetes in pregnancy.

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North Wood Group Practice	Guideline	016	025	We note the importance of specific side effects with SGLT-2 inhibitors however would recommend adding in side effects linked to the three MHRA alerts currently published for SGLT-2 inhibitors -risk of DKA, fourniers gangrene and amputations. These are currently hidden on page 28, row 19 as a generic statement. If listing a side effect such as fluid volume depletion, we would welcome the advice that the patient should be counselled to ensure adequate hydration whilst taking SGLT-2 inhibitors and further details on renal parameters that would indicate cessation of therapy for example	Thank you for your comment. The committee were aware that the aim of very-low carbohydrate and ketogenic diets is to replace dietary carbohydrate with fat with the specific intention of inducing a ketotic state. In people with type 2 diabetes taking an SGLT2 inhibitor (SGLT2i) this may increase the risk of diabetic ketoacidosis (DKA). DKA is a rare, but serious, complication in type 2 diabetes. The committee highlighted this risk because the SGLT2 inhibitors are comparatively new drugs and, in the committees' view, clinical experience with them is low in primary care in some areas, but the new recommendations are expected to greatly increase their use in this setting. Additionally, the summary of product characteristics (SmPC) for SGLT2i advise caution in people with restricted food intake in relation to ketosis. However, taking stakeholder comments into account, the committee have revised the wording to better reflect the need to check whether the individual would be at an increased risk of DKA if they take an SGLT2i rather than causative effect of such diets. They also included mention of several risk factors for DKA as examples, including the use of very-low carbohydrate and ketogenic diets. The list is not meant to be exhaustive but to highlight some risk factors that the committee thought were particularly important for prescribers to be aware of. The committee made an additional recommendation to highlight to the clinician that they should try to address any modifiable risk factors before starting SGLT2i treatment. The committee discussed the stakeholder comments about the renal impact of SGLT2 inhibitors (SGLT2i). They agreed that the existing recommendation was unclear and potentially confusing because it gave no indication of the frequency or when the monitoring should take place. They also recognised that although SGT2i can have a negative effect on renal function this is usually a small reduction in function and not a reason to stop taking the SGLT2i. Taking

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					these points into account the committee have now removed this draft recommendation.. They declined to add information to the patient advice recommendation about ensuring adequate hydration because they would need to define what this what this meant and the amount of liquid a person needed to consume to be adequately hydrated would vary between individuals, depending on their clinical circumstances.
North Wood Group Practice	Guideline	017	006	There are additional lifestyle factors that could increase the risk of DKA e.g. drugs and alcohol. It would also be helpful to include the importance of hydration to prevent dehydration given the mechanism of action of these drugs	Thank you for your comment. Following stakeholder comments at consultation the committee have amended the wording of the recommendation on things to check before starting the SGLT2 inhibitor to focus on whether the person is at increased risk of diabetic ketoacidosis (DKA) if they take an SGLT2 inhibitor. They have included some examples that, in the committee's view, could lead to increased risk, but this is not meant to be an exhaustive list. This is noted in the rationale that accompanies the recommendation.The committee agreed that prescribers should consult the summary of product characteristics for further information. The committee made an additional recommendation to highlight to the clinician that they should try to address any modifiable risk factors before starting SGLT2i treatment. The committee declined to add information to the patient advice recommendation about ensuring adequate hydration because they would need to define what this what this meant and the amount of liquid a person needed to consume to be adequately hydrated would vary between individuals, depending on their clinical circumstances.
North Wood Group Practice	Guideline	017	010	We welcome the addition of sick day rules for SGLT-2 inhibitors. Could these be expanded e.g. to include metformin, when to re-start, additional information regarding stopping for surgery – see 3.-Covid-19-Type-2-Sick-Day-Rules-Crib-Sheet-06042020.pdf (england.nhs.uk)	Thank you for your comment. The recommendation which included sick day rules was reviewed following stakeholder comments and the bullet point on sick day rules has now been removed as the committee agreed it would be inconsistent to present this information for one class of drugs

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					but not any others. They expected that sick day rules and other safety related advice would be discussed with the individual with type 2 diabetes as part of the decision-making process regarding drug choice and wanted to keep the guidance as simple and clear as possible. We have therefore been unable to include the additional information you suggested.
North Wood Group Practice	Guideline	017	012	Choosing treatments - First bullet point discusses person's individual clinical circumstances, preference and needs. Could bullet point 4 be incorporated given that the persons cardiovascular risk and status would be a clinical circumstance. If so, the first bullet point could read 'the person's individual clinical circumstances (including cardiovascular disease [CVD] risk and status) and their preferences and needs	Thank you for your comment. 'Comorbidities' has been included in the first bullet in the visual summary and bullet 3 has been changed to 'the effectiveness of the drug treatments in terms of metabolic response and cardiovascular and renal protection' to make the distinction between existing conditions and the mode of action of the drug.
North Wood Group Practice	Guideline	017	012	Reviewing and changing treatments – Should the last bullet point 'check adherence to diet and lifestyle' be the first bullet point given diet and lifestyle is the cornerstone of T2DM management	Thank you for your comment. Diet and lifestyle advice has been moved to the top of the first page of the visual summary.
North Wood Group Practice	Guideline	017	012	Reviewing and changing treatments - We would suggest that the bullet point starting with 'stop medicines that have not worked or not tolerated' state 'check adherence and stop medicines that have not worked or are not tolerated'. If medicines have not worked as people are not taking them, we need to review medication adherence rather than stopping the medication and taking it out of future options due to being ineffective. We would then suggest the bullet point below starting with Optimise…. Given that adherence has already been covered in the bullet point above	Thank you for your comment. The committee have reworded the draft recommendation on reviewing drug treatments following stakeholder consultation to make its intentions clearer. However, it decided not to amend the order of the bullets as the entire recommendation should be read before beginning to act on the points included in it.
North Wood Group Practice	Guideline	018	General	Visual Summary 2 - Need to be clearer about when to add in SGLT2 with respect to HbA1c response to metformin. With established/high risk CVD is the aim to start with metformin and then add in SGLT2 depending on response? This makes it seem that SGLT2 is added irrespective of response to metformin (except tolerability). More clarity needed on this step around HbA1c target/response to metformin.	Thank you for your comment. We have added the wording 'Start the SGLT2 inhibitor as soon as metformin tolerability is confirmed' to the recommendation.
North Wood Group Practice	Guideline	018	General	Visual summary 2: first line treatment - First line treatment in the algorithm– should this also state lifestyle interventions alongside pharmacological options?	Thank you for your comment. Diet and lifestyle has been added to the top of the first page of the visual summary.

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North Wood Group Practice	Guideline	018	General	Visual summary 2: first line treatment - Bottom left hand side box, SLGT2 needs to be changed to SGLT2	Thank you for your comment. The typo has been amended.
North Wood Group Practice	Guideline	018	General	Visual summary 2: first line treatment - Bottom left hand side box states The Guideline update recommends SGLT2i use in wider population than technology appraisals published before August 2021.Does this statement mean that all previous TA's are now superseded? However the guideline links to the TA's. This could be made clearerr. If this guideline accepts wider use, should the original TA's be superseded?	Thank you for your comment. The TAs still apply for people not at high CVD risk so we have made that clearer in the visual summaries.
North Wood Group Practice	Guideline	019	General	Visual summary 4, medicines table - Contra-indications - For all drugs listed in the table, looking at the SPC's and BNF often the only contra-indication is hypersensitivity to the ingredients only. In reality we know that thre are clinical contra-indications and some have been listed however others haven't e.g. pancreatitis is missing from GLP-1 analogues and DPP-4 inhibitors. Would it be appropriate to title this section contra-indications and cautions for use and add in further information? Information on use in pregnancy and breast feeding are also missing from this table. We would ask that this section is updated and made more comprehensive. Having some information that is missing or incorrect is a concern as some prescribers may use this table as a sole resource.	Thank you for your comment. The content in the table has been updated for specific medicines rather than for medicine classes. The committee agreed that contraindications were useful in the table but that prescribers should consult the BNF and SPCs for additional cautions.
North Wood Group Practice	Guideline	019	General	Visual summary 4, medicines table - Hepatic impairment - DPP-4 inhibitors – the information in the table is mis-leading as there are differences between the DDP-4 inhibitors. For example linagliptin states no dose adjustments needed however clinical experience is lacking in hepatic impairment - Trajenta 5 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk), sitagliptin states no dose adjustment mild-moderate and in severe, care to be exercised as not been studies however sever hepatic impairment not expected to affect pharmacokinetics JANUVIA 100mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk). Vildagliptin states not to be used in hepatic impairment - Galvus 50 mg Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk). Please can this section be reviewed. Having some information that is missing or incorrect is a concern as some prescribers may use this table as a sole resource.	Thank you for your comment. The content in the table has been updated for specific medicines rather than for medicine classes.

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North Wood Group Practice	Guideline	019	General	Visual summary 4, medicines table - Hepatic impairment - GLP-1 analogues – this section states that there are no warnings on use of GLp-1 analogues in hepatic impairment. Please can this section be updated as this statement is not correct – for example for liraglutide, no dose adjustment is required for mild to moderate impairment however it is not recommended for severe impairment - Victoza 6 mg/ml solution for injection in pre-filled pen - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk), semaglutide – no dose adjustment in mild to moderate hepatic impairment, limited experience in severe therefore caution in use - Ozempic 1 mg solution for injection in pre-filled pen - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk), dulaglutide – no dose adjustment - TRULICITY 1.5 mg solution for injection in pre-filled pen - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) Please can this section be reviewed. Having some information that is missing or incorrect is a concern as some prescribers may use this table as a sole resource.	Thank you for your comment. The content in the table has been updated for specific medicines rather than for medicine classes.
North Wood Group Practice	Guideline	019	General	Visual summary 4, medicines table - Hepatic impairment - Sulfonylureas – under this section, it states to avoid if severe. A number of the summary of product characteristic documents (www.medicines.org.uk) state that they are contra-indicated in severe hepatic impairment, rather than 'avoid where possible' e.g. glimepiride Glimepiride 1 mg Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) and gliclazide - Diamicron 80mg Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) Please can this section be reviewed. Having some information that is missing or incorrect is a concern as some prescribers may use this table as a sole resource.	Thank you for your comment. The content in the table has been updated for specific medicines rather than for medicine classes.
North Wood Group Practice	Guideline	019	General	Visual summary 4, medicines table - Hepatic impairment - Metformin – the glucophage SPC states that metformin is contra-indicated in hepatic insufficiency - Glucophage 500 mg film coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk).	Thank you for your comment. We have used contraindication content from the BNF (checked November 2021) and have highlighted this to the BNF regarding the BNF content discrepancy with the SPCs.
North Wood Group Practice	Guideline	019	General	Visual summary 4, medicines table - Hepatic impairment - SGLT-2i – the document states that caution is needed in severe hepatic impairment. The advice in the SPCs differ for example in dapagliflozin, it states it can be used with dose adjustments - Forxiga 10 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk). However in empagliflozin and canagliflozin it states not recommended	Thank you for your comment. The content in the table has been updated for specific medicines rather than for medicine classes.

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				Jardiance 10 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk), Invokana 100 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) Please can this section be reviewed. Having some information that is missing or incorrect is a concern. Some prescribers may use this table as a sole resource.	
North Wood Group Practice	Guideline	019	General	Visual summary 4, medicines table - Options and BNF link - SGLT-2i – we welcome that the MHRA warnings on DKA and genital infections are noted here. The MHRA warning on lower limb amputations - SGLT2 inhibitors: updated advice on increased risk of lower-limb amputation (mainly toes) - GOV.UK (www.gov.uk) is not listed however is still a live MRA alert. We recognise that there is conflicting evidence around this. By omitting the MHRA alert, are NICE stating that this is no longer a concern and clinicians and patients do not need to discuss?	Thank you for your comment. We realised that the MHRA warnings did not provide an exhaustive list if used as a sole resource. We have therefore removed all MHRA warnings as we would expect prescribers to consult the MHRA, BNF, and SPCs before prescribing.
North Wood Group Practice	Guideline	019	General	Visual summary 4, medicines table - Renal impairment - DPP-4 inhibitors – the information under this section is not fully correct. The statement says that dose adjustment is required for DPP-4 inhibitors in moderate to severe renal impairment. This is not the case for linagliptin for example. We would ask that this table is updated in line with the licensing documents. Having some information that is missing or incorrect is a concern as some prescribers may use this table as a sole resource.	Thank you for your comment. The content in the table has been updated for specific medicines rather than for medicine classes.
North Wood Group Practice	Guideline	019	General	Visual summary 4, medicines table - Renal impairment - Compatibility in dialysis or end stage renal disease is missing for all. We would ask that this table is updated in line with the licensing documents. Having some information that is missing or incorrect is a concern as some prescribers may use this table as a sole resource.	Thank you for your comment. The content in the table has been updated for specific medicines rather than for medicine classes.
North Wood Group Practice	Guideline	019	General	Visual summary 4, medicines table - Renal impairment - GLP-1 analogues – the information under this section is incorrect. Most of the GLP-1 analogues have had their licenses updated allowing them to be used at lower eGFR levels (see www.medicines.org.uk). Please can this section be reviewed. Having some information that is missing or incorrect is a concern as some prescribers may use this table as a sole resource.	Thank you for your comment. The content in the table has been updated for specific medicines rather than for medicine classes.
North Wood Group Practice	Guideline	019	General	Visual summary 4, medicines table - Renal impairment - Insulin – given the risk of hypoglycaemia is higher with lower renal function, we would recommend a statement being added to this effect, before the statement that starts 'insulin requirements may decrease'	Thank you for your comment. The committee agreed to keep the information in this column to a minimum as prescribers should check the individual drug monographs and SPCs before prescribing.

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North Wood Group Practice	Guideline	019	General	Visual summary 4, medicines table - Renal impairment - Sulfonylureas – under this section, it states to avoid where possible if severe. A number of the summary of product characteristic documents (www.medicines.org.uk) state that they are contra-indicated in severe renal impairment, rather than 'avoid where possible' e.g. glimepiride Glimepiride 1 mg Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) and gliclazide - Diamicron 80mg Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) Please can this section be reviewed. Having some information that is missing or incorrect is a concern as some prescribers may use this table as a sole resource.	Thank you for your comment. The content in the table has been updated for specific medicines rather than for medicine classes.
North Wood Group Practice	Guideline	019	General	Visual summary 4, medicines table - Renal impairment - Metformin- please could this section be updated with the dose adjustments that need to be made when eGFR is between 30-45ml/min which are outlined in the SPC - Glucophage 500 mg film coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) Please can this section be reviewed. Having some information that is missing or incorrect is a concern as some prescribers may use this table as a sole resource.	Thank you for your comment. The content in the table has been updated to indicate that dose adjustment may be required and that prescribers should check the BNF for eGFR thresholds.
North Wood Group Practice	Guideline	019	General	Visual summary 4, medicines table - Please see comments below on visual summary 4. Medicines table, which are separately listed	Thank you for your comment. The content in the table has been updated for specific medicines rather than for medicine classes. The committee agreed that contraindications were useful in the table but that prescribers should consult the BNF and SPCs for additional cautions. We have used contraindication content from the BNF (checked November 2021) and have highlighted this to the BNF regarding the BNF content discrepancy with the SPCs. We realised that the MHRA warnings did not provide an exhaustive list if used as a sole resource. We have therefore removed all MHRA warnings as we would expect prescribers to consult the MHRA, BNF, and SPCs before prescribing. The content in the table has been updated to indicate that dose adjustment may be required and that prescribers should check the BNF for eGFR thresholds. Please see individual responses below.

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North Wood Group Practice	Guideline	019	General	Visual summary 4, medicines table - We would welcome a section being added to this table to highlight key side effects - this is partly been added for the MHRA alerts for SGLT-2i however not consistent for all e.g. MHRA alert is missing - GLP-1 receptor agonists: reports of diabetic ketoacidosis when concomitant insulin was rapidly reduced or discontinued - GOV.UK (www.gov.uk). Side effects such as risk of worsening retinopathy for those on insulin and existing retinopathy when starting semaglutide are key prescribing points to consider. Having some information that is missing or incorrect is a concern as some prescribers may use this table as a sole resource	Thank you for your comment. The committee agreed that prescribers should check the BNF and SPCs for side effects. The MHRA warnings have been removed as they did not provide an exhaustive list. We have therefore not included the specific MHRA alert that you have pointed out to us.
North Wood Group Practice	Guideline	020	001	Reviewing drug treatments – at each review of T2DM, adherence to lifestyle and diet interventions should be assessed given that these interventions work synergistically with medications. We would ask that lifestyle and diet are added into the sections e.g. in line 6, could it state 'how to optimise their current treatment regimen (including non-pharmacological management)	Thank you for your comment. The committee added a reference to revisiting advice about diet and lifestyle to the reviewing recommendation in response to your request. The committee agreed that it is important to revisit advice about diet and lifestyle because part of this discussion is to ensure the person is supported with both non-pharmacological and pharmacological interventions to improve their current health and prognosis.
North Wood Group Practice	Guideline	020	005	We would suggest that the bullet point starting with 'stopping medicines that have not worked or not tolerated' state 'check adherence and stop medicines that have not worked or are not tolerated'. If medicines have not worked as people are not taking them, we need to review medication adherence rather than stopping the medication and taking it out of future options due to being ineffective. We would then suggest removing 'adherence to existing medication' in the bullet point below given that adherence has already been covered in the bullet point above	Thank you for your comment. The committee have reworded the recommendation on reviewing drug treatments following stakeholder consultation to bring the points about optimising current treatment regimens, including checking adherence, to the top. They decided against making your suggested changes as they agreed that checking adherence was a key component to facilitate optimising the current regimen. The point about stopping medicines is now directly below this one.
North Wood Group Practice	Guideline	023	013	Choosing treatments - First bullet point discusses person's individual clinical circumstances, preference and needs. Could bullet point 4 be incorporated given that the persons cardiovascular risk and status would be a clinical circumstance. If so, the first bullet point could read 'the person's individual clinical circumstances (including cardiovascular disease [CVD] risk and status) and their preferences and needs	Thank you for your comment. The committee have reworded the recommendation on reviewing drug treatments following stakeholder consultation to make their intentions clearer. However, it decided not to amend the order of the bullets as the entire recommendation should be read before beginning to act on the points included in it.

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North Wood Group Practice	Guideline	023	013	Reviewing and changing treatments - Last bullet point 'check adherence to diet and lifestyle' should be the first bullet point given diet and lifestyle is the cornerstone of T2DM management	Thank you for your comment. Diet and lifestyle advice has been moved to the top of the first page.
North Wood Group Practice	Guideline	023	013	Reviewing and changing treatments - We would suggest that the bullet point starting with 'stop medicines that have not worked or not tolerated' state 'check adherence and stop medicines that have not worked or are not tolerated'. If medicines have not worked as people are not taking them, we need to review medication adherence rather than stopping the medication and taking it out of future options due to being ineffective. We would then suggest the bullet point below starting with Optimise…. Given that adherence has already been covered in the bullet point above	Thank you for your comment. The committee have reworded the recommendation on reviewing drug treatments following stakeholder consultation to make their intentions clearer. However, it decided not to amend the order of the bullets as the entire recommendation should be read before beginning to act on the points included in it.
North Wood Group Practice	Guideline	024	General	If the patient is not at high CVD risk and on metformin only, you would move on to the disease progression flow chart. It is not clear which combinations NICE are recommending without clicking into each of the TA documents. In the previous algorithm, the language used for SGLT-2i is 'offer' and 'consider'. In the metformin monotherapy scenario for those not at high CVD risk, the language reverts back to a TA and uses the words 'may be an option'. For this cohort, are NICE stating that we should be using a DPP-4i, pioglitazone or sulfonylurea over a SGLT-2i and follow the TA's for SGLT-2i? The flow charts could be clearer.	Thank you for your comment. The visual summary reflects the guideline recommendations in that people would be offered a DPP4, pioglitazone, or a sulfonylurea second line. The TAs are included as they are options for some people. We have opted to link to the TAs rather than write out the TA recommendations to keep the summary clear and to one side of A4. We are not recommending that DPP4s, pioglitazone, and sulfonylureas are used in preference to SGLT2s. Where the TA recommendations apply, these should be considered as part of shared decision making alongside the other options.
North Wood Group Practice	Guideline	024	General	The algorithm is less clear on use of triple oral therapies and beyond. The disease progression flow chart may be better set out as a flow chart cascading downwards rather than sideways. It would be clearer if options were detailed as first, second and third line options/intensification as per previous guidance.	Thank you for your comment. We have not detailed 1st, 2nd, and 3rd line intensifications to allow for shared decision making, a person's values and preferences, and clinician discretion based on the factors detailed in the prescribing guidance and the table of options.
North Wood Group Practice	Guideline	024	General	Insulin is mentioned as an option to 'consider' when dual therapy has not controlled HbA1c. What about as third or fourth line? The algorithm suggests insulin should only be considered when dual therapy has not achieved the persons individualised target. Please can insulin be detailed in the algorithm as per the narrative on pages 26-28	Thank you for your comment. The purpose of the visual summaries is to summarise the recommendations in the drug treatment section of the guideline. If prescribers opted to try three oral medicines before insulin and it did not work, we would assume that they would then try insulin. We feel this does not need to be stated in the visual as we did not receive any other stakeholder comments about this.

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North Wood Group Practice	Guideline	024	General	The bottom box states 'switch or add treatments from different drug classes up to triple therapy (dual therapy if metformin contra-indicated). Is the guidance stating that quadruple therapy (triple oral plus GLP-1 analogue) is not recommended? If so, please state this	Thank you for your comment. The GLP mimetic recommendation states that triple therapy, including a GLP-mimetic should be used and this has been reflected in the visual summary.
North Wood Group Practice	Guideline	024	General	Bottom box states The Guideline update recommends SGLT2i use in wider population than technology appraisals published before August 2021.Does this statement mean that all previous TA's are now superseded? However the guideline links to the TA's. This is confusing. Could this be made clearer. If this guideline accept wider use, should the original TA's not be superseded?	Thank you for your comment. The TAs still apply for people not at high CVD risk so we have made that clearer in the visual summaries.
North Wood Group Practice	Guideline	024 022	General 019	We welcome the changes to the GLP-1 mimetic section, specifically the changes from the previous guidance which only recommended their use with metformin and a sulfonylurea out of all oral agents and after three oral drugs have failed to achieve target levels. Given the evidence for cardiovascular risk reduction, should these agents not be classified as third line for those with existing CVD and those at high risk of CVD? In addition, the guidance is suggesting that three oral agents have to be tried prior to offering GLP-1 analogues. We would also ask that the committee reconsider the requirement to try three oral agents prior to considering a GLP-1 analogue and consider a GLP-1 analogue after two oral agents. Adding on a DDP-4 to an SGLT2 and metformin would be the similar cost to that of changing to a GLP-1 as a 3rd line and likely to produce good glycaemic control, reduce CVD risks and less polypharmacy. If using after three oral agents have failed to meet the HbA1c target, does the committee have a preference on which agent should be stopped (other than a DPP-4 inhibitor) in order to start a GLP-1 analogue? Please could we ask for clarity on where oral semaglutide fits within the treatment pathway. Do NICE suggest that oral semaglutide is offered as an equal offer alongside those injectable GLP-1 analogues with cardiovascular outcome trials showing cardiovascular benefits	Thank you for your comment. The committee reviewed the stakeholder comments regarding the use of GLP-1 mimetics and examined the updated economic evidence relating to GLP-1 mimetic treatment for people with type 2 diabetes and high cardiovascular risk. In the NICE health economic analyses, when looking at GLP-1 mimetics as a class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of £20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the

					intervention as an effective use of NHS resources will specifically take account of the following factors." and • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis." Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-

					effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors. In addition, the committee noted that there were differences in the clinical effectiveness of the 2 forms of semaglutide. Although the acquisition costs for injectable and oral semaglutide are similar they showed marked differences in cost-effectiveness in the economic analyses. This was caused by differences in the effect estimates for stroke, myocardial infarction and severe hypoglycaemia. From earlier discussions about the clinical evidence (see the discussion sections in the evidence review for more details) the committee had agreed that it was uncertain whether the observed differences in effect on all-cause mortality compared to placebo between the 2 forms of semaglutide were real and they therefore decided not to place undue weight on them. They had also noted that this uncertainty and any other differences in effects between the drugs for other outcomes was probably due to wide 95% confidence intervals for many outcomes with these drugs, due to the smaller numbers of participants and events in the trials compared to other CVOTs. Due to the higher level of uncertainty surrounding the cost-effectiveness of the GLP-1 mimetics as a class compared to the SGLT2 inhibitors, the committee considered whether to recommend injectable semaglutide for people at high cardiovascular risk in whom an SGLT2 is contraindicated or not tolerated. However, taking into account the uncertainty in the cost-effectiveness and clinical effectiveness the committee decided against recommending injectable semaglutide for this population. In the absence of the GLP-1s being cost-effective treatments for people with high CV risk or established cardiovascular

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					disease, the existing 2015 recommendations for when to use GLP-1s were retained. These apply to the general population of people with type 2 diabetes. Since no new non- cardiovascular outcome trial evidence regarding the benefits of GLP-1s was included in this review the committee were unable to amend or rewrite the 2015 criteria for GLP-1 use in this current update. They were therefore unable to add any information to indicate which agent should be stopped in order to start a GLP-1 analogue. Oral semaglutide was not cost-effective in any of the base case scenarios for people with high CV risk or with established cardiovascular disease. The committee were therefore unable to make any recommendations for use within this population. As noted above the 2015 recommendations that placed GLP-1s as a class later in the treatment pathway were retained and so oral semaglutide would be an option at this point but not before.
North Wood Group Practice	Guideline	024	General	Insulin therapy box - Dapagliflozin TA 418 does not include insulin. Empagliflozin (TA 336) does include insulin however is not listed as an option here. Please can this section be reviewed to ensure the correct options are listed	Thank you for your comment. Dapagliflozin TA288 does include insulin and has been linked in this section. Empagliflozin has now been listed as an option here also.
North Wood Group Practice	Guideline	024	General	Insulin therapy box - The term 'antidiabetic' drugs is used. Given the NHS England language matters document, please could this language be reviewed.	Thank you for your comment. The word 'antidiabetic' has been removed.
North Wood Group Practice	Guideline	024	General	Switching or adding treatment box - Technology Appraisal for empagliflozin for dual therapy and triple therapy should read (and link to) TA336 and not 366	Thank you for your comment. The error has been amended.
North Wood Group Practice	Guideline	024	General	Switching or adding treatment box - The different SGLT-2i are listed in different orders, should this be consistent ie alphabetically, in order of TA number, or other?	Thank you for your comment. These have now been put alphabetical order.
North Wood Group Practice	Guideline	025	General	Patient decision aid - Whilst we welcome a patient decision aid that is not overwhelming, the previous NICE guidance had a summary for patients on benefits vs risks of the different agents for glucose lowering. Could this document have a brief table summarising risks versus benefits for each	Thank you for your comment. The information summarising the advantages and disadvantages of medicine is now within the guideline visual summary. Regarding the PDA, The Flesch-Kincaid reading ease score suggests it will be

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				agent? We would also recommend that the language within the patient decision aid be reviewed.	understandable by people with a reading age of 11-13. This is in line with the NICE PDA standards.
North Wood Group Practice	Guideline	025	General	Patient decision aid - First sentence in the document states' if you have type 2 diabetes, you will have higher levels of glucose (sugar) in your blood.' This assumes that all people with T2DM have high glucose levels which is not the case. Should the words ' you will' be changed to ' you may'?	Thank you for your comment. We have amended the PDA as you suggest: 'If you have type 2 diabetes you may have higher levels of glucose (sugar) in your blood.'
North Wood Group Practice	Guideline	025	General	Visual summary 4. Medicines table - Please see comments above on visual summary 4. Medicines table, which are separately listed	Thank you for your comment. The content in the table has been updated for specific medicines rather than for medicine classes. The committee agreed that contraindications were useful in the table but that prescribers should consult the BNF and SPCs for additional cautions. We have used contraindication content from the BNF (checked November 2021) and have highlighted this to the BNF regarding the BNF content discrepancy with the SPCs. We realised that the MHRA warnings did not provide an exhaustive list if used as a sole resource. We have therefore removed all MHRA warnings as we would expect prescribers to consult the MHRA, BNF, and SPCs before prescribing. The content in the table has been updated to indicate that dose adjustment may be required and that prescribers should check the BNF for eGFR thresholds. Please see individual responses below.
North Wood Group Practice	Guideline	General	General	We would welcome a link to the draft recommendations (will be final when this document is finalised) on treatment for adults with chronic kidney disease and type 2 diabetes (2021)	Thank you for your comment. The renal benefits of using SGLT2 inhibitors in people with type 2 diabetes and CKD have been assessed in a separate piece of work that has recently been out for stakeholder consultation and was published in November 2021. The final recommendations on renal and cardiovascular benefits will be brought together in a single updated guideline document when this current work on cardiovascular benefits is published in 2022.
Novo Nordisk	Evidence review A	036	022 - 038	**10.Given the heterogeneity in the CVOT trials, the use of unadjusted Hazard Ratios is entirely inappropriate.**	Thank you for your comment. You are correct that unadjusted hazard ratios were used in the analysis. In the absence of individual patient data, the committee agreed that there were no established methods for adjusting these

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				The guideline update makes no to attempt to control for these differences, despite acknowledging the affect this may have on the results. The committee state that they '*acknowledged differences in the included trials which may have an effect on the outcomes. For example, six of the 16 studies only included people with established CVD, and the remaining trials included people with established CVD and those at risk'* and went on to acknowledge caution should be taken when generalising these findings. This, surely, is not the level of certainty to base the guideline on. The effect of not adjusting the HR is demonstrated in the published literature, for example, a published matching-adjusted indirect comparison (MAIC) aimed to assess how the efficacy of once-weekly injectable semaglutide would change if the CVOT had enrolled the REWIND population. This analysis found that the HR for MACE for semaglutide versus placebo fell from 0.75 to 0.65, which would have a notable impact on the health economic analysis published by NICE. This shows how important controlling for differences in the study populations is in order to generate a robust comparison of relative efficacy. It is hard to understand the logic of the decision, given the fact that a "surrogate marker" was derived for the comparison arm rather than use the standard care arms in the CVOT trials, justified on the basis that their *"limited applicability to the population being considered in this guideline update (all people with Type 2 diabetes) as they are restricted to people with high cardiovascular risk"* (HE report, page 10, line 30). How the guideline can then proceed to apply HR from these "high risk" populations to "all people with Type 2 diabetes"; is logically inconsistent. That no attempts to control for this have been made in the analysis is a significant weakness of the analysis, and the results of the analysis are unreliable. **Reference:** Evans LM, Mellbin L, Johansen P, Lawson J, Paine A, Sandberg A. A population-adjusted indirect comparison of cardiovascular benefits of once-weekly subcutaneous semaglutide and dulaglutide in the treatment	data that could be conducted that would increase their confidence in the effect estimated. In particular, they noted that standard MAIC analyses required access to the individual patient data from at least some of the trials in the analysis (see NICE DSU Technical Support Document 18), and as such data were not available to them, they agreed no such analyses could be robustly undertaken. They noted that simply having populations at different risk levels in different trials would not be a source of bias in the results, as this should not impact on the relative effects estimated in the trials and subsequently used to populate the model. A concern would only arise if there were systematic differences between the trials in characteristics that would affect relative (and not just absolute) treatment effectiveness and, while the data did not allow the committee to completely rule out this possibility, there were not clear clinical reasons they were aware of to suspect that such a pattern would exist. Nonetheless, the committee agreed the between trial heterogeneity was a source of uncertainty in the analysis, and considered this as part of their decision-making, as detailed in the committee discussion-section of the evidence review. In particular, they noted that uncertainty would in general lead towards making weaker rather than stronger recommendations, and therefore any factors that led them to be more uncertain would lead to a smaller number of treatment options being recommended as cost-effective, rather than a larger number of options. With regard to the specific quotation cited about extrapolating the results of the included RCTs to the lower risk population, the committee agreed applying the hazard ratios from the trials to this lower risk population was a significant extrapolation, and one they were uncomfortable

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				of patients with type 2 diabetes, with or without established cardiovascular disease. Endocrinol Diabetes Metab. 2021;4(3):e00259.	with, as detailed in the committee discussion section. This is one of the reasons why no additional recommendations were made for the population of all people with type 2 diabetes, and the positive new recommendations made for SGLT2 inhibitors were restricted to those individuals at high cardiovascular risk, to better match the included populations in the RCTs.
Novo Nordisk	Guideline	001 - 032	General	**4. The draft guideline and the narrow scope has resulted in weight not being prioritised or even considered as a relevant factor in guiding clinical decision making.** Weight is mentioned only 11 times in the guideline text, all of which relate to existing 2015 recommendations. Of these 11, only 3 relate to treatment decision-making and are in relation to the BMI restriction for initiation of GLP-1RAs (x1) and the stopping rules for GLP-1RAs (x2). At no point in the draft guideline is the positive need for weight reduction considered as a relevant factor in clinical decision-making. Over 90% of people with Type 2 diabetes live with overweight or obesity[1]. It is a risk factor for CVD[2], depression[3] and death from COVID-19[4]. It seems implausible that NICE has not considered assessment of weight as an important clinical characteristic informing treatment choice, either as part of decision-making for reducing CV risk or in the wider recommendations for individualised care. Retaining recommendations from the 2015 glycaemic-focused guideline disadvantages patients for whom weight is a significant issue as no individualised guidance is provided in terms of prescribing decisions and medicines which cause weight gain are recommended for use over GLP-1RAs which support weight loss. We recommend NICE conducts an urgent review of the 2015 recommendations to provide up-to-date guidelines for this important and significant group of patients. **References** 1. Public Health England, Adult obesity and type 2 diabetes. 2014. Available from	Thank you for your comment. The way the data on weight and BMI from the included cardiovascular outcome trials was reported was very variable and, in most cases, not comparable. The data was therefore not included in the clinical review findings, but weight was taken into consideration for the economic modelling as follows. For changes in weight, it was noted it was important not to double count the impact of changes in the economic model, as the effects on cardiovascular outcomes should already be captured in the outcomes of those trials. It was therefore agreed that the most appropriate approach was to only include the direct quality of life gains associated with reductions in weight, with the other benefits captured through the cardiovascular event data. The committee noted that if anything the approach taken in the economic model may overestimate the benefits of weight reduction, as some of the estimated quality of life gains may be the result of avoided cardiovascular events, but it was agreed to be the best data source available. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted.

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				ttps://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/338934/Adult_obesity_and_type_2_diabetes_.pdf. Accessed Sep 21 2. Tiffany M. Powell-Wiley et al. Obesity and Cardiovascular Disease: A Scientific Statement From the American Heart Association . Circulation. Volume 143, Issue 21, 25 May 2021; Pages e984-e1010 3. F Luppino et al. Overweight, Obesity, and Depression. A Systematic Review and Meta-analysis of Longitudinal Studies. Arch Gen Psychiatry. 2010;67(3):220-229 4. N Holman et al, Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study; Lancet Diabetes Endocrinology. 2020; 8(10): p. 823-833; Available from: https://doi.org/10.1016/S2213-8587(20)30271-0 [Accessed Sep 2021]	This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand..
Novo Nordisk	Guideline	010	General	**24.Figure 1 Your target HbA1c: weighing it up decision aid in its current form risks the adoption of inappropriate target HbA1c levels** • Having severe hypos would be a significant issue for any individual, irrespective of whether they drive or operate machinery. Similarly, logically it can be assumed that most people would prefer not to live with side effects from their medicine. Dividing quality of life decisions into shorter and longer term is overly simplistic and unlikely to lead to constructive decision-making. • Used in isolation and in the absence of a joined-up discussion about treatment and management choices that affect these factors, the current wording in this decision aid is very likely to encourage people to choose a higher HbA1c, putting them at increased risk of complications from their diabetes as well as impacting their immediate quality of life as a result of unnecessarily high blood sugar levels. We suggest this is re-worded in places and supporting information included to provide the necessary context about how treatment and management	Thank you for your comments. We have removed reference to driving from the visual analogue scale (the PDA text retains the words '. some [hypos] can cause people to feel dizzy or faint and, they might need help from someone else to treat the hypo. There are special rules for some drivers who have diabetes – talk to your diabetes team to see if they affect you.') The figure is intended as a basis for discussion between the healthcare professional and the person with diabetes. Moreover, the choices are not binary but the visual analogue scale enables the person to indicate the extent to which they agree with either statement. We agree that most people would wish to avoid side effects and not take unnecessary medicines. However, we hope that putting these considerations alongside others, such as life expectancy, will encourage discussions between the healthcare professional and person with diabetes to support informed decision making and a better shared understanding of the issues at play.

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				choices are part of the informed decision-making process on agreeing a target HbA1c.	
Novo Nordisk	Guideline	015	007 - 028	**21.Lack of clinical application to evidence of CV outcome data.** Whilst we are encouraged that NICE have reviewed the cardiovascular outcomes trials evidence, the clinical guidance is not sufficiently clear beyond the initiation of an SGLT-2i, or for those patients where an SGLT2i is deemed unsuitable (contra-indicated, not tolerated or no longer responding). Omitting an alternative choice medicine with evidence of CV risk reduction will create additional confusion for clinicians in conversations with their patients on medicine decisions. Instead, NICE has retained second and third line therapy recommendations from the 2015 guideline (DPP-4 inhibitors, pioglitazone, sulphonylureas), including for patients with high CV risk and established CVD. This is despite some of these medicines not demonstrating a CV benefit and without assessing their overall risk-benefit for specific patient needs such as hypoglycaemia, weight reduction and CKD. We recommend NICE reviews the recommendations and provides an alternative medicine choice with clinical evidence of CV risk reduction to SGLT-2is for patients with established CVD or at high CV risk, to help clinicians with their decision-making.	Thank you for your comment. Although there were a number of stakeholder comments asking for clarification of the treatment options for people with type 2 diabetes in whom SGLT2 inhibitors (SGLT2i) were contraindicated or not tolerated, there were no cardiovascular outcome trial style clinical trials identified that looked at the effectiveness of treatments for people at high cardiovascular (CV) risk in this population. The committee therefore used the evidence for effectiveness and cost effectiveness for other interventions from the same economic modelling scenarios as those looking at the cost- effectiveness of SGLT2i. The committee reviewed the stakeholder comments regarding the use of GLP-1 mimetics and examined the updated economic evidence. In the NICE health economic analyses, when looking at GLP-1 mimetics as a class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of £20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the

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					intervention as an effective use of NHS resources will specifically take account of the following factors." and • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis." Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori

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					that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors. In addition, the committee noted that there were differences in the clinical effectiveness of the 2 forms of semaglutide. Although the acquisition costs for injectable and oral semaglutide are similar they showed marked differences in cost-effectiveness in the economic analyses. This was caused by differences in the effect estimates for stroke, myocardial infarction and severe hypoglycaemia. From earlier discussions about the clinical evidence (see the discussion sections in the evidence review for more details) the committee had agreed that it was uncertain whether the observed differences in effect on all-cause mortality compared to placebo between the 2 forms of semaglutide were real and they therefore decided not to place undue weight on them. They had also noted that this uncertainty and any other differences in effects between the drugs for other outcomes was probably due to wide 95% confidence intervals for many outcomes with these drugs, due to the smaller numbers of participants and events in the trials compared to other CVOTs. The committee therefore agreed that they were unable to recommend injectable semaglutide for people with type 2 diabetes and high cardiovascular risk who were unable to take an SGLT2i. As a result, the committee noted that people with high CV risk who could not take the recommended dual therapy of metformin and SGLT2, because they are unable to take the SGLT2, would be

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					offered metformin alone at treatment initiation. If they were also unable to take metformin then the clinician would select another treatment from the remaining options, namely sulfonylureas, DPP-4s or pioglitazone, depending on the individual's clinical circumstances and preferences. The committee decided against listing the options for people with type 2 diabetes who were at high CV risk and could not take an SGLT2i because they thought that this was an unnecessary level of detail given that they could not recommend a GLP-1 mimetic in place of the SGLT2i, that the treatment options were therefore the same for these people as for the rest of the type 2 diabetes population and because, apart from for metformin, the guideline does not include details of which drug to take if a particular drug is contraindicated or not tolerated but rather expects the prescriber to use their clinical judgment. The committee wanted to keep the pathway as simple as possible, and they agreed that it would not be possible to do this if alternative options were provided every time a drug was not contradicted or not tolerated. However, they agreed that it was appropriate to have recommendations for metformin being contradicted or not tolerated because this is the drug that the majority of people would take as first-line therapy.
Novo Nordisk	Guideline	015 016 017	022 - 0028 001 - 028 001 - 0011	**23.In direct answer to question 4 asked by NICE**: *Should the recommendation for treatment options for people with type 2 diabetes in whom metformin is contraindicated / not tolerated after treatment initiation be retained or stood down? We propose retaining the recommendations for treatment initiation for these people but standing down recommendation 1.7.20 covering later treatment options. Do you agree or disagree and why?* The proposed recommendations for alternatives to Metformin as initial treatment therapy are confusing, both in the guideline text and in visual summary 2. Additionally, the addition of 'as dual therapy' to the recommendation for Repaglinide as an alternative to Metformin could	Thank you for your feedback to this question. Based on stakeholder feedback the recommendation that refers to repaglinide has been stood down as stakeholders advised that this treatment is rarely used in practice now. We asked this question to determine whether it was useful to retain the recommendations *for* people with type 2 diabetes in whom metformin is contraindicated / not tolerated after treatment initiation because the committee thought that they made the pathway unnecessarily complex and hard to follow. We do not need to have updated the recommendations in a particular section to stand down

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				cause additional confusion as it doesn't exclude it's use in triple therapy (off license use). We agree in reference to recommendation 1.7.20 that this should be stood down. Although insulin is ultimately a consequence for treatment for many people living with type 2 diabetes, alternative options should be explored if clinically relevant before commencing insulin. However, we are unclear as to why this particular question is being asked when none of the broader glycaemic control evidence or recommendations have been evaluated and the rest of the 2015 recommendations are being retained unchanged?	existing recommendations if they are thought to be out of date, like the repaglinide recommendation.
Novo Nordisk	Guideline	018	General	**26.The overall impression of Visual Summary 2 is that it is confusing and not patient centred.** The top box suggests an assessment of HbA1c, cardiovascular risk and kidney function; however, there is no guidance as to how HbA1c and kidney function influence choice of treatment. Additionally, weight, frailty and hypoglycaemia risk have not been identified as a consideration. This visual summary does not correspond to prescribing guidance in visual summary 1 (page 17) where the very first point for choosing treatments is the person's individual clinical circumstances and their preferences and needs.	Thank you for your comment. The approach to pulling together guideline recommendations in a visual form is a proof of concept. We will be continually reviewing our processes and will be updating the visual summaries based on changes to recommendations and following feedback from stakeholders and users. Factors that influence patient choice and prescribing are given in the choosing medicines table.
Novo Nordisk	Guideline	022	019 - 020	**8.Inaccurate and misleading recommendation with respect to GLP-1RA indication** The statement "*Do not offer GLP-1 mimetic therapy to adults with type 2 diabetes solely for cardiovascular risk reduction*" may misleadingly give the impression that this class of medication is indicated solely for CV risk reduction which they are not. Furthermore, this may create confusion and be interpreted that these medicines are contra-indicated for patients with high CV risk, contrary to published evidence. We strongly recommend that this statement is removed.	Thank you for your comment. The committee have taken stakeholder comments into account and agreed to remove the recommendation about not using GLP1-mimetic therapy solely for cardiovascular risk reduction in people with type 2 diabetes. Upon reviewing the recommendation, the committee agreed that it was inappropriate to make a decision about treatment choice based solely on a single factor (cardiovascular risk) and that, as detailed in the recommendation on choosing drug treatments, multiple factors should be taken into account instead.

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Novo Nordisk	Guideline	024	General	**27.The overall impression of Visual Summary 3 is that it is confusing and not patient centred.** The visual is entitled 'Disease progression' which, in itself, is not clear that it applies to drug treatment decisions after 1st line therapy. Furthermore, additional consideration for disease progression beyond HbA1c and CV risk have not been included. The GLP-1RA box is not linked within the flow of a treatment pathway to clearly indicate at what point a therapy from the class should be considered. It replicates (excepting one small change) existing restrictive recommendations for this class that, given that new evidence has not been assessed, cannot be said to remain valid. The box entitled 'insulin therapy' is limited only to consideration of insulin after dual therapy, a recommendation NICE is considering removal of. There is no guidance on which type of insulin to consider when and where. This seems to be a backwards step from the existing NG28 algorithm which includes some guidance on this. The reduced scope has meant that new evidence and costs of insulins has not been considered, resulting in lack of up-to-date guidance for clinicians for a therapy that requires careful consideration. This visual summary provides no clear guidance to a clinician on how to choose treatments sequentially based on the evidence base and individualised care.	Thank you for your comment. The committee reviewed the stakeholder comments regarding the use of GLP-1 mimetics and examined the updated economic evidence relating to GLP-1 mimetic treatment for people with type 2 diabetes and high cardiovascular risk. In the NICE health economic analyses, when looking at GLP-1 mimetics as a class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of £20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the intervention as an effective use of NHS resources will specifically take account of the following factors." and • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending

					a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis." Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors. In addition, the committee noted that there were differences in the clinical effectiveness of the 2 forms of semaglutide. Although the acquisition costs for injectable and oral semaglutide are similar they showed marked differences in

					cost-effectiveness in the economic analyses. This was caused by differences in the effect estimates for stroke, myocardial infarction and severe hypoglycaemia. From earlier discussions about the clinical evidence (see the discussion sections in the evidence review for more details) the committee had agreed that it was uncertain whether the observed differences in effect on all-cause mortality compared to placebo between the 2 forms of semaglutide were real and they therefore decided not to place undue weight on them. They had also noted that this uncertainty and any other differences in effects between the drugs for other outcomes was probably due to wide 95% confidence intervals for many outcomes with these drugs, due to the smaller numbers of participants and events in the trials compared to other CVOTs. Due to the higher level of uncertainty surrounding the cost-effectiveness of the GLP-1 mimetics as a class compared to the SGLT2 inhibitors, the committee considered whether to recommend injectable semaglutide for people at high cardiovascular risk in whom an SGLT2 is contraindicated or not tolerated. However, taking into account the uncertainty in the cost-effectiveness and clinical effectiveness the committee decided against recommending injectable semaglutide for this population. In the absence of the GLP-1s being cost-effective treatments for people with high CV risk or established cardiovascular disease, the existing 2015 recommendations for when to use GLP-1s were retained. The committee agreed with the need to produce guidance to help promote personalised treatment. The original scope of this work covered additional groups of interest including people with renal impairment, people in specific ethnic groups, adults aged 65 years and older, as well as people in specific cardiovascular risk groups. It aimed to fully update the drug treatment sections of the NG28 guideline. However,

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					once work on the topic commenced it was determined that updating evidence reviews and health economics for such a wide scope, within the resources available to NICE for this topic, would take an unacceptably lengthy period. Taking such an approach for this guideline update would have further delayed publication of updated treatment recommendations in this rapidly changing area. In view of the timescales involved and the appetite from the committee and stakeholders for an update within an acceptable time period, we worked with our committee members to identify the priority areas for this update. The committee members agreed that our initial focus should be on reviewing the evidence from trials looking at cardiovascular outcomes. This reflected the changing evidence base as a result of the significant investment in clinical trials to directly capture cardiovascular outcomes, feedback from stakeholders that assessing this evidence was a priority and the impact that this new evidence could have on recommendations for the treatment of people with diabetes. We therefore revised the scope to reflect this and carried out the current piece of work.
Novo Nordisk	Guideline	025	General	Visual summary 4 **22.Factually incorrect recommendation regarding GLP-1RA use in renal impairment.** The guidance for GLP-1RA "avoid or use with caution" is incorrect. Four out of the seven GLP-1RAs can be used without dose adjustment in severe renal impairment. To say that the class should be avoided or used with caution is unhelpful, particularly when there are already such limited options for these patients. There appears to have been greater consideration given to the information provided for the other classes.	Thank you for your comment. This content has been updated for specific medicines rather than for medicine classes.

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				This statement needs to be corrected to reflect that certain medications in the GLP-1RA class can be used in this group of patients where options are limited.	
Novo Nordisk	Guideline	056 - 058 057	General 027 - 031	**25.Appendix A Patient decision aid** • The decision aid should include the NICE agreed HbA1c targets[1]. Without this as a baseline people with type 2 diabetes will be unable to make an informed decision about what their own HbA1C target should be. • Line 29 should be amended so that people understand that there is a link between certain types of medicines and the risk of hypoglycaemia. We suggest it is amended to read: '*Depending on what medicines you are taking* there might be times when your blood sugar level goes too low' • It is incorrect to state that the 'lower the target HbA1c you aim for, the more likely you are to get hypos'; this is biased against medicines which have a low risk of causing hypoglycaemia and will encourage people to aim for a higher HbA1C, putting them unnecessarily at higher risk of developing complications from their diabetes. We suggest this line is removed. • The decision aid sets out with the intent to help people with Type 2 diabetes choose and agree an HbA1c target. However, by excluding information about what the suggested target levels are and by excluding the direct link between medicines and their effect on HbA1c, including side effects, it is currently an incomplete document which will not help people with type 2 diabetes to make an informed decision. We recommend the decision aid is re-written to include all the relevant information required. **Reference** 1. NICE. Type 2 diabetes in adults: management. 2015. Section 1.6 (1.6.1-1.6.11). Available from	Thank you for your comments. The starting point is the targets given in recommendations 1.6.7 and 1.6.8. The aim of the PDA is to support an individualised discussion between the healthcare professional and person with diabetes. The committee felt that putting specific target values in the PDA or visual analogue scale could be too restrictive and counter-productive to the aim of support shared decision making. They emphasised the need for dialogue that is tailored to the person's individual circumstances, preferences, goals and values. Although certain medicines may directly cause hypoglycaemic episodes (hypos), intensive control is associated with an increased risk of severe hypos (see NG28 full guideline and appendix D). We have amended the wording in the PDA and highlighted that some medicines are more likely to cause hypos than others. Information on the pros and cons of different medicines is included in the visual summary that can be used alongside the PDA.

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				https://www.nice.org.uk/guidance/ng28/chapter/Recommendations. Accessed Sep 2021	
Novo Nordisk	Guideline	General	General	**1.The significant change in scope has led to an incomplete evidence review and the partial update of the guideline has limited clinical applicability.** There is significant change versus the published scope in July 2020. This narrowed scope does not sufficiently cover areas identified during surveillance and is inconsistent with the committee's conclusion that a "larger scale update of the antidiabetic drug pathway in NICE NG28 be undertaken". This decision was based on an evidence review, unanimous expert opinion and stakeholder comments. To be precise just over 100 publications were identified by NICE at the surveillance phase as "new evidence identified that may change current recommendations." In contrast, this 'rapid update' has resulted in less than 20% of this evidence being assessed (16 cardiovascular outcome trials) and has retained the majority of the recommendations from the 2015 drug pathway. It has been 6 years since the previous update and clinical practice has significantly evolved. In the absence of NICE guideline updates in type 2 diabetes, many local pathways have been developed to reflect evidence-based decision making; this partial update therefore will have limited clinical applicability. A more comprehensive review and update is urgently needed to provide guidance for the holistic management of people with type 2 diabetes and to ensure this key guideline is based on up-to-date evidence. We, therefore, propose that NICE retract this draft guideline and issue a draft scope based on the surveillance decision for consultation.	Thank you for your comment. The original scope of the update to the drug treatment sections of NG28 was to fully update the treatment section of the guideline as your comment notes. However, once work on the topic commenced it was determined that updating evidence reviews and health economics for such a wide scope, within the resources available to NICE for this topic, would take an unacceptably lengthy period. Taking such an approach for this guideline update would have further delayed publication of updated treatment recommendations in this rapidly changing area. In view of the timescales involved and the appetite from the committee and stakeholders for an update within an acceptable time period, we worked with our committee members to identify the priority areas for this update. The committee members agreed that our initial focus should be on reviewing the evidence from trials looking at cardiovascular outcomes. This reflected the changing evidence base as a result of the significant investment in clinical trials to directly capture cardiovascular outcomes, feedback from stakeholders that assessing this evidence was a priority and the impact that this new evidence could have on recommendations for the treatment of people with diabetes. We therefore revised the scope to reflect this carried out the current piece of work. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder

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					comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand.
Novo Nordisk	Guideline	General 042	General 028 - 030	**2.The draft guideline does not reflect the totality of evidence to inform prescribing decisions for GLP-1RAs and is biased against the GLP1-RA class.** The evidence base for all currently available Glucagon-like peptide 1 receptor agonists (GLP-1RAs) has not been reviewed by Technology Appraisals nor by the Guidelines Programme and NICE, in this draft, defer to the 2015 GLP-1RA recommendations. Since 2015, three GLP-1RAs have been licensed (Trulicity®, Ozempic®, and Rybelsus®) but, unlike SGLT2-is, the evidence for these medicines in terms of metabolic benefits (glycaemic efficacy and weight loss), CV benefit and cost effectiveness has not been formally assessed by NICE. This narrow update only reviews the Cardiovascular Outcome Trials (CVOTs) and has not assessed where GLP-1RAs should appropriately be placed within the overall treatment pathway. There has been no evaluation or review of BMI initiation criteria, stopping rules or differentiation within the class or of recommending their use prior to insulin. Clinical benefits of GLP1-RAs for cardiovascular risk reduction have also been disregarded on the grounds of a lack of cost-effectiveness (please refer to our comments about economic modelling). In addition, the draft guideline provides no clear recommendation on what to do if an SGLT2i is contraindicated, not tolerated or unsuitable, and classes of glucose-lowering therapy without CV benefit are still being recommended in the CV pathway prior to initiation of GLP-1RAs. Moreover, there is a particular concern, that despite this narrow review there are assumptions made on lack of cost-effectiveness for GLP1-RAs.	Thank you for your comment. The original scope of the update to the drug treatment sections of NG28 was to fully update the treatment section of the guideline as your comment notes. However, once work on the topic commenced it was determined that updating evidence reviews and health economics for such a wide scope, within the resources available to NICE for this topic, would take an unacceptably lengthy period. Taking such an approach for this guideline update would have further delayed publication of updated treatment recommendations in this rapidly changing area. In view of the timescales involved and the appetite from the committee and stakeholders for an update within an acceptable time period, we worked with our committee members to identify the priority areas for this update. The committee members agreed that our initial focus should be on reviewing the evidence from trials looking at cardiovascular outcomes. This reflected the changing evidence base as a result of the significant investment in clinical trials to directly capture cardiovascular outcomes, feedback from stakeholders that assessing this evidence was a priority and the impact that this new evidence could have on recommendations for the treatment of people with diabetes. We therefore revised the scope to reflect this carried out the current piece of work.

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				The points outlined in the committee's deliberation of the guideline, page 42, lines 28-30 state: *"These recommendations set tight limits on who should be offered a GLP-1 mimetic, based on the lack of cost effectiveness of this treatment for most people in the 2015 guideline".* The full evidence base for these products has not been reviewed by NICE and therefore NICE cannot know whether its 2015 recommendations remain valid (many of which date back even further to the 2009 predecessor guidelines). Given that three new GLP1RAs have become available since the publication of the 2015 guidelines, demonstrating increased efficacy to existing GLP1-RAs at no additional cost, there is no evidence to support that that this conclusion is still accurate. In fact, there is evidence to suggest it is inaccurate[1-5], and such sweeping generalisations may unduly bias the committee on this class of medicines. **References:** 1. Capehorn M, Hallén N, Baker-Knight J, Glah D, Hunt B. Evaluating the Cost-Effectiveness of Once-Weekly Semaglutide 1 mg Versus Empagliflozin 25 mg for Treatment of Patients with Type 2 Diabetes in the UK Setting. Diabetes Ther. 2021 Feb;12(2):537-555. doi: 10.1007/s13300-020-00989-6. Epub 2021 Jan 9. PMID: 33423240; PMCID: PMC7846640. 2. Viljoen A, Hoxer CS, Johansen P, Malkin S, Hunt B, Bain SC. Evaluation of the long-term cost-effectiveness of once-weekly semaglutide versus dulaglutide for treatment of type 2 diabetes mellitus in the UK. Diabetes Obes Metab. 2019 Mar;21(3):611-621. doi: 10.1111/dom.13564. Epub 2018 Nov 28. PMID: 30362224; PMCID: PMC6587509. 3. Bain SC, Hansen BB, Malkin SJP, Nuhoho S, Valentine WJ, Chubb B, Hunt B, Capehorn M. Oral Semaglutide Versus Empagliflozin, Sitagliptin and Liraglutide in the UK: Long-Term Cost-Effectiveness Analyses Based on the PIONEER Clinical Trial Programme. Diabetes Ther. 2020 Jan;11(1):259-277. doi: 10.1007/s13300-019-00736-6. Epub 2019 Dec 12. PMID: 31833042; PMCID: PMC6965564. 4. Johansen P, Chubb B, Hunt B, Malkin SJP, Sandberg A, Capehorn M. Evaluating the Long-Term Cost-Effectiveness of	When producing guidelines, NICE considers both effectiveness and cost-effectiveness for all of the recommendations it makes. As well as helping to ensure the recommendations made represent the best use of NHS resources (in particular, the opportunity costs of spending additional resources), this is also required by the legislation that originally established NICE (the Health and Social Care Act 2012), which states that when exercising its functions, NICE must have regard to "the broad balance between the benefits and costs of the provision of health services or of social care in England." NICE's principles further refine this by explicitly stating that "if possible, NICE considers value for money by calculating the incremental cost-effectiveness ratio" and "interventions with an ICER of less than £20,000 per QALY gained are generally considered to be cost effective." This guidance was developed in line with both these statutory requirements, and NICE's stated principles, methods and processes. Although there were a number of stakeholder comments asking for clarification of the treatment options for people with type 2 diabetes in whom SGLT2 inhibitors (SGLT2i) were contraindicated or not tolerated, there were no cardiovascular outcome trial style clinical trials identified that looked at the effectiveness of treatments for people at high cardiovascular (CV) risk in this population. The committee therefore used the evidence for effectiveness and cost effectiveness for other interventions from the same economic modelling scenarios as those looking at the cost-effectiveness of SGLT2i. The committee reviewed the stakeholder comments regarding the use of GLP-1 mimetics and examined the updated economic evidence relating to GLP-1 mimetic treatment for people with type 2 diabetes and high cardiovascular risk.

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				5. Once-Weekly Semaglutide Versus Once-Daily Liraglutide for the Treatment of Type 2 Diabetes in the UK. Adv Ther. 2020 May;37(5):2427-2441. doi: 10.1007/s12325-020-01337-7. Epub 2020 Apr 18. PMID: 32306244; PMCID: PMC7467468. Johansen P, Sandberg A, Capehorn M. A Relative Cost of Control Analysis of Once-Weekly Semaglutide Versus Exenatide Extended-Release, Dulaglutide and Liraglutide in the UK. Adv Ther. 2020 Mar;37(3):1248-1259. doi: 10.1007/s12325-020-01242-z. Epub 2020 Feb 11. PMID: 32048148; PMCID: PMC7089718.	In the NICE health economic analyses, when looking at GLP-1 mimetics as a class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of £20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the intervention as an effective use of NHS resources will specifically take account of the following factors." and • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis." Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable

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					semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors. In addition, the committee noted that there were differences in the clinical effectiveness of the 2 forms of semaglutide. Although the acquisition costs for injectable and oral semaglutide are similar they showed marked differences in cost-effectiveness in the economic analyses. This was caused by differences in the effect estimates for stroke, myocardial infarction and severe hypoglycaemia. From earlier discussions about the clinical evidence (see the

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					discussion sections in the evidence review for more details) the committee had agreed that it was uncertain whether the observed differences in effect on all-cause mortality compared to placebo between the 2 forms of semaglutide were real and they therefore decided not to place undue weight on them. They had also noted that this uncertainty and any other differences in effects between the drugs for other outcomes was probably due to wide 95% confidence intervals for many outcomes with these drugs, due to the smaller numbers of participants and events in the trials compared to other CVOTs. The committee therefore agreed that they were unable to recommend injectable semaglutide for people with type 2 diabetes and high cardiovascular risk who were unable to take an SGLT2i. As a result, the committee noted that people with high CV risk who could not take the recommended dual therapy of metformin and SGLT2, because they are unable to take the SGLT2, would be offered metformin alone at treatment initiation. If they were also unable to take metformin then the clinician would select another treatment from the remaining options, namely sulfonylureas, DPP-4s or pioglitazone, depending on the individual's clinical circumstances and preferences. The committee decided against listing the options for people with type 2 diabetes who were at high CV risk and could not take an SGLT2i because they thought that this was an unnecessary level of detail given that they could not recommend a GLP-1 mimetic in place of the SGLT2i, that the treatment options were therefore the same for these people as for the rest of the type 2 diabetes population and because, apart from for metformin, the guideline does not include details of which drug to take if a particular drug is contraindicated or not tolerated but rather expects the prescriber to use their clinical judgment.

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					In the absence of the GLP-1s being cost-effective treatments for people with high CV risk or established cardiovascular disease, the existing 2015 recommendations for when to use GLP-1s were retained. These apply to the general population of people with type 2 diabetes. Since no new non- cardiovascular outcome trial evidence regarding the benefits of GLP-1s was included in this review the committee were unable to amend or rewrite the 2015 criteria for GLP-1 use in this current update. When these recommendations were made in 2015 these criteria were used because of the lack of cost-effectiveness of this treatment for most people. As you note, three new GLP1RAs have become available since the publication of the 2015 guidelines, and these may change the cost-effectiveness of the GLP-1s and their place in the treatment pathway. We recognise that we have focused on CV benefit for this update and only looked at the evidence from the cardiovascular outcome trials. However, please note that at no stage during the development process was a decision taken to focus our efforts on a particular drug or drug class. Rather, we reviewed all the evidence on cardiovascular outcomes, for the reasons explained above and in line with the revised scope. The evidence review included evidence on the impact of treatments – including GLP1 receptor agonists - on cardiovascular outcomes, the details of which were incorporated into the health economic model. It did not consider trials that did not have cardiovascular outcomes as these were out of scope. It should also be noted that it is not the case that only additional outcomes beneficial to GLP-1 drug therapy were excluded from the modelling. Whilst it is likely there would be differences found in the results of the cost-effectiveness analysis were a different set of outcomes to be included, it is not clear in which direction the results would change for any

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					given agent, and whether they would become more or less cost-effective. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand.
Novo Nordisk	Guideline	General	General	**3 The draft guideline is confusing, lacks patient centredness and limits individualisation of care. This will lead to more variation of care.** The narrow scope has resulted in a guideline that limits the options to individualise care to specific patient needs, despite a visual "choosing medicine for type 2 diabetes" recommending such an approach. By limiting the scope of the update to assessment of cardiovascular outcome trials, the assessment of important clinical characteristics identified by NICE at surveillance as requiring update, such as weight, frailty, chronic kidney disease (CKD), are notably missing from the guideline. Whilst patients in CVOTs were at high cardiovascular risk or had established cardiovascular disease (CVD), the actual risk profiles of the majority of people living with diabetes are broader than CV risk alone and their related health priorities are diverse. Whilst NICE has consulted separately on a guideline for use of SGLT-2is for managing CKD in patients with type 2 diabetes, it is unclear how this	Thank you for your comment. The committee agreed with the need to produce guidance to help promote personalised treatment. As you note, the original scope of this work covered additional groups of interest including people with renal impairment, people in specific ethnic groups, adults aged 65 years and older, as well as people in specific cardiovascular risk groups. It aimed to fully update the drug treatment sections of the NG28 guideline. However, once work on the topic commenced it was determined that updating evidence reviews and health economics for such a wide scope, within the resources available to NICE for this topic, would take an unacceptably lengthy period. The committee therefore agreed that our initial focus should be on reviewing the evidence from trials looking at cardiovascular outcomes. However, to make it easier for prescribers to select appropriate treatment options that match the needs of each

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				will be integrated within NG28 or why it has been developed as a separate piece of guidance. In the absence of NICE updating their guidelines, many areas in the interim have adopted the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) Consensus Statement[1,2] (ADA-EASD) and their clinical practice has evolved to reflect the new available evidence. If this draft guideline is published it will result in increased variation of care and a post code lottery of care delivery where some areas will continue to use ADA-EASD based on the new evidence while others will adhere to NICE guidelines. **References** 1. Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, Rossing P, Tsapas A, Wexler DJ, Buse JB. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2018; 41(12):2669-2701. 2. Buse JB, Wexler DJ, Tsapas A, Rossing P, Mingrone G, Mathieu C, D'Alessio DA, Davies MJ. 2019 Update to: Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2020;43(2):487-493.	individual we have developed a summary table listing relevant factors such as whether the drug is associated with weight loss or weight gain. It is hoped that this table, together with the recommendation about choosing drug treatments that covers tailoring drug choice to individual needs and circumstances, will support personalised care. As you note, renal benefits of using SGLT2 inhibitors in people with type 2 diabetes and CKD has been assessed in a separate piece of work that has recently been out for stakeholder consultation and will be published before the end of 2021. The final recommendations on renal and cardiovascular benefits will be brought together in a single updated guideline document when this current work on cardiovascular benefits is published in 2022. The committee were aware of the ADA guidance, but their decisions were made according to the NICE guideline manual and took into account the evidence relevant to our review question. Although the NICE guidance may differ to the guidance provided by ADA, the committee were confident that their recommendations reflected the evidence they reviewed and their clinical judgement. It is of particular importance to note that the NICE guideline used an original economic model as the basis to recommend the most clinically and cost-effective options while the ADA guidance did not systematically take cost-effectiveness into account. When producing guidelines, NICE considers both effectiveness and cost-effectiveness for all of the recommendations it makes. As well as helping to ensure the recommendations made represent the best use of NHS resources (in particular, the opportunity costs of spending additional resources), this is also required by the legislation that originally established NICE (the Health and Social Care Act 2012), which states that when exercising its functions,

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					NICE must have regard to "the broad balance between the benefits and costs of the provision of health services or of social care in England." NICE's principles further refine this by explicitly stating that "if possible, NICE considers value for money by calculating the incremental cost-effectiveness ratio" and "interventions with an ICER of less than £20,000 per QALY gained are generally considered to be cost effective." This guidance was developed in line with both these statutory requirements, and NICE's stated principles, methods and processes. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand.
Novo Nordisk	Guideline	General	General	**5.By not assessing the evidence on the clinical and cost-effectiveness of GLP-1RAs to control blood glucose levels, NICE has not fully considered the rapidly changed healthcare environment and landscape of clinical evidence since 2015 in this update.** Since the start of the COVID-19 pandemic there has been a wealth of evidence showing how UK patients with diabetes have been disproportionally affected by COVID-19 relative to the general nondiabetic population with high blood glucose levels and high BMI identified as modifiable risk factors for severe consequences of, and death from,	Thank you for your comment. While the committee were obviously aware of the issues raised by the current COVID-19 pandemic, treatment of type 2 diabetes concurrent with or during the pandemic was out-of-scope for this guideline update. The original scope of the update to the drug treatment sections of NG28 was to fully update the treatment section of the guideline as your comment notes. However, once work on the topic commenced it was determined that

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				COVID-19[1,2]. The impact of postponement of essential diabetes services for people with type 2 diabetes has been significant with blood testing falling by as much as 69% between March to December 2020, diagnosis for type 2 diabetes reducing by as much as 70% in April 2020 in primary care, and now a problematic backlog of poorly controlled patients needing to be supported by clinicians[3]. Whilst additional factors and clinical characteristics are of key importance in treatment decisions, glycaemic control remains a fundamental driver for diabetes management. When considering the evidence above, it is therefore of paramount importance that the clinical guidance set out by NICE is holistically reviewed and considers the complete evidence underpinning the type 2 diabetes management pathway rather than the narrow focus on cardiovascular outcomes alone. In line with this, Novo Nordisk strongly recommends that the clinical and cost-effectiveness for the use of GLP-1RAs to control blood glucose levels, body weight and hypoglycaemia risk, in addition to cardiovascular risk reduction are assessed together in a revised scope. **References** 1. Barron, E et al. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. The Lancet Diabetes & Endocrinology. 2020; 8(10): p813-822 2. Hollman, et al. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. The Lancet Diabetes & Endocrinology. 2020; 8(10): p813-822 3. Carr, MJ, et al. Impact of COVID-19 on diagnoses, monitoring, and mortality in people with type 2 diabetes in the UK. Lancet Diabetes Endocrinol. 2021; 9(7): 413–415	updating evidence reviews and health economics for such a wide scope, within the resources available to NICE for this topic, would take an unacceptably lengthy period. Taking such an approach for this guideline update would have further delayed publication of updated treatment recommendations in this rapidly changing area. In view of the timescales involved and the appetite from the committee and stakeholders for an update within an acceptable time period, we worked with our committee members to identify the priority areas for this update. The committee members agreed that our initial focus should be on reviewing the evidence from trials looking at cardiovascular outcomes. This reflected the changing evidence base as a result of the significant investment in clinical trials to directly capture cardiovascular outcomes, feedback from stakeholders that assessing this evidence was a priority and the impact that this new evidence could have on recommendations for the treatment of people with diabetes. We therefore revised the scope to reflect this and carried out the current piece of work. You are correct that the model does not contain every outcome that could potentially be of interest for modelling adults with type 2 diabetes. However, the committee agreed these were the most important outcomes for assessing the additional cardiovascular and other benefits associated with drug treatment for type 2 diabetes, for the majority of the type 2 diabetes population. The committee agreed the cardiovascular outcome trials were the most appropriate data source to assess cardiovascular benefits of these drugs, being powered to specifically detect differences in hard outcomes, rather than only surrogate outcomes. The committee noted these studies were not representative of the full population of people with type 2 diabetes but agreed this was a lesser limitation than the need to extrapolate from

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					surrogate endpoints to cardiovascular outcomes, particularly given the findings from those studies suggesting these surrogate extrapolations are often not very robust. They also agreed that taking data on weight and hypoglycaemic events from these cardiovascular outcome trials was the most appropriate approach, in order to match the data used for cardiovascular event rates. For hypoglycaemic events, the approach taken is broadly in line with that taken in many other evaluations in diabetes, attaching costs and quality of life outcomes to the incidence of severe hypoglycaemic events, as these are the ones that make the most difference to a person's life. For changes in weight, it was noted it was important not to double count the impact of changes, as the effects on cardiovascular outcomes should already be captured in the outcomes of those trials. It was therefore agreed that the most appropriate approach was to only include the direct quality of life gains associated with reductions in weight, with the other benefits captured through the cardiovascular event data. The committee noted that if anything the approach taken in the guideline may overestimate the benefits of weight reduction, as some of the estimated quality of life gains may be the result of avoided cardiovascular events, but it was agreed to be the best data source available. There are of course other benefits that could have been considered as part of the modelling, including renal (or other microvascular) outcomes, or additional benefits directly related to improved glycaemic control, but the committee considered these to be of lower priority than those included in the model. They also noted that it would not be appropriate for any modelling approach to simply look at benefits on different outcomes from different trials or data sources, and assume those benefits are additive, and therefore increase the cost-effectiveness of drugs when

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					included together. They noted that in many circumstances these benefits are not additive, and which benefits are likely to be realised may depend on the individual characteristics of the people included in studies. As an example, in the separate evaluation of SGLT2 inhibitors for people with CKD and type 2 diabetes, SGLT2 inhibitors were found to significantly improve renal outcomes, but this is a population in which a large benefit would not be expected for glycaemic control (hence why these agents were not originally licensed for use in people with impaired renal function). It should also be noted that it is not the case that only additional outcomes beneficial to drug therapy were excluded from the modelling. As an example, adverse events related to drug treatment (excluding hypoglycaemia) were not included as part of the analysis. As a number of the analyses in the guideline explicitly compare the addition of new treatments (for example, using 3 drugs versus 2) rather than simply switching drugs, it would be expected that inclusion of adverse events would decrease the cost-effectiveness for any additional treatments, as they would add to the adverse event burden. Therefore, whilst it is likely there would be differences found in the results of the cost-effectiveness analysis were a different set of outcomes to be included, it is not clear in which direction the results would change for any given agent, and whether they would become more or less cost-effective. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update

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					of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand.
Novo Nordisk	Guideline / Health Economic report	General	General	**12.While there is some variation, the CVOTs enrolled patients at high risk of cardiovascular disease, which is not generalisable to the whole type 2 population.** The REWIND trial including the patient population at the lowest risk, but even in this study 31% of participants had prior cardiovascular disease. In the health economic analysis, the baseline population (based on The Health Improvement Network (THIN) database, now named UK IQVIA Medical Research Data UK IMRD), less than 3% of the simulated patients had prior cardiovascular disease. As discussed above, the HR generated have been shown to vary as the percentage of patients with prior cardiovascular disease changes[1]. The assumption that HR are equivalent in populations at high and low risk of cardiovascular disease cannot be supported based on current evidence, and therefore the approach of the analysis is questionable, and not generalisable across the whole type 2 patient population. **Reference:** 1. Evans LM, Mellbin L, Johansen P, Lawson J, Paine A, Sandberg A. A population-adjusted indirect comparison of cardiovascular benefits of once-weekly subcutaneous semaglutide and dulaglutide in the treatment of patients with type 2 diabetes, with or without established cardiovascular disease. Endocrinol Diabetes Metab. 2021;4(3):e00259.	Thank you for your comment. The committee agreed applying the hazard ratios from the trials to this lower risk population was a significant extrapolation, and one they were uncomfortable with, as detailed in the committee discussion section. This is one of the reasons why no additional recommendations were made for the population of all people with type 2 diabetes, and the positive new recommendations made for SGLT2 inhibitors were restricted to those individuals at high cardiovascular risk, to better match the included populations in the RCTs. While the HRs from CVOT studies were applied to all type 2 diabetes patients (generated from the THIN database), subgroup analysis were done on subsets of the THIN population classed as primary high CV risk (with no prior event), secondary high CH risk (with a prior event) and an all-high CV risk groups which was a combination of the primary and secondary groups. As shown in section 4.2 in the economic modelling report, the trend in results in these subgroups did not differ significantly in the subgroup results when compared to the base case analysis.
Novo Nordisk	Guideline / Health Economic report	General	General	**6.Overall approach to cost-effectiveness modelling based on CVOTs only is inconsistent with accepted diabetes modelling approaches**	Thank you for your comment. You are correct that the model does not contain every outcome that could potentially be of interest for modelling adults with type 2 diabetes. However, the committee agreed these were the most important

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				The approach taken is inconsistent with the basic premise of cost-effectiveness modelling in which the acquisition cost of a new technology is assessed in relation to all relevant expected downstream costs and health outcomes. The guideline and evidence review fails to consider the complexity of type 2 diabetes management in relation to glycaemic control, risk and management of complications and the inter-connected relationship between the two. The scope and the economic plan both state that the review under consideration is: "*What pharmacological therapies are most effective at providing cardiovascular and other benefits in addition to blood glucose control in people with type 2 diabetes?*" However, the effectiveness of glucose management has not been updated, making the results biased; the most recently licenced drug treatments are not given their weight in effectiveness on glycaemic control – the review only considered CV benefits. While Novo Nordisk welcome the inclusion of CV - as it is an important factor in the treatment of type 2 diabetes - failing to capture other microvascular outcomes, renders the guideline misaligned with current clinical practice, and results in inaccurate modelling. The economic analysis is based on data from the CVOT trials, associations between patient characteristics and CV events from these trials are unknown. It is thus challenging to apply these data to an economic model and produce accurate results. For example, medications that have previously shown greater HbA1c and weight reductions in head-to-head clinical trials were associated with poorer outcomes in this new health economic analysis. The Health Economic (HE) Report estimates that dulaglutide is associated with increased quality-adjusted life expectancy, however, trial data from SUSTAIN-7 shows that semaglutide was associated with a superior change in HbA1c and body weight. There are many more examples like this for semaglutide in the guideline update with assessments versus sitagliptin, where the model estimates sitagliptin is associated with increased quality-adjusted life expectancy, however, trial data from PIONEER 3[1] shows that semaglutide is associated with a	outcomes for assessing the additional cardiovascular and other benefits associated with drug treatment for type 2 diabetes, for the majority of the type 2 diabetes population. The committee agreed the cardiovascular outcome trials were the most appropriate data source to assess cardiovascular benefits of these drugs, being powered to specifically detect differences in hard outcomes, rather than only surrogate outcomes. The committee noted these studies were not representative of the full population of people with type 2 diabetes, but agreed this was a lesser limitation than the need to extrapolate from surrogate endpoints to cardiovascular outcomes, particularly given the findings from those studies suggesting these surrogate extrapolations are often not very robust. They also agreed that taking data on weight and hypoglycaemic events from these cardiovascular outcome trials was the most appropriate approach, in order to match the data used for cardiovascular event rates. For hypoglycaemic events, the approach taken is broadly in line with that taken in many other evaluations in diabetes, attaching costs and quality of life outcomes to the incidence of severe hypoglycaemic events, as these are the ones that make the most difference to a person's life. For changes in weight, it was noted it was important not to double count the impact of changes, as the effects on cardiovascular outcomes should already be captured in the outcomes of those trials. It was therefore agreed that the most appropriate approach was to only include the direct quality of life gains associated with reductions in weight, with the other benefits captured through the cardiovascular event data. The committee noted that if anything the approach taken in the guideline may overestimate the benefits of weight reduction, as some of the estimated quality of life gains may

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				superior change in HbA1c and body weight. These contradictory results are also estimated for comparisons with canagliflozin and empagliflozin, which are extremely concerning. The results are contradictory to numerous published cost-effectiveness analyses for Ozempic® and Rybelsus® which have demonstrated cost-effectiveness where the full evidence base has been included[2-6]. The results range from dominant (more effective and less costly) to cost effective, significantly below the accepted UK willingness to pay threshold compared with several relevant treatments across the pathway. Furthermore, Novo Nordisk have conducted several analyses in line with NICE methods (Data on File) across three key comparators demonstrating that Ozempic® is cost-effective when considering all the available evidence on efficacy: • Ozempic® vs dipeptidyl peptidase-4 (sitagliptin (Januvia)) with an incremental cost effectiveness ratio (ICER) of £4,886 • Ozempic® vs SGLT2-is (empagliflozin (Jardiance)) with an ICER of £7,653 • Ozempic® vs Insulin glargine (Lantus based on Semglee price) with an ICER of £6,458 Demonstrating that despite lower prices of comparator insulin, Ozempic still remains a cost-effective alternative. By focusing on CVOT data only and not considering all the outcome evidence, the current draft guideline cost-effective results are invalid. They only account for part of the benefit of the medications but apply the full acquisition cost. **References:** 1. Rosenstock J, Allison D, Birkenfeld AL, Blicher TM, Deenadayalan S, Jacobsen JB, Serusclat P, Violante R, Watada H, Davies M; PIONEER 3 Investigators. Effect of Additional Oral Semaglutide vs Sitagliptin on Glycated Hemoglobin in Adults With Type 2 Diabetes Uncontrolled With Metformin Alone or With Sulfonylurea: The PIONEER 3 Randomized Clinical Trial. JAMA.	be the result of avoided cardiovascular events, but it was agreed to be the best data source available. There are of course other benefits that could have been considered as part of the modelling, including renal (or other microvascular) outcomes, or additional benefits directly related to improved glycaemic control, but the committee considered these to be of lower priority than those included in the model. They also noted that it would not be appropriate for any modelling approach to simply look at benefits on different outcomes from different trials or data sources, and assume those benefits are additive, and therefore increase the cost-effectiveness of drugs when included together. They noted that in many circumstances these benefits are not additive, and which benefits are likely to be realised may depend on the individual characteristics of the people included in studies. As an example, in the separate evaluation of SGLT2 inhibitors for people with CKD and type 2 diabetes, SGLT2 inhibitors were found to significantly improve renal outcomes, but this is a population in which a large benefit would not be expected for glycaemic control The three cost-effectiveness studies quoted are distinctly different to the analysis we have performed as they do not model treatment effect by considering CV outcomes and instead uses surrogate outcomes to account for treatment effect. The reasons as to why we have accounted for treatment effects by looking at CV outcomes is mentioned above.

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				2019 Apr 16;321(15):1466-1480. doi: 10.1001/jama.2019.2942. PMID: 30903796; PMCID: PMC6484814. 2. Capehorn M, Hallén N, Baker-Knight J, Glah D, Hunt B. Evaluating the Cost-Effectiveness of Once-Weekly Semaglutide 1 mg Versus Empagliflozin 25 mg for Treatment of Patients with Type 2 Diabetes in the UK Setting. Diabetes Ther. 2021 Feb;12(2):537-555. doi: 10.1007/s13300-020-00989-6. Epub 2021 Jan 9. PMID: 33423240; PMCID: PMC7846640. 3. Viljoen A, Hoxer CS, Johansen P, Malkin S, Hunt B, Bain SC. Evaluation of the long-term cost-effectiveness of once-weekly semaglutide versus dulaglutide for treatment of type 2 diabetes mellitus in the UK. Diabetes Obes Metab. 2019 Mar;21(3):611-621. doi: 10.1111/dom.13564. Epub 2018 Nov 28. PMID: 30362224; PMCID: PMC6587509. 4. Bain SC, Hansen BB, Malkin SJP, Nuhoho S, Valentine WJ, Chubb B, Hunt B, Capehorn M. Oral Semaglutide Versus Empagliflozin, Sitagliptin and Liraglutide in the UK: Long-Term Cost-Effectiveness Analyses Based on the PIONEER Clinical Trial Programme. Diabetes Ther. 2020 Jan;11(1):259-277. doi: 10.1007/s13300-019-00736-6. Epub 2019 Dec 12. PMID: 31833042; PMCID: PMC6965564. 5. Johansen P, Chubb B, Hunt B, Malkin SJP, Sandberg A, Capehorn M. Evaluating the Long-Term Cost-Effectiveness of Once-Weekly Semaglutide Versus Once-Daily Liraglutide for the Treatment of Type 2 Diabetes in the UK. Adv Ther. 2020 May;37(5):2427-2441. doi: 10.1007/s12325-020-01337-7. Epub 2020 Apr 18. PMID: 32306244; PMCID: PMC7467468. 6. Johansen P, Sandberg A, Capehorn M. A Relative Cost of Control Analysis of Once-Weekly Semaglutide Versus Exenatide Extended-Release, Dulaglutide and Liraglutide in the UK. Adv Ther. 2020 Mar;37(3):1248-1259. doi: 10.1007/s12325-020-01242-z. Epub 2020 Feb 11. PMID: 32048148; PMCID: PMC7089718.	
Novo Nordisk	Guideline / Health	General	General	**7.The model used in the guideline update is not fit for purpose.**	Thank you for your comment. The clinical review carried out as a part of this update has not extracted data on surrogate risk factors as explained in sections detailing to the clinical

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	Economic report			The description of the modelling approach states, "*Because the CVOT studies explored in the clinical review for this update do not collect data on surrogate risk factors it is not possible to model them directly through the UKPDS*" (HE report, page 10, line 27). This is not factually correct, for example, the study by McEwan et al.[1] combined data from the CV outcomes and modifiable risk factors reported in the SGLT2-is CVOTs to model macrovascular and microvascular complications. In addition, the Mount Hood Challenge Network published a review of various models' ability to accurately model CVOT data[2] which could have been used in the assessment of model selection. Whilst the CVOTs provide an evidence base to model CV endpoints directly, the progression of other diabetes-related endpoints (such as microvascular disease) must still be captured; otherwise, the economic evaluation will not include all the expected future healthcare costs and outcomes. Furthermore, the reported change in modifiable risk factors reported in these CVOTs reflected changes on top of standard of care. Consequently, their omission further biases the analyses. Novo Nordisk understand there is a paucity of modelling options in diabetes to allow for the modelling of both CV and glycaemic outcomes and other microvascular events, but we believe that these guidelines should have tried to incorporate all benefits from treatment or tested the results using other modelling approaches to establish the robustness. It is not acceptable to simply focus on one aspect of treatment. While Novo Nordisk are not saying this is the only option, NICE could have looked at developing an alternative model such as that described in McEwan noted above or Shah et al. 2018[3]. While the latter is based on a US setting, that does not impact the modelling approach used to accurately capture all aspects of treatment. Novo Nordisk also used this publication (Shah et al. 2018) as a basis for exploratory modelling based on the LEADER trial (Data on File), to include all events from the evidence. The objective of this study was to assess the cost-effectiveness of liraglutide as add-on to standard of care (SOC) compared to SOC in type 2 patients with a high CV risk from a UK perspective. SOC for glucose monitoring included medications such as	review. The committee agreed CV outcomes were the most important outcomes for assessing the additional cardiovascular and other benefits associated with drug treatment for type 2 diabetes, for the majority of the type 2 diabetes population. The committee agreed the cardiovascular outcome trials were the most appropriate data source to assess cardiovascular benefits of these drugs, being powered to specifically detect differences in hard outcomes, rather than only surrogate outcomes. The committee noted these studies were not representative of the full population of people with type 2 diabetes, but agreed this was a lesser limitation than the need to extrapolate from surrogate endpoints to cardiovascular outcomes, particularly given the findings from those studies suggesting these surrogate extrapolations are often not very robust. There are of course other benefits that could have been considered as part of the modelling, including renal (or other microvascular) outcomes, or additional benefits directly related to improved glycaemic control, but the committee considered these to be of lower priority than those included in the model. They also noted that it would not be appropriate for any modelling approach to simply look at benefits on different outcomes from different trials or data sources, and assume those benefits are additive, and therefore increase the cost-effectiveness of drugs when included together. They noted that in many circumstances these benefits are not additive, and which benefits are likely to be realised may depend on the individual characteristics of the people included in studies. As an example, in the separate evaluation of SGLT2 inhibitors for people with CKD and type 2 diabetes, SGLT2 inhibitors were found to significantly improve renal outcomes, but this is a population

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				metformin, sulfonylureas, alpha-glucosidase inhibitors, thiazolidinediones, SGLT2-is, glinides and insulin treatments. The analysis was conducted using a cohort-level state-transition, simulating multiple health states: (1) alive without events, (2) alive with non-fatal events [stroke, myocardial infarction (MI), hospitalized heart failure, coronary revascularisation, unstable angina, transient ischemic attack, retinopathy, and nephropathy), and (3) death (from fatal CV events, after non-fatal events, and other causes). For the base case analysis results, liraglutide + SOC was cost-effective with an ICER of £21,059 per quality adjusted life year (QALY) gained. Novo Nordisk acknowledge that the model suggested above is not necessarily the only option, but at the very least, it highlights the huge level of uncertainty over the draft guideline results, even if the model only accounts for CV outcomes. The model used in this guideline update is not fit for purpose, and this is clearly demonstrated by the spurious results reported above, which are contradictory to clinical intuition. **References:** 1. McEwan P, Bennett H, Khunti K, et al. Assessing the cost-effectiveness of sodium-glucose cotransporter-2 inhibitors in type 2 diabetes mellitus: A comprehensive economic evaluation using clinical trial and real-world evidence. Diabetes Obes Metab. 2020;22(12):2364-74. 2. Si L, Willis M, Asseburg C, Nilsson A, Tew M, Clarke P, Lamotte M, Ramos M, Shao H, Shi L, Zhang P, McEwan P, Ye W, Herman W, Kuo S, Isaman D, Schramm W, Sailer F, Brennan A, Pollard D, Smolen H, Leal J, Gray A, Patel R, Feenstra T, Palmer A. Evaluating the Ability of Economic Models of Diabetes to Simulate New Cardiovascular Outcomes Trials: A Report on the Ninth Mount Hood Diabetes Challenge, Value in Health, Volume 23, Issue 9,2020, Pages 1163-1170, ISSN 1098-3015. doi.org/10.1016/j.jval.2020.04.1832. 3. Shah D, Risebrough NA, Perdrizet J, Iyer NN, Gamble C, Dang-Tan T. Cost-effectiveness and budget impact of liraglutide in type 2 diabetes patients with elevated cardiovascular risk: a US-managed care perspective. Clinicoecon Outcomes Res.	in which a large benefit would not be expected for glycaemic control. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs.

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				2018;10:791-803. Published 2018 Nov 14. doi:10.2147/CEOR.S180067	
Novo Nordisk	Guideline / Health Economic report	General	General	**9.There is significant heterogeneity between the CVOT trials, but no steps to explain the difference or control for the potential effects on the analysis were made.** The differences, include study durations, populations, background therapies, and endpoint definitions, for example: • The percentage of the population with prior cardiovascular disease ranges from 31% in REWIND to 100% in ELIXA • Age at baseline ranges from 60.3 years to 66.2 years (ELIXA and REWIND, respectively) • Duration of diabetes at baseline in the placebo arm of EXAMINE is less than half that of the population in PIONEER 6 (7.1 years vs 14.9 years, respectively) • Baseline HbA1c in TECOS was 7.2% and in LEADER and SUSTAIN 6 was 8.7%, whilst baseline BMI in EXAMINE was 28.7 kg/m2 but in SUSTAIN 6 BMI was 32.8 kg/m2 • If the CVOTs were comparable it would be expected that the placebo arms of the trials would be associated with similar rates of cardiovascular death, non-fatal MI, and non-fatal stroke (MACE), the MACE rates for the placebo arms range from 2.42 events per 100 patient years in DECLARE to 5.33 events per 100 patient years in CARMELINA • Study durations differed greatly, ranging from 1.3 years (PIONEER) to 5.4 years (REWIND) Furthermore, in several studies, such as SUSTAIN 6, PIONEER 6 and LEADER; silent MI was included, but in EMPA-REG OUTCOME silent MI was excluded. This is highly significant, as when the FDA requested a re-analysis of the primary three-point MACE endpoint from EMPA-REG OUTCOME with silent MI included, the hazard ratio (HR) for MACE increased from 0.86 to 0.92, with the difference for empagliflozin versus placebo no longer statistically significant. This shows how the endpoint definitions are crucial, and that the variation across the CVOTs drives differences in efficacy that are not due to the medications themselves.	Thank you for your comment. You are correct that unadjusted hazard ratios were used in the analysis. In the absence of individual patient data, the committee agreed that there were no established methods for adjusting these data that could be conducted that would increase their confidence in the effect estimated. In particular, they noted that standard MAIC analyses required access to the individual patient data from at least some of the trials in the analysis analysis (see NICE DSU Technical Support Document 18), and as such data were not available to them, they agreed no such analyses could be robustly undertaken. They noted that simply having populations at different risk levels in different trials would not be a source of bias in the results, as this should not impact on the relative effects estimated in the trials and subsequently used to populate the model. A concern would only arise if there were systematic differences between the trials in characteristics that would affect relative (and not just absolute) treatment effectiveness and, while the data did not allow the committee to completely rule out this possibility, there were not clear clinical reasons they were aware of to suspect that such a pattern would exist. Nonetheless, the committee agreed the between trial heterogeneity was a source of uncertainty in the analysis, and considered this as part of their decision-making, as detailed in the committee discussion-section of the evidence review. In particular, they noted that uncertainty would in general lead towards making weaker rather than stronger recommendations, and therefore any factors that led them to be more uncertain would lead to a smaller number of treatment options being recommended as cost-effective, rather than a larger number of options.

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				Reference: FDA Briefing Document, Endocrine and Metabolic Drug Advisory Committee, Meeting June 28, 2016. https://www.fda.gov/files/advisory%20committees/published/FDA-Briefing-Information-for-the-June-28--2016-Meeting-of-the-Endocrinologic-and-Metabolic-Drugs-Advisory-Committee.pdf	
Novo Nordisk	Guideline / Health Economic report	General 070	General 016	**11.Another key concern is that no data are reported on the changes in risk factors over time in the standard care arm.** The aim of the standard care arm was to reflect current clinical practice and providing the data on risk factor progression would allow for comparison with real-world evidence to assess whether this has been achieved. Without such data this is impossible, and therefore it is difficult to state how appropriate the standard care arm is. The report states that the progression equations applied for HbA1c, systolic blood pressure (SBP), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, BMI, microalbuminuria, creatinine, heart rate, white blood cell count, haemoglobin, atrial fibrillation and peripheral vascular disease are academic in confidence and therefore cannot be reported. However, the risk factor progression equations used in the UKPDS Outcomes Model 2 have recently been published by Leal et al[1]. Therefore, the confidentiality issue is no longer relevant, and the risk factor progression data should be fully described. Cumulative incidence of complications is another area where comparison cannot be made between the report and clinical reality, due to an absence of data. The cumulative incidence of complications is the key driver of differences in quality-adjusted life expectancy and costs between treatment arms, with the HR from the CVOTs applied to the event rates from the standard of care arm. Therefore, understanding the events rates in the standard of care arm is crucial to assessing the validity of the analysis.	Thank you for your comment. The HE model report has been updated with the said reference, and the version of the model with the said equations has been released.

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				Reporting of the cumulative incidence of complications in the standard care arm (and those generated in the new medication arms) would increase the transparency of the analysis. **Reference:** 1. Leal J, Alva M, Gregory V, Hayes A, Mihaylova B, Gray AM, Holman RR, Clarke P. Estimating risk factor progression equations for the UKPDS Outcomes Model 2 (UKPDS 90). Diabet Med. 2021;38(10):e14656.	
Novo Nordisk	Health economic model - CVOTinjections	Cell 02		**15.There appears to be an error in the model in the calculation of the injection disutility associated with once-weekly injectable semaglutide.** In the Excel workbook "CVOTinjections", it appears that once-weekly injectable semaglutide has been assigned a daily injection. Cell O2 contains the value 1, rather than 0.142857. This has a notable impact on the results. To use the results sheet "First IntensificationmetforminCVReplace Results" as an example, cell G11 shows that once-weekly injectable semaglutide was associated with a loss in quality adjusted life expectancy due to injections of 0.31 QALYs, whereas other once-weekly injectable medications such as dulaglutide (cell G7) and exenatide (cell G8) are associated with a loss in quality adjusted life expectancy due to injections of 0.04 QALYs. This shows how the quality-adjusted life expectancy with once-weekly semaglutide has been underestimated in all analyses.	Thank you for your comment. This has been corrected and the results have been updated. The changes have resulted in the ICERs for injectable Semaglutide falling in the range of £20,000 to £30,000 in the base case. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the intervention as an effective use of NHS resources will specifically take account of the following factors." and • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis." Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this

					decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors. In addition, the committee noted that there were differences in the clinical effectiveness of the 2 forms of semaglutide. Although the acquisition costs for injectable and oral semaglutide are similar they showed marked differences in cost-effectiveness in the economic analyses. This was caused by differences in the effect estimates for stroke, myocardial infarction and severe hypoglycaemia. From earlier discussions about the clinical evidence (see the discussion sections in the evidence review for more details) the committee had agreed that it was uncertain whether the observed differences in effect on all-cause mortality

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					compared to placebo between the 2 forms of semaglutide were real and they therefore decided not to place undue weight on them. They had also noted that this uncertainty and any other differences in effects between the drugs for other outcomes was probably due to wide 95% confidence intervals for many outcomes with these drugs, due to the smaller numbers of participants and events in the trials compared to other CVOTs. The committee therefore agreed that they were unable to recommend injectable semaglutide for people with type 2 diabetes and high cardiovascular risk who were unable to take and SGLT2i. As a result, the committee noted that people with high CV risk who could not take metformin with an SGLT2i would be offered metformin alone at treatment initiation. If they were also unable to take metformin then the clinician would select another treatment from the remaining options, namely sulfonylureas, DPP-4s or pioglitazone, depending on the individual's clinical circumstances and preferences. The committee decided against listing the options for people with type 2 diabetes who were at high CV risk and could not take an SGLT2i because they thought that this was an unnecessary level of detail given that they could not recommend a GLP-1 mimetic in place of the SGLT2i, that the treatment options were therefore the same for these people as for the rest of the type 2 diabetes population and because apart from for metformin, the guideline does not include details of which drug to take if a particular drug is contraindicated or not tolerated but rather expects the prescriber to use their clinical judgment. The committee wanted to keep the pathway as simple as possible, and they agreed that it would not be possible to do this if alternative options were provided every time a drug was not contradicted or not tolerated. However, they agreed that it was appropriate to have recommendations for metformin

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					being contradicted or not tolerated because this is the drug that the majority of people would take as first-line therapy
Novo Nordisk	Health economic report	013	017 - 020	**19.Treatment intensification is incorrectly uniform across all treatment arms.** Differences in HbA1c were not applied to each treatment arm, and therefore the timing of treatment intensification was assumed to be the same with all interventions. An HbA1c level of 7.5% was used as the threshold for intensification, but the analysis does not take into account potential differences in time to reach this threshold with each treatment. This oversimplification of the analysis underestimates the benefits of interventions associated with good glycaemic control which would be associated with delayed initiation of insulin, and therefore delayed weight gain, injection burden, increased hypoglycaemia risk and increased costs. The benefits of interventions associated with good glycaemic control have been underestimated.	Thank you for your comment. The use of non-treatment specific timing of intensification is a minor limitation in our analysis as we have not extracted this data in our evidence review, with intensification timings informed by the data available. We have added an acknowledgement of this limitation in the discussion section of the economic report, as some people may remain on a specific treatment pathway for longer than in a situation where intensification was defined by HbA1c levels. It is worth noting that there would be a negligible impact on CV events due to this, as we are not modelling CV events using surrogate outcomes. You are correct that the model does not contain every outcome that could potentially be of interest for modelling adults with type 2 diabetes. However, the committee agreed these were the most important outcomes for assessing the additional cardiovascular and other benefits associated with drug treatment for type 2 diabetes, for the majority of the type 2 diabetes population. The committee agreed the cardiovascular outcome trials were the most appropriate data source to assess cardiovascular benefits of these drugs, being powered to specifically detect differences in hard outcomes, rather than only surrogate outcomes. The committee noted these studies were not representative of the full population of people with type 2 diabetes, but agreed this was a lesser limitation than the need to extrapolate from surrogate endpoints to cardiovascular outcomes, particularly given the findings from those studies suggesting these surrogate extrapolations are often not very robust. There are of course other benefits that could have been considered as part of the modelling, including renal (or other

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					microvascular) outcomes, or additional benefits directly related to improved glycaemic control, but the committee considered these to be of lower priority than those included in the model. They also noted that it would not be appropriate for any modelling approach to simply look at benefits on different outcomes from different trials or data sources, and assume those benefits are additive, and therefore increase the cost-effectiveness of drugs when included together. They noted that in many circumstances these benefits are not additive, and which benefits are likely to be realised may depend on the individual characteristics of the people included in studies.
Novo Nordisk	Health economic report	018	013	**16.As with the other inputs, unadjusted hypoglycaemia rate ratios taken directly from the CVOTs have been used. These model inputs are again subject to all of the confounding discussed above, and the hypoglycaemia rates cannot be considered comparable.** Hypoglycaemia rates are affected by numerous factors in randomized controlled trials, such as concomitant medications, HbA1c target and hypoglycaemia definition, none of which have been controlled for. Moreover, rates of hypoglycaemia are low across the CVOTs and the statistical significance of differences has not been tested. Therefore, these outcomes are highly susceptible to differences due to chance. For example, the severe hypoglycaemia incidence rate ratio for oral semaglutide was 1.77, based on severe hypoglycaemia experienced by 1.4% and 0.8% of participants in PIONEER 6 receiving oral semaglutide and standard care, respectively. This ratio of 1.77 would suggest that oral semaglutide is 3 times as hypogenic as lixisenatide, which was associated with a rate ratio of 0.58 (based on 14 patients reporting 16 events with lixisenatide and 24 patients reporting 37 events with placebo). For clinicians experienced in using these medicines, this difference will be untenable (and unbelievable).	Thank you for your comment. You are correct that unadjusted changes in hypoglycaemic event rates were used in the analysis. In the absence of individual patient data, the committee agreed that there were no established methods for adjusting these data that could be conducted that would increase their confidence in the effect estimated. They noted that simply having populations at different risk levels in different trials would not be a source of bias in the results, as this should not impact on the relative effects estimated in the trials and subsequently used to populate the model. A concern would only arise if there were systematic differences between the trials in characteristics that would affect relative (and not just absolute) treatment effectiveness and, while the data did not allow the committee to completely rule out this possibility, there were not clear clinical reasons they were aware of to suspect that such a pattern would exist. Nonetheless, the committee agreed the between trial heterogeneity was a source of uncertainty in the analysis, and considered this as part of their decision-making.

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				This extreme difference in hypoglycaemia rates is likely to be due to differences in the trial populations, which differed substantially, rather than true differences in the impact of the medications on hypoglycaemia risk.	
Novo Nordisk	Health economic report	021	004	**20.There is uncertainty over the way cardiovascular deaths have been calculated.** The clinical review extracted data on all-cause mortality and cardiovascular mortality with the guidelines suggesting that it "*was not appropriate to include both measures of mortality in the model as cardiovascular mortality contributes to all-cause mortality; including both could lead to the double counting of cardiovascular deaths*". It is standard practice to subtract CV mortality from all-cause mortality in order to account for double counting. It is unclear why this has not been undertaken. Furthermore, CV mortality is modelled indirectly; it is contingent on experiencing a non-fatal MI, stroke or HF event. The rationale for this appears to be that non-fatal MI/stroke/HF events are associated with increased risk of mortality and therefore any CV mortality benefit is mediated via a reduction in CV morbidity. This does not appear to be evidence based; indeed, Table HE011 on page 21-22 of the HE report demonstrates how poorly this approach operates.	Thank you for your comments. The committee spent some time considering the relative merits of the two possible approaches (modelling cardiovascular mortality directly, or as a function of cardiovascular events). Ultimately, they decided the later was preferable, as the higher number of cardiovascular events in the studies (compared to the number of cardiovascular events) meant that more precise estimates could be obtained, in turn leading to reduced uncertainty in the analyses. A sensitivity analysis was performed where cardiovascular mortality was modelled using information from the trials. In this sensitivity analysis the rankings of injectable Semaglutide did change substantially, with injectable Semaglutide being less cost-effective than the base case. The committee did also consider the results of this sensitivity analysis, and concluded that, given they had decided to make recommendations at the class rather than individual drug level, the results of that analysis did not substantially change the conclusions they had drawn from the base-case analysis. The results in this sensitivity analysis being very similar to the base case, also signalled of good model fit.
Novo Nordisk	Health economic report	022 - 023	016 - 001	**13.The health economic analysis used change in weight directly from the CVOTs, with no adjustments made which has resulted in spurious results.** As noted above, the CVOTs are not comparable, and therefore the weight changes are confounded by aspects such as baseline weight, concomitant medication use, particularly medications associated with weight gain such as insulin, and study duration. The SUSTAIN 6 CVOT included both once-weekly semaglutide 0.5 mg and 1 mg, with change in weight reported for both doses. The health economic analysis used the change in weight for the low dose, without	Thank you for your comment. You are correct that unadjusted changes in weight were used in the analysis. In the absence of individual patient data, the committee agreed that there were no established methods for adjusting these data that could be conducted that would increase their confidence in the effect estimated. They noted that simply having populations at different risk levels in different trials would not be a source of bias in the results, as this should not impact on the relative effects estimated in the trials and subsequently used to populate the model. A concern would only arise if there were systematic differences between the trials in characteristics that would affect relative (and not just

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				justifying this approach. Given the greater efficacy of semaglutide 1 mg and the equal cost of the two doses, it is likely that the majority of patients will be prescribed the higher dose. The 0.5 mg dose was associated with a change in weight of −3.6 kg while the 1 mg dose was associated with a change in weight of −4.9 kg, equating to a BMI difference of 0.5 kg/m2. Therefore, the annual utility associated with once-weekly semaglutide has been underestimated by 0.003 annually. The changes in weight are not comparable across the trials, and therefore these inputs are highly unreliable, driving spurious results.	absolute) treatment effectiveness and, while the data did not allow the committee to completely rule out this possibility, there were not clear clinical reasons they were aware of to suspect that such a pattern would exist. Nonetheless, the committee agreed the between trial heterogeneity was a source of uncertainty in the analysis, and considered this as part of their decision-making. With regard to the information used from the SUSTAIN 6 CVOT the -3.6kg figure used in the model does not stem solely from the 0.5mg arm – the -3.6kg was calculated by looking at the differences in weight reduction between the Semaglutide and Placebo arms in both the 0.5mg and 1mg arms and averaging it out.
Novo Nordisk	Health economic report	029	002	**18.A minor correction in the costs of needles is required as part of the calculation of treatment costs.** Needle costs were included for neutral protamine hagedorn (NPH) insulin, injectable semaglutide, liraglutide, dulaglutide, exenatide and lixisenatide. However, needles are included in the packs for injectable semaglutide, dulaglutide and exenatide. Therefore, for some treatments needle costs have been included unnecessarily, over-estimating treatment costs by approximately £3 per year.	Thank you for your comment. This has been corrected with the model results updated with the treatment decisions not being affected by this correction.
Novo Nordisk	Health economic report	031	010 - 028	**17.The utilities applied to diabetes-related complications raises multiple issues that can have a bearing on the outcomes of the analysis.** The utilities sourced from Beaudet et al.[1] and described in Table HE028 are not internally consistent. For example, ulcer has a greater impact on quality of life than MI, stroke, and haemodialysis. Therefore, these values are likely to be inappropriate.	Thank you for your comment. You are indeed correct that the values included have been sourced from Beaudet et al who have sourced the information for CV events, amputations and severe vision loss from Clarke et al (UKPDS 62). The Alva et al paper you refer to is indeed a more recent analysis of the UKPDS data set. However there were inconsistencies in the paper relating to Alva et al, particular relating to the positive impact on quality of life from blindness in one eye, and for patients with prior history of MI (reported in their Fixed effects model, which was the results

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				The authors considered the values published by Alva et al.[2] based on the UKPDS patients, and the decision to not use these values has not been justified. Ignoring UKPDS values for use in a UKPDS Outcomes Model 2 implementation requires additional supporting information. There is also a significant lack of information regarding the application of the utility values within the model, specifically the differentiation between the values used for year of event and previous years. As no utility values for previous years or history of event were provided, it is assumed that either no disutility for previous years was applied, underestimating the impact of complications, or the year of event disutility was applied in all subsequent years, overestimating the impact of complications. The lack of clarity around this makes it difficult to interpret the results of the health economic analysis. **References:** 1. Beaudet A, Clegg J, Thuresson P-O, Lloyd A, McEwan P. Review of utility values for economic modeling in type 2 diabetes. Value Heal. 2014;17(4):462-470. 2. Alva M, Gray A, Mihaylova B, Clarke P. The effect of diabetes complications on health-related quality of life: the importance of longitudinal data to address patient heterogeneity. Health Econ. 2014;23(4):487-500.	recommended to be used by the Authors) which bought about questions relating to the validity of the results from the model relating to impact of QoL from diabetic events. Hence we used the results from Beaudet et al in our analysis, especially given its wide use within validated diabetic models such as the IQVIA CORE Diabetes model. However given that the results from Alva et al are from a more recent dataset, we have updated our analysis to include the baseline QoL value from Alva et al. An additional sensitivity analysis has also been performed where we have sourced the impact on QoL (where available) from Alva et al for the second intensification replace population, with Dapagliflozin remaining the most cost-effective treatment in the all ype 2 diabetes population, followed by the other SGLT-2's and then injectable semaglutide. Hence the interpretation of results did not differ from our base case analysis. You are correct in pointing out that no differentiation was made between utility values used for year of event and history of event with the model assuming no disutility for previous years. This has been made clear in additions made to section 2.3.5.1 in the health economic report. The potential limitations caused by this with regard to either underestimating or overestimating (depending on the nature of the complication) the overall impact of quality of life due to complications has been added as a limitation to the discussion section of the health economic report.
Novo Nordisk	Health economic report	035	039	**14.Patients were assumed to receive medications for the duration of their lifetimes, which does not reflect clinical reality.** An analysis of the treatment and dosing patterns among patient with type 2 diabetes receiving GLP-1 RA in six countries (Belgium, France, Germany, Italy, Netherlands, Canada) showed that most patients do not remain on their index therapy for the duration of their lifetimes, and instead discontinued the treatment or switched to a new treatment within 3 years[1]. While these data are not from the UK, there is no reason to expect	Thank you for your comment. You are correct the analysis did not model the impact of treatment discontinuation. The committee noted there was uncertainty over the likely rates of treatment discontinuation in clinical practice, but importantly there was also uncertainty over the duration of treatment effect, and how long this would persist for. They agreed it would be inappropriate to include the impact of reduced costs through discontinuation, but not the impact of reduced efficacy, both from discontinuations after the trial

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				differences from the consistent patterns observed in the six countries included in the analysis. The same pattern is seen with the oral medications, as well as injectable GLP-1 RAs. A study of treatment persistence of oral anti-diabetic therapies in the UK showed that patients do not remain on a prescribed therapy for the duration of their lifetimes[2]. Median persistence was longest with metformin at 3.04 years, with 39.6% of patients continuing this medication 5 years after initiation. With SGLT2-is, data only extended to 2 years, but only 54.8% of patients were continuing therapy at this time point. Persistence rates were lower with DPP-4 inhibitors than with SGLT2-is, with only 45.5% continuing therapy at 2 years. As discontinuation of treatments is not considered in the analyses, the HR for CVOTs are applied and costs are accrued past where patients would have stopped taking the new medication in the real-world. Therefore, the health economic analysis does not reflect clinical reality, and is of limited use to healthcare decision makers. **References:** 1. Divino V, Boye KS, Lebrec J, DeKoven M, Norrbacka K. GLP-1 RA Treatment and Dosing Patterns Among Type 2 Diabetes Patients in Six Countries: A Retrospective Analysis of Pharmacy Claims Data. Diabetes Ther. 2019;10(3):1067-1088. 2. McGovern A, Hinton W, Calderara S, Munro N, Whyte M, de Lusignan S. A Class Comparison of Medication Persistence in People with Type 2 Diabetes: A Retrospective Observational Study. Diabetes Ther. 2018;9(1):229-242.	time horizon, but also from possible reduced efficacy in people still on treatment. Given these uncertainties, the committee agreed an appropriate approach was to model lifetime use of the drugs which, whilst it will not 100% accurately reflect practice, will at least mean the impacts of discontinuation and treatment effect waning are treated consistently, in the absence of evidence to take a different approach.
Oxford Centre for Diabetes, Endocrinology & Metabolism (OCDEM), Oxford	Guideline	014	029	Suggest wording changed from congestive heart failure to heart failure with reduced ejection fraction (	Thank you for your comment. The committee discussed the stakeholder comments about the use of the term 'congestive' heart failure. They agreed that it would be inappropriate to change this to say symptomatic chronic heart failure with reduced ejection fraction because people with heart failure are a larger group of people than those with heart failure with reduced ejection fraction. In addition, the recommendations deliberately cover people with type 2

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University Hospitals NHS Foundation Trust					diabetes and heart failure to match the clinical and economic evidence. Based on stakeholder requests the committee decided to change congestive heart failure to chronic heart failure. This change was made because this term refers to the same population of people with heart failure as congestive heart failure does and it was thought that the wider medical society will understand this term better because it is in wider use currently.
Oxford Centre for Diabetes, Endocrinology & Metabolism (OCDEM), Oxford University Hospitals NHS Foundation Trust	Guideline	015 016	007 / 013 / 022 025	Suggest that an upper age limit is included about the use of SGLT2i in line with the SPCs. Licensing for SGLT-2 inhibitors as exemplified by empagliflozin does not extend to those over 85 years old so perhaps there should be alternative first line suggestions in this age group. As such, the risk/benefit of the guidelines in the very elderly should be considered and blanket statements such as in line 25 (page 16) should be qualified.	Thank you for your comment. Please note that none of the SGLT2 (apart from empagliflozin) have SPC that recommend against use in older people with type 2 diabetes. The SPC for dapagliflozin, canagliflozin and ertugliflozin all state that there is limited therapeutic experience in older adults and highlight the increased risk of volume depletion in older adults. The SPC for empagliflozin also states limited clinical experience as the reason for not initiating in treatment in those over 85 years. No SGLT2 inhibitor is directly contraindicated for use in this age group. The purpose of assessing CV risk (and commencing any subsequent therapy) is to prevent any avoidable premature CV events or CV mortality. The potential benefit to an individual from taking a drug to help reduce the risk of CV disease in type 2 diabetes should be balanced against the risks of taking it, taking into account their individual factors. These are covered in recommendation on choosing drug treatments and it is expected that the prescriber would take the individual's clinical needs into account as part of the decision making process.
Oxford Centre for Diabetes, Endocrinology & Metabolism (OCDEM),	Guideline	015	007 / 013 / 022	In the EMPA-REG trial fewer than 2% of the participants had a new diagnosis of diabetes (i.e. under 1 year) so extension of the benefits to first line treatment should be considered with caution	Thank you for your comment. The committee noted that the trials all recruited people with established cardiovascular (CV) disease and a proportion also included people with high CV risk, but no prior CV event. They agreed that there was highest certainty that the results of the NMAs, the economic model and any CV benefits identified applied to people with established CV disease and that the uncertainty

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Oxford University Hospitals NHS Foundation Trust					increased as the populations in the model became more removed from this group. They also noted that the CVOTs mainly contained participants who had been diagnosed with type 2 diabetes between 6 and 15 years ago on average, depending on the trial, and very few participants were likely to have been on metformin alone. However, they agreed it was likely that any CV protection should also be available to people with type 2 diabetes who were at an earlier stage of the treatment pathway, and it would be appropriate to allow them access to drugs with CV benefits if they had established CVD or were judged to be at high risk of developing CVD irrespective of the duration of their diabetes. In addition, the committee observed that individuals who are diagnosed with type 2 diabetes have often had the condition for several years already.
Oxford Centre for Diabetes, Endocrinology & Metabolism (OCDEM), Oxford University Hospitals NHS Foundation Trust	Guideline	015 020	009 & 024 021	Suggest specify use in heart failure in line with NICE TA679 (symptomatic heart failure, reduced ejection fraction, use of other heart failure drugs optimised). The use of SGLT2 inhibitors in the presence of congestive cardiac failure is too generalised a statement. The evidence, the licence and the NICE TA for the use of SGLT2is in heart failure are very specific. This class of drugs should be used when there is symptomatic heart failure with a reduced ejection fraction after all other heart failure therapies have been optimised. If this guideline is going to recommend SGLT2i specifically for people with heart failure, it should be more specific about the evidence for its use (eg including the same criteria as in the NICE TA for the use of SGLT2i eg including symptoms of heart failure and specifying the ejection fraction below which there is evidence of benefit).	Thank you for your comment. Please note that less than 50% the population under consideration for NICE TA679 had diabetes. This means that the results of that analyses are of very limited relevance compared to the populations in the CV outcome trials included in the evidence review for this guideline update. For first line treatment we are not recommending off-label use of the SGLT2 inhibitors (SGLT2i) because all currently available SGLT2i have a marketing authorisation for glycaemic control in adults with type 2 diabetes. Some SGLT2i (dapagliflozin and empagliflozin) have a marketing authorisation which includes symptomatic chronic heart failure with reduced ejection fraction alone, but we are not making recommendations for people who have heart failure with reduced ejection fraction who do not have type 2 diabetes. Symptomatic chronic heart failure with reduced ejection fraction is a subgroup of heart failure, which is one of the populations covered by the recommendations for people who also have type 2 diabetes. The committee did not limit the recommendations to adults with type 2 diabetes and symptomatic chronic heart failure with reduced ejection fraction because they intended the

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					recommendation to cover the broader heart failure population, which was defined based on the participants in the cardiovascular outcome trials. In the recommendations for using SGLT2i for initial treatment in addition to metformin or in place of metformin if it is contraindicated / not tolerated, the SGLT2i is being used to provide glycaemic control and cardiovascular benefit. It is only if the use of an SGLT2i is retained despite not providing any glycaemic control that this would potentially be an off-label use. NICE expects that prescribers will use the drugs within the marketing authorisation over off-label use of a licensed medicine where appropriate. Please see additional information on prescribing medicines and off-label or unlicensed use.
Oxford Centre for Diabetes, Endocrinology & Metabolism (OCDEM), Oxford University Hospitals NHS Foundation Trust	Guideline	015	011	For high risk cardiovascular disease it is later suggested this would be a QRISK2 score of over 10% but there is a more up to date QRISK3 risk assessment tool that should be used	Thank you for your comment. The committee deliberated over the definition of high risk of developing CV risk disease (high risk of future major adverse cardiovascular event such as an MI or stroke) to capture this population. They agreed that a QRISK2 score of >10% would be appropriate because this score takes into account most of the factors that were used to define this population in the economic model (and factors such as age, gender and ethnicity. They noted that QRISK2 is recommended for the assessment of CV risk in people with the 2 diabetes in the NICE guideline on NICE guideline on Cardiovascular disease: risk assessment and reduction, including lipid modification and is widely used and accepted in current general practice. Although other algorithms for assessing CVD risk exist, such as QRISK3, they are not in widespread use currently. Since a review of the evidence about the accuracy of such algorithms in comparison to each other and QRISK2 was not within the scope of this work, the committee agreed that QRISK2 was

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					a pragmatic choice for assessing CV risk in people with type 2 diabetes.
Oxford Centre for Diabetes, Endocrinology & Metabolism (OCDEM), Oxford University Hospitals NHS Foundation Trust	Guideline	015	011 / 027	Surely diabetes in itself is a significant cardiovascular risk factor for cardiovascular disease and thus the majority of patients will be funnelled down the combination metformin and SGLT-2 inhibitor first line pathway	Thank you for your comment. You are correct that having diabetes does increase your cardiovascular risk and a large proportion of people with type 2 diabetes are expected to fall into the category of being at high cardiovascular disease risk (or having cardiovascular disease). However, the committee agree that the cost-effective use of SGLT2 inhibitors in reducing the risk of premature mortality for those at high cardiovascular disease risk or with established cardiovascular disease is a positive step in the treatment of this condition. NICE is undertaking a resource impact assessment of the draft recommendations in preparation for finalisation of the guideline update. This includes consideration of the sizes of the populations that would be covered by the SGLT2 inhibitor recommendations for people with established cardiovascular disease (CVD) and high risk of CVD. This document will be available on the guideline website for commissioners to look at resource implications of these recommendations.
Oxford Centre for Diabetes, Endocrinology & Metabolism (OCDEM), Oxford University Hospitals NHS Foundation Trust	Guideline	015	014	Please clarify the timelines for "starting [medication] sequentially" Metformin and SGLT2i should be started sequentially. We are unclear as to what "sequentially" actually means. If this is being recommended, then these guidelines should be more specific as to the time sequence of starting different drugs. Should the second drug be started after a week? A month? 6 months?	Thank you for your comment. Following stakeholder comments the committee have reworded this recommendation to emphasise the need introduce the SGLT2 inhibitor without delay once metformin tolerability is confirmed. This is aimed at reducing the risk of clinical inertia delaying the introduction of the SGLT2i.

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Oxford Centre for Diabetes, Endocrinology & Metabolism (OCDEM), Oxford University Hospitals NHS Foundation Trust	Guideline	016	026	The wording suggesting adverse effect on renal function is confusing as it is suggested elsewhere SGLT-2 inhibitors provide renal protection and they are licensed for delaying nephropathy	Thank you for your comment. The committee discussed the stakeholder comments about the renal impact of SGLT2 inhibitors (SGLT2i). They agreed that the existing recommendation was unclear and potentially confusing because it gave no indication of the frequency or when the monitoring should take place. They also recognised that although SGT2i can have a negative effect on renal function this is usually a small reduction in function and not a reason to stop taking the SGLT2i. Taking these points into account the committee have now removed this draft recommendation.
Oxford Centre for Diabetes, Endocrinology & Metabolism (OCDEM), Oxford University Hospitals NHS Foundation Trust	Guideline	017	004	The sick day rule advice should include metformin in addition to SGLT-2 inhibitors	Thank you for your comment. The recommendation that included sick day rules was reviewed following stakeholder comments and the bullet point on sick day rules has now been removed as the committee agreed it would be inconsistent to present this information for one class of drugs but not any others. They expected that sick day rules and other safety related advice would be discussed with the individual with type 2 diabetes as part of the decision-making process regarding drug choice and wanted to keep the guidance as simple and clear as possible.
Oxford Centre for Diabetes, Endocrinology & Metabolism (OCDEM), Oxford University Hospitals	Guideline	017	010 - 011	Suggest include the need to stop SGLT2i when there is a planned procedure. Whilst it is important to highlight "sick day rules" for when to stop SGLT2 inhibitors, it would also be important to highlight the need to stop SGLT2i when planned physiological challenges occur such as procedure like planned surgery. Of the 15 cases of SGLT2i induced DKA we have identified in our clinical service in the last 2 years, 9 have been associated with a procedure.	Thank you for your comment. The recommendation which included sick day rules (including for planned procedures) was reviewed following stakeholder comments and the bullet point on sick day rules has now been removed as the committee agreed it would be inconsistent to present this information for one class of drugs but not any others. They expected that sick day rules and other safety related advice would be discussed with the individual with type 2 diabetes as part of the decision-making process regarding drug choice and wanted to keep the guidance as simple and clear

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NHS Foundation Trust					as possible. We have therefore been unable to include the additional information you suggested.
Oxford Centre for Diabetes, Endocrinology & Metabolism (OCDEM), Oxford University Hospitals NHS Foundation Trust	Guideline	018	General	Suggest removal or caution over the inclusion of ertugloflozin on par with the other SGLT-2 inhibitors as it has not been shown to have the cardiovascular benefit compared to the others Ertugliflozin has not shown any CV benefit, in contrast to other SGLT2i listed. It is therefore unclear as to why it is listed equally with canagliflozin, dapagliflozin and empagliflozin. Indeed the NICE TA (TA572) for ertugliflozin does not specifically recommend its use in people with established CV disease.	Thank you for your comment. The committee reviewed the stakeholder comments but decided to continue treating SGLT2 inhibitors (SGLT2i) as a class for the following reasons: • There was a degree of uncertainty around whether there were real differences in cardiovascular (CV) benefits between the SGLT2i based on the clinical trial evidence and results from the NMAs. o Firstly, for hospitalisation for heart failure, the SGLT2i empagliflozin, canagliflozin, and dapagliflozin produced a clinically meaningful reduction compared with placebo in the random effects NMA model. However, in the sensitivity analyses using a fixed effect model ertugliflozin also showed a clinically meaningful reduction compared to placebo, which reflects the original clinical trial data. The NMA results could not differentiate between the SGLT2i for this outcome. o Secondly, for the 3 point MACE outcome, only canagliflozin and empagliflozin produced a statistically significant reduction compared to placebo but the SGLT2i could not be differentiated from each other in the NMA. o Thirdly for all cause and CV mortality empagliflozin showed a clinically meaningful reduction compared to placebo and the other SGLT2i, but the remaining SGLT2i could not be differentiated from each other or placebo in the NMA. o Fourthly, for non-fatal MI and non-fatal stroke the NMAs could not differentiate between empagliflozin, canagliflozin, ertugliflozin and

					placebo. The data for dapagliflozin was reported differently and could not be included in the NMAs. From the clinical trial data dapagliflozin could not be differentiated from placebo for MI and was not meaningfully different from placebo for stroke. ○ Finally, only dapagliflozin showed a clinically meaningful improvement in severe hypoglycaemia compared to placebo but the remaining SGLT2i could not be differentiated from each other and placebo in the NMA. • There was also a degree of uncertainty around the cost-effectiveness of individual SGLT2i in the economic modelling. Although only dapagliflozin was cost-effective at a threshold of £20,000/quality-adjusted life year (QALY) across all model scenarios and CV risk groups it could not be differentiated from the other SGLT2i in the NMA apart from for the all-cause and CV mortality outcomes where it was clinically meaningfully worse than empagliflozin. The ranking of ICERs for the other SGLT2i varied across model scenarios and risk groups. The committee agreed that there was sufficient uncertainty in the economic modelling (caused in turn by uncertainty in the underlying clinical data) to mean that they were not sufficiently confident that these different ICERs represented true underlying differences in cost-effectiveness, as opposed to simply random variation in the results between different SGLT2 trials. • Taking the cost-effectiveness and clinical results into account the committee decided against only recommending dapagliflozin and instead made recommendations for the SGLT2i as a class. However, they recognised that there was a greater degree of uncertainty around the CV benefit associated with ertugliflozin because, depending on the choice of model used in the NMA, it did not consistently show a clinically meaningful reduction in hospitalisation for heart failure compared to placebo, unlike empagliflozin, canagliflozin

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					and dapagliflozin. It was also not statistically significantly better than placebo for the 3-point MACE outcome unlike canagliflozin and empagliflozin. The committee therefore recommended SGLT2i with proven CV benefit because this wording would enable the prescribers to select a particular drug from within the SGLT2 class if they thought this was clinically justified based on the individual characteristics of their patient, whilst future proofing the recommendation should additional evidence or new SGLT2s be made available. As per the recommendation on choosing drug treatment, once the clinical circumstances and needs of the person with type 2 diabetes, including their need for CV protection, have been taken into account, if 2 drugs in the same class are suitable for that individual then the prescriber is still expected to choose the option with the lowest acquisition cost to help use NHS resources wisely. Please see evidence review A for more a more detailed explanation of the analyses that were carried out and the committee's discussion of the results.
Oxford Centre for Diabetes, Endocrinology & Metabolism (OCDEM), Oxford University Hospitals NHS Foundation Trust	Guideline	024	General	There is no guidance on stopping medication just on addition of medications	Thank you for your comment. We have expanded the section on reviewing and changing treatments to include the bullets '• stop medicines that are not tolerated • stop medicines that have had no impact on glycaemic control or weight, unless they are being prescribed for cardiovascular or renal protection.'

Type 2 diabetes in adults: management (update)

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Oxford Centre for Diabetes, Endocrinology & Metabolism (OCDEM), Oxford University Hospitals NHS Foundation Trust	Guideline	General	General	GLP-1 receptor agonists cardiovascular benefit seems slightly overlooked and the BMI criteria remain quite high and strict. Especially when there are reduced risks of hypoglycaemia, testing and the benefit of weight loss compared to insulin.	Thank you for your comment. The cardiovascular benefit of the GLP-1 receptor agonists is explored in the pairwise, and network meta-analyses and the economic model. However, the committee decided against recommending them. Their reasons are detailed below. In the NICE health economic analyses, when looking at GLP-1 mimetics as a class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of £20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the intervention as an effective use of NHS resources will specifically take account of the following factors." and • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis."

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					Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors. The committee agreed that the evidence from the cardiovascular outcome trials was most relevant to people with established cardiovascular disease and those at high risk of developing cardiovascular disease. The therefore

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					limited their recommendations to these groups. The GLP-1s were not cost-effective for these people and no new non-cardiovascular outcome trial evidence regarding the benefits of GLP-1s was included in this review. Therefore, the committee were unable to amend or rewrite the 2015 criteria for GLP-1 use in this current update. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand.
Oxford University, Diabetes Trials Unit	Guideline	General	General	Regarding the advice for SGLT-2 for people with 'heart failure' this is a outside of the marketing authorisation, and NICE does not make recommendations outside of the MA. The MAs for SGLT-2 is limited to **symptomatic** people with **reduced** ejection fraction. To extend recommendation beyond this group is in appropriate.	Thank you for your comment. Please note that NICE guidelines have previously made, and continue to make, recommendations for off-label prescribing in line with MHRA guidance. The NICE guideline manual (section 9.2 Recommendations on medicines, including off-label use of licensed medicines) sets out the considerations and process for making recommendations about off-label use of licensed medicines. For first line treatment we are not recommending off-label use of the SGLT2 inhibitors (SGLT2i) because all currently available SGLT2i have a marketing authorisation for glycaemic control in adults with type 2 diabetes. Some SGLT2i (dapagliflozin and empagliflozin) have a marketing

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					authorisation which includes symptomatic chronic heart failure with reduced ejection fraction alone, but we are not making recommendations for people who have heart failure with reduced ejection fraction who do not have type 2 diabetes. Symptomatic chronic heart failure with reduced ejection fraction is a subgroup of heart failure, which is one of the populations covered by the recommendations for people who also have type 2 diabetes. The committee did not limit the recommendations to adults with type 2 diabetes and symptomatic chronic heart failure with reduced ejection fraction because they intended the recommendation to cover the broader heart failure population, which was defined based on the participants in the cardiovascular outcome trials. In the recommendations for using SGLT2i for initial treatment in addition to metformin or in place of metformin if it is contraindicated / not tolerated, the SGLT2i is being used to provide glycaemic control and cardiovascular benefit. It is only if the use of an SGLT2i is retained despite not providing any glycaemic control that this would potentially be an off-label use. NICE expects that prescribers will use the drugs within the marketing authorisation over off-label use of a licensed medicine where appropriate. Please see additional information on prescribing medicines and off-label or unlicensed use.
Oxford University, Diabetes Trials Unit	Guideline	General	General	The MA for empafliflozin (and perhaps other SGLT-2s) discourages use in the over 80s because of lack of evidence. The guidelines appear to include all ages. Clinically, I would be uncomfortable with this, and the MA specifically mentions volume depletion in the elderly.	Thank you for your comment. The purpose of assessing cardiovascular risk (and commencing any subsequent therapy) is to prevent any avoidable premature cardiovascular events or cardiovascular mortality. The committee agreed that a healthcare professional should assess the potential benefit to, in this example, an older person taking a drug to help reduce the risk of future cardiovascular disease in type 2 diabetes and should balance this against the risks of taking it, considering the

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					persons individual factors. Please see the choosing drug treatment recommendation for further details of factors to consider during the decision-making process.
Oxford University, Diabetes Trials Unit	Guideline	General	General	The guidelines advocated dual treatment in newly diagnosed diabetes with metformin, and then, SGLT-2 for people at 'high' risk of CVD. However, I believe this goes **beyond** the evidence, where, the proportion of people with a diabetes duration of less than one year in the SGLT-2 CVD safety trials was very small; for example, less that 2% in the EMPA-Reg trail. The numbers on metformin for only a short period and who have newly diagnosed diabetes will be even fewer. These guidelines do not reflect the evidence, and if there is effect modification by duration of diabetes, then these guidelines will have generated biased estimates.	Thank you for your comment. The committee noted that the trials all recruited people with established cardiovascular (CV) disease and a proportion also included people with high CV risk, but no prior CV event. They agreed that there was highest certainty that the results of the NMAs, the economic model and any CV benefits identified applied to people with established CV disease and that the uncertainty increased as the populations in the model became more removed from this group. They also noted that the CVOTs mainly contained participants who had been diagnosed with type 2 diabetes between 6 and 15 years ago on average, depending on the trial, and very few participants were likely to have been on metformin alone or newly diagnosed. However, they agreed it was likely that any CV protection should also be available to people with type 2 diabetes who were at an earlier stage of the treatment pathway, and it would be appropriate to allow them access to drugs with CV benefits if they had established CVD or were judged to be at high risk of developing CVD irrespective of the duration of their diabetes. In addition, the committee observed that individuals who are diagnosed with type 2 diabetes have often had the condition for several years already.
Oxford University, Diabetes Trials Unit	Guideline	General	General	It is confusing when the guidelines state that SGLT-2 drugs can adversely affect renal function when dapafliflozin has a specific indication to prevent (delay) renal disease which today NICE is addressing in TA Comm D.	Thank you for your comment. The committee discussed the stakeholder comments about the renal impact of SGLT2 inhibitors (SGLT2i). They agreed that the existing recommendation was unclear and potentially confusing because it gave no indication of the frequently or when the monitoring should take place. They also recogniszed that although SGT2i can have a negative effect on renal function this is usually a small reduction in function and not a reason to stop taking the SGLT2i. Taking these points into account committee have now removed this draft recommendation.

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Oxford University, Diabetes Trials Unit	Guideline	General	General	The analysis of the GLP-1 seem to reflect the prior evidence for glycaemic benefit (when, compared with insulin they weren't much better). However, because there were associated with weight loss, then it made sense to optimise the recommendation to people most likely to benefit, notably, overweight people (and further, there were stopping rules). However, with the evidence now based on outcomes trials, it's not clear if the guidance would change under the scenario of 'for CVD benefit' vs. 'for glycaemic control'.	Thank you for your comment. The committee agreed with the need to produce guidance to help promote personalised treatment. The original scope of this work covered additional groups of interest including people with renal impairment, people in specific ethnic groups, adults aged 65 years and older, as well as people in specific cardiovascular risk groups. The committee also wanted to include people who are obese as a group of particular interest. This work aimed to fully update the drug treatment sections of the NG28 guideline. However, once work on the topic commenced it was determined that updating evidence reviews and health economics for such a wide scope, within the resources available to NICE for this topic, would take an unacceptably lengthy period. Taking such an approach for this guideline update would have further delayed publication of updated treatment recommendations in this rapidly changing area. In view of the timescales involved and the appetite from the committee and stakeholders for an update within an acceptable time period, we worked with our committee members to identify the priority areas for this update. The committee members agreed that our initial focus should be on reviewing the evidence from trials looking at cardiovascular outcomes. This reflected the changing evidence base as a result of the significant investment in clinical trials to directly capture cardiovascular outcomes, feedback from stakeholders that assessing this evidence was a priority and the impact that this new evidence could have on recommendations for the treatment of people with diabetes. We therefore revised the scope to reflect this and carried out the current piece of work. The committee agreed that the evidence from the cardiovascular outcome trials was most relevant to people with established cardiovascular disease and those at high risk of developing cardiovascular disease. They therefore

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					limited their recommendations to these people. The GLP-1s were not cost-effective for these groups and no new non-cardiovascular outcome trial evidence regarding the benefits of GLP-1s was included in this review. Therefore, the committee were unable to amend or rewrite the 2015 criteria for GLP-1 use in this current update. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand. In the meantime, to make it easier for prescribers to select appropriate treatment options that match the needs of each individual we have developed a summary table listing relevant factors such as whether the drug is associated with weight loss or weight gain. It is hoped that this table, together with the recommendation about choosing drug treatments that covers tailoring drug choice to individual needs and circumstances, will support personalised care.
Oxford University, Diabetes Trials Unit	Guideline	General	General	Because of point 4 these guidelines are not up-to-date, but, alas, this is inevitable.	Thank you for your comment. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work

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					looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand.
Perspectum Ltd	Guideline	General	General	The use of Magnetic Resonance Imaging (MRI) techniques to assess and monitor cardiovascular status and comorbidities in other organs is not mentioned within these guidelines. **Recommendation 1.7.4. and page 32:** High risk of developing cardiovascular disease, the QRISK2 tool and clinical judgement of cardiovascular (CV) risk factors are listed as methods for assessing cardiovascular status and cardiovascular disease (CVD) risk in adults with type 2 diabetes. **Recommendation 1.7.1.** comorbidities are listed in the factors of consideration when choosing drug treatments for adults with type 2 diabetes. We propose that **multi-organ magnetic resonance imaging (MRI) techniques** be included as a method for **quantitatively assessing cardiovascular status** and for **assessing other comorbidities** including progression of co-prevalent **non-alcoholic fatty liver disease (NAFLD)**. There is a 32.2% prevalence of cardiovascular disease (CVD) in patients with type 2 diabetes (T2D)[1]. MRI technology has been proven to be a powerful technique to diagnose, monitor and stratify risk for CVD. For example, vessel wall MRI is a useful technique to examine the arterial wall to identify risk of CVD, characterise atherosclerosis in various regions of the cardiovascular system[2-7] and evaluate plaque composition and	Thank you for your comment. NG28 covers the management of Type 2 diabetes in adults. Although the recommendations on choosing drug treatments mention taking co-morbidities into account they do not cover how to diagnose these comorbidities. In particular, diagnosis of NAFLD is covered by another NICE guideline (NG49): Non-alcoholic fatty liver disease (NAFLD): assessment and management. Should the use of MRI techniques to non-invasively diagnose and monitor NAFLD be recommended by the NICE Diagnostic Assessment Programme then this can be incorporated into future updates of that guideline. It is expected that clinicians will refer to the NAFLD and cardiovascular disease guidelines for information to aid with the assessment of CV risk and to diagnose the presence of NAFLD. Any reference to the use of MRI techniques for these assessments would fall under the scope of these guidelines and the evidence would need to be reviewed as part of their future updates. Assessment of the use of MRI for assessing CVD risk or NAFLD is not within the scope of the current type 2 guideline work and the committee are therefore unable to review any evidence on this topic or make any of the requested changes to recommendations. The committee deliberated over the definition of high risk of developing CV risk disease (high risk of future major

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				physiology to assess risk of severe acute cardiovascular events[8,9]. In addition, cardiac MRI has proven useful to assess left ventricle structure and function, aortic stiffness and ventricular-arterial interaction to inform on risk of cardiovascular disease in patients with T2D[10]. Cardiac MRI measures including carotid artery wall thickness are also accurate indicators of risk for CV events in asymptomatic patients[11]. Non-contrast cardiac MRI techniques have been adopted in **clinical guidelines for diagnosis of cardiac diseases**[12,13,14]. For example, T1 maps provide diagnostic information in the heart over a wide range of T1 values, so that increased T1 can be diagnostic of oedema (increased tissue water) or increased interstitial space[15,16,17], even before clinical symptoms develop[18,19]; whilst shortening of T1 characterises thrombus formation[20] and cardiac fat in lipomatous hypertrophy[21]. T1 maps reliably diagnose a range of conditions, including acute myocardial infarction, myocarditis, amyloidosis, iron overload and Fabry disease[15,22-25], and the derived extracellular volume is a powerful independent predictor of mortality in patients with severe aortic stenosis[26]. In support, the 2014 European Society of Cardiology guidelines for the diagnosis and treatment of aortic diseases state that MRI is well suited to diagnosing aortic disease due to the technical reliability of aortic measurements. There is high prevalence of other co-morbidities in patients with T2D: CKD[27] is prevalent in 34-51% of T2D patients and there is a 60% prevalence of non-alcoholic fatty liver disease (NAFLD)[28,29]. This is supported in the non-alcoholic fatty liver disease (NAFLD): assessment and management NICE guideline; Recommendation 1.1.1. states that non-alcoholic fatty liver disease (NAFLD) is more common in people who have T2D or metabolic syndrome. The prevalence of NAFLD is increasing alongside the level of obesity in the population, and in the UK, cirrhosis and other liver diseases are the leading cause of mortality in persons aged 35 to 49 (Public Health England, 2020). For patients with NAFLD,	adverse cardiovascular event such as an MI or stroke) to capture this population. They agreed that a QRISK2 score of >10% would be appropriate because this score takes into account most of the factors that were used to define this population in the economic model (and factors such as age, gender and ethnicity. They noted that QRISK2 is recommended for the assessment of CV risk in people with the 2 diabetes in the NICE guideline on NICE guideline on Cardiovascular disease: risk assessment and reduction, including lipid modification (CG181) and is widely used and accepted in current general practice. Although other algorithms for assessing CVD risk exist, such as QRISK3, they are not in widespread use currently. Since a review of the evidence about the accuracy of such algorithms in comparison to each other and QRISK2 was not within the scope of this work, the committee agreed that QRISK2 was a pragmatic choice for assessing CV risk in people with type 2 diabetes.

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				the presence of fibrosis increases the risk of death, with the stage of fibrosis being a predictor of liver-related mortality[30]. Therefore, early diagnosis and accurate staging of NAFLD is important to identify the most suitable care pathway and provides opportunity to slow or prevent disease progression to advanced stages of inflammation and/or fibrosis, including non-alcoholic steatohepatitis (NASH) and cirrhosis. Early diagnosis and management of liver disease is essential for improving outcomes and reducing the risk of complications in patients with NAFLD[31]. The use of MRI techniques to non-invasively diagnose and monitor NAFLD is supported in the NICE Final Scope for the guidance in development: MRI-based technologies for the assessment of non-alcoholic fatty liver disease (GID-DG10045). MRI techniques have been shown to accurately diagnose and stage NAFLD, monitored as a change in the MRI biomarker liver PDFF (proton density fat fraction), which has shown to have superior accuracy in diagnosing and stratifying grades of liver steatosis in NAFLD[32,33,34] even compared to histology[35]. Diagnosing and/or monitoring NAFLD or the progressive form non-alcoholic steatohepatitis (NASH) also requires evaluation of other liver tissue characteristics, inflammation, hepatocellular injury (ballooning) and fibrosis, which strongly correlate with MRI biomarker cT1 (corrected T1)[36]. cT1 can predict clinical outcomes[37,38,39] and has shown diagnostic accuracy in identifying NASH in type 2 diabetes[40,41,42]. cT1 shows low measurement failure rates, and high repeatability and reproducibility that are best in class for imaging[43-47] in NAFLD. The evidence for support of cT1 and PDFF in diagnosis of NAFLD is currently under consideration by the NICE Diagnostic Assessment Programme for adoption in the NICE guidelines for non-alcoholic fatty liver disease as a replacement for biopsy. Therefore, we propose that **MRI-based technologies** be included in the assessment of **co-prevalent NAFLD in patients with T2D** and that this disease is appropriately aligned and linked to guidance in	

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				development MRI-based technologies for the assessment of non-alcoholic fatty liver disease (GID-DG10045) to ensure the cross-referral is current. As argued by the Chief Medical Officer for England, the high prevalence of comorbidities in patients type 2 diabetes highlights the need for a multi-specialty approach to the monitoring of the disease[48] and these should include multi-organ MRI technologies. Multi-organ MRI provides quantitative tissue characterisation of multiple organs as well as functional and structural information[49,50]. Multi-organ MRI techniques have the potential to complement existing diagnostics by allowing clinicians to diagnose, monitor and stratify co-prevalent diseases in patients with T2D. The use of multi-organ MRI on patients with T2D has demonstrated a high prevalence of multi-organ abnormality including fatty infiltration and/or fibroinflammatory changes in the liver (75% of patients), pancreas (66%), spleen (58%), kidney (17%), aorta (67%) in type 2 diabetes patients[51]. Data from the UK BioBank indicate that body muscle and fat composition and liver steatosis and fibroinflammation differ between T2D patients with and without obesity[52]. Utilising multi-organ MRI on T2D patients show that changes in kidney volume are associated with change in fasting glucose and abdominal visceral adipose tissue[53,54]. Furthermore, fat in the liver and pancreas were shown in multiple studies to be important in driving T2D in both obese and healthy weight people. The ReTUNE trial measured the impact of body weight loss on ectopic fat via MRI in T2D patients with a healthy weight[55]. Weight loss was able to induce remission in 67% of this patient population and correlated with a reduction in fat in the liver and pancreas[55]. In the DiRECT trial weight loss and fat reduction in liver and pancreas induced remission in obese T2D patients[55]. Thus, understanding and assessing intra-organ fat via multi-organ MRI is important in the management of patients with T2D regardless of obesity status or BMI.	

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				Evidence on the applicability of multi-organ MRI techniques to examine multi-organ abnormality is also provided by studies on post-COVID syndrome (PCS), another disease area that exhibits multi-organ involvement and for which diabetes is a risk factor[56]. A prospective cohort study of 201 PCS individuals from two UK centres applied quantitative MRI techniques to assess injury the heart, kidneys, liver, pancreas, and spleen, which revealed multi-organ injury in 29% of patients with recovering from COVID-19[57]. Organ impairment was associated with hospitalisation during acute COVID-19, with liver volume, fat accumulation in the liver and pancreas and pancreatic inflammation displaying a positive association with hospitalisation, whilst severe PCS was associated with evidence of myocarditis. In support, a separate study also revealed multi-organ impairment in the lungs, brain, heart liver and kidneys in 58 PCS patients in the UK by use of multi-organ MRI technology[58]. Earlier detection of complications and co-prevalent disease provides opportunity to prevent or slow disease progression, reverse disease, and improve outcomes. The high prevalence of comorbidities including CVD in adults with type 2 diabetes highlights the need for an accurate, reliable and repeatable method for diagnosing and monitoring complications and comorbidities. Therefore, we recommend the use of multi-organ MRI techniques to monitor comorbidities including CVD in adults with type 2 diabetes. *References* (1) Einarson, T.R. Acs, A. Ludwig, C. and Panton, U.H. (2018). Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017. Cardiovascular diabetology, 17(1), 1-19.	

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Primary Care Diabetes Society (PCDS)	Guideline	014	007	1. Importance of cardiovascular protection is emphasised; however, there is no reference to management of chronic kidney disease, in accordance with NICE NG203 (published 25 Aug 2021). Given that SGLT2 inhibitors are included in NG203, it is important that this information is also present in the new type 2 diabetes guidance. It is very confusing for clinicians to have to navigate through multiple NICE guidelines in order to treat type 2 diabetes. This advice is very fragmented and may be detrimental to holistic type 2 diabetes care.	Thank you for your comment. The renal benefits of using SGLT2 inhibitors in people with type 2 diabetes and CKD have been assessed in a separate piece of work that has recently been out for stakeholder consultation and was published in November 2021. The final recommendations on renal and cardiovascular benefits will be brought together in a single updated guideline document when this current work on cardiovascular benefits is published in 2022. The CKD recommendations are situated in the section on CKD in the

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					type 2 diabetes guideline with a cross reference from the drug treatment section.
Primary Care Diabetes Society (PCDS)	Guideline	014	028	Only CV risk/CHF/ACVD is mentioned; there is no reference to management of chronic kidney disease, in accordance with NICE NG203 (published 25 Aug 2021). Given that SGLT2 inhibitors are included in NG203, it is important that this information is also present in the new type 2 diabetes guidance.	Thank you for your comment. The renal benefits of using SGLT2 inhibitors in people with type 2 diabetes and CKD have been assessed in a separate piece of work that has recently been out for stakeholder consultation and was published in November 2021. The final recommendations on renal and cardiovascular benefits will be brought together in a single updated guideline document when this current work on cardiovascular benefits is published in 2022.
Primary Care Diabetes Society (PCDS)	Guideline	015	003	1. NICE CG181 clearly states that a CVD risk assessment tool should not be used in people with established CKD (eGFR <60 and/or albuminuria). 2. It should be emphasised in the present guidance that established CKD is an independent risk factor for CVD. We note that QRISK3 factors in CKD but that this is not currently available on primary care clinical systems.	Thank you for your comment. The guideline cross refers to CG181 NICE's guideline on cardiovascular disease: risk assessment and reduction, including lipid modification from the recommendation to assess cardiovascular risk. Therefore prescribers will have access to the stated recommendation for not using CVD risk tools in people with CKD. The committee declined to add your requested text about established CKD being an independent risk factor for CVD because the type 2 guideline does not focus on CVD risk assessment. This information would sit better in CG181 when it is updated in the future. Please note, the new recommendations on the use of SGLT2 inhibitors in people with type 2 diabetes and CKD that have recently been out for consultation have been added to this version of the guideline. There is a cross reference directing reader to them from the start of the first-line drug treatment recommendations. The committee deliberated over the definition of high risk of developing CV risk disease (high risk of future major adverse cardiovascular event such as an MI or stroke) to capture this population. They agreed that a QRISK2 score of >10% would be appropriate because this score takes into account most of the factors that were used to define this population in the economic model (and factors such as age,

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					gender and ethnicity. They noted that QRISK2 is recommended for the assessment of CV risk in people with the 2 diabetes in the NICE guideline on NICE guideline on Cardiovascular disease: risk assessment and reduction, including lipid modification and is widely used and accepted in current general practice. Although other algorithms for assessing CVD risk exist, such as QRISK3, they are not in widespread use currently. Since a review of the evidence about the accuracy of such algorithms in comparison to each other and QRISK2 was not within the scope of this work, the committee agreed that QRISK2 was a pragmatic choice for assessing CV risk in people with type 2 diabetes. In the future if QRISK3 is recommended by CG181 and is more wisely used then it may be possible to update this recommendation to refer to QRISK3.
Primary Care Diabetes Society (PCDS)	Guideline	016	016 - 024	Please add to this list: • Those with a short duration of diabetes or those in whom there is any doubt about the diagnosis of type 2 diabetes, and where type 1 diabetes (or other diabetes) is possible • People with active diabetic foot disease • People with previous history of Fournier's gangrene • Advise caution in people with a history of recurrent genitourinary infections Advise caution in people with low BMI, severe frailty and/or at risk of hypovolaemic orthostatic hypotension	Thank you for your comment. The committee agreed that expanding the safety recommendations to cover all the points suggested by stakeholders was unfeasible and was inappropriate because the guideline is the not intended to cover all the safety advice that should be taken into account when prescribing drug treatments and some of the suggested safety events were quite rare. In order to keep the guideline as simple and easy to follow as possible, the committee rewrote the safety recommendations to focus on some key points relating to the safety of SGLT2 inhibitors because they are not widely used in practice yet in some areas, and in particular may be unfamiliar to many clinicians in primary care, and the new recommendations will greatly increase the number of people who are eligible to take them. They removed some of the safety information that was in the consultation version of the guideline where it was not specific to SGLT2s, was not thought to be useful by stakeholders or was thought to be widely known. The committee agreed that prescribers are expected to consult MHRA alerts, the BNF and summary of product characteristics (SPC) for more comprehensive safety

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					information. This is highlighted in the recommendation on choosing drug treatments which includes safety as one of the factors to take into account.
Primary Care Diabetes Society (PCDS)	Guideline	016	026	The stated adverse effect of SGLT2is on kidney function is misleading. SGLT2is have been demonstrated to be renoprotective in CKD, although they may result in an initial dip in eGFR.	Thank you for your comment. The committee discussed the stakeholder comments about the renal impact of SGLT2 inhibitors (SGLT2i). They agreed that the existing recommendation was unclear and potentially confusing because it gave no indication of the frequency or when the monitoring should take place. They also recognised that although SGT2i can have a negative effect on renal function this is usually a small reduction in function and not a reason to stop taking the SGLT2i. Taking these points into account the committee have now removed this draft recommendation.
Primary Care Diabetes Society (PCDS)	Guideline	017	004 – 011	This section lacks sufficient detail and should include reference to: • Signs and symptoms of (euglycaemic) DKA • Risk of genitourinary infections (including Fournier's gangrene) When to seek urgent medical help	Thank you for your comment Following stakeholder consultation, the committee agreed that adding all the links proposed to additional safety issues was inappropriate because the guideline is the not intended to cover all the safety advice that should be taken into account when prescribing drug treatments and some of the suggested safety events were quite rare. In order to keep the guideline as simple and easy to follow as possible, the committee only included some key points regarding the safety of SGLT2 inhibitors because they are not widely used in practice yet in some areas and the new recommendations will greatly increase the number of people who are eligible to take them. Prescribers are expected to consult MHRA alerts, the BNF and summary of product characteristics (SPC) for more comprehensive safety information.. Additionally, following stakeholder comments at consultation the committee have amended the wording of the recommendation on things to check before starting the SGLT2 inhibitor to focus on whether the person is at increased risk of diabetic ketoacidosis (DKA) if they take an SGLT2 inhibitor. They have included some examples that, in

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					the committee's view, could lead to increased risk, but this is not meant to be an exhaustive list. This is noted in the rationale that accompanies the recommendation. The committee agreed that prescribers should consult the summary of product characteristics for further information. The committee made an additional recommendation to highlight to the clinician that they should try to address any modifiable risk factors before starting SGLT2i treatment.
Primary Care Diabetes Society (PCDS)	Guideline	017	010 - 011	This needs to be better qualified to highlight the risks associated with dehydration.	Thank you for your comment. The committee declined to add information to the patient advice recommendation about ensuring adequate hydration because they would need to define what this what this meant and the amount of liquid a person needed to consume to be adequately hydrated would vary between individuals, depending on their clinical circumstances.
Primary Care Diabetes Society (PCDS)	Guideline	017	012	Visual summary 1: 1. Rescue therapy section should be moved to the top of the prescribing guidance. For people with hyperglycaemia and severe osmotic symptoms, need for insulin or an SU should always be the first consideration. 2. Bullet point 2 of *Choosing treatments*: Replace cardiovascular protection with cardiorenal protection. Bullet point 4 of *Choosing treatments*: Add renal risk/status to the list of considerations.	Thank you for your comment. We have moved symptomatic hyperglycaemia to the top of both visual summaries and have added renal protection to bullet 4.
Primary Care Diabetes Society (PCDS)	Guideline	018	001	Visual summary 2: 1. Clinicians with an interest in diabetes have successfully been following the ADA/EASD Consensus Report algorithm for several years. The ADA/EASD algorithm has far greater clarity than the algorithm proposed here, and it is likely that it will continue to be used in preference to the proposed advice. 2. The algorithm should start with a consideration of hyperglycaemia/severe osmotic symptoms and the management thereof. For people with hyperglycaemia and severe osmotic symptoms, need for insulin or an SU should always be the first consideration.	Thank you for your comment. The approach to pulling together guideline recommendations in a visual form is a proof of concept. We will be continually reviewing our processes and will be updating the visual summaries based on changes to recommendations and following feedback from stakeholders and users. Symptomatic hyperglycaemia is covered on the first page of the visual summary. This has now been moved to the top of the page. At the time of consultation, the CKD recommendations were not available. We have now linked to these from the visual summaries.

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				First-line treatment section: While the importance of assessing kidney function is stated, the presence of kidney disease does not change any treatment advice within the algorithm.	
Primary Care Diabetes Society (PCDS)	Guideline	020	005	SGLT2is may not show benefit with HbA1c reduction (especially in those with lower eGFR) but will offer renal and CVD/HF benefit so should not be stopped if there appears no HbA1c benefit found in patients with CVD/CKD.	Thank you for your comment. As requested the committee have amended the recommendation on reviewing drug treatments, to take account of the less apparent or measurable benefits such as cardiovascular and renal protection.
Primary Care Diabetes Society (PCDS)	Guideline	021	012	1. There is no mention of the need for retinal screening before start of GLP-1RA therapy with insulin. GLP-1RAs and insulin still can only be initiated under a 'consultant' directive; we suggest this be changed to specialist, so that it would include DSNs and GPwSIs, who are more likely to use these therapies in primary care.	Thank you for your comment. Whilst this section of the guideline was in scope for the original planned update, following the prioritisation of the outcome of cardiovascular benefit, insulin was no longer included in the review protocol as an intervention of interest because no cardiovascular outcome trials had been carried out for insulin . No evidence for combination treatment with GLP-1RA and insulin was searched for or reviewed as part of this update and the committee were therefore unable to make any additions or changes the existing recommendations for this drug combination. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand.

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Primary Care Diabetes Society (PCDS)	Guideline	022	008 - 013	We note that this advice is in direct contradiction to ADA/EASD guidance, in which GLP-1 RAs are considered the first injectable treatment of choice (in the absence of severe hyperglycaemia, osmotic symptoms or evidence of severe weight loss/low BMI). Clinicians with an interest in diabetes have successfully been following the ADA/EASD Consensus Report algorithm for several years. The ADA/EASD algorithm has far greater clarity than the algorithm proposed here, and it is likely that it will continue to be used in preference to the proposed advice.	Thank you for your comment. The committee were aware of the ADA guidance, but their decisions were made according to the NICE guideline manual and took into account the evidence relevant to our review question. Although the NICE guidance may differ to the guidance provided by ADA, the committee were confident that their recommendations reflected the evidence they reviewed and their clinical judgement. It is of particular importance to note that the NICE guideline used an original economic model as the basis to recommend the most clinically and cost-effective options while the ADA guidance did not systematically take cost-effectiveness into account. When producing guidelines, NICE considers both effectiveness and cost-effectiveness for all of the recommendations it makes. As well as helping to ensure the recommendations made represent the best use of NHS resources (in particular, the opportunity costs of spending additional resources), this is also required by the legislation that originally established NICE (the Health and Social Care Act 2012), which states that when exercising its functions, NICE must have regard to "the broad balance between the benefits and costs of the provision of health services or of social care in England." NICE's principles further refine this by explicitly stating that "if possible, NICE considers value for money by calculating the incremental cost-effectiveness ratio" and "interventions with an ICER of less than £20,000 per QALY gained are generally considered to be cost effective." This guidance was developed in line with both these statutory requirements, and NICE's stated principles, methods and processes.
Primary Care Diabetes Society (PCDS)	Guideline	024	General	Visual summary 3: 1. While the importance of assessing kidney function is stated, the presence of kidney disease does not change any treatment advice within the algorithm.	Thank you for your comment. We have included information in the choosing medicines table on use of medicines in renal impairment. Furthermore, the renal benefits of using SGLT2 inhibitors in people with type 2 diabetes and CKD have been assessed in a separate piece of work that has recently been

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				2. We note that insulin as the preferred first option for injectable therapy is in contradiction with ADA/EASD guidance. Clinicians with an interest in diabetes have successfully been following the ADA/EASD Consensus Report algorithm for several years. The ADA/EASD algorithm has far greater clarity than the algorithm proposed here, and it is likely that it will continue to be used in preference to the proposed advice. 3. There is still the weight start criteria for GLP-1 Ras. The advice needs clarification when a person has CVD. GLP-1 RA stop criteria of both weight and HbA1c reduction remains. We recommend that the criteria should be either a weight **or** HbA1c reduction, in view of the extra CVD benefit that may be offered by these therapies.	out for stakeholder consultation and was published in November 2021. The final recommendations on renal and cardiovascular benefits will be brought together in a single updated guideline document when this current work on cardiovascular benefits is published in 2022 and linked from the visual summaries. The committee were aware of the ADA guidance, but their decisions were made according to the NICE guideline manual and took into account the evidence relevant to our review question. Although the NICE guidance may differ to the guidance provided by ADA, the committee were confident that their recommendations reflected the evidence they reviewed and their clinical judgement. It is of particular importance to note that the NICE guideline used an original economic model as the basis to recommend the most clinically and cost-effective options while the ADA guidance did not systematically take cost-effectiveness into account. The committee agreed that the evidence from the cardiovascular outcome trials was most relevant to people with established cardiovascular disease and those at high risk of developing cardiovascular disease. They therefore limited their recommendations to these people. The GLP-1s were not cost-effective for these groups and no new non- cardiovascular outcome trial evidence regarding the benefits of GLP-1s was included in this review. Therefore, the committee were unable to amend or rewrite the 2015 criteria for GLP-1 use in this current update.
Primary Care Diabetes Society (PCDS)	Guideline	034	004 – 007	Research recommendations should also consider exploring the differences in acceptability between GLP-1 Ras and insulin to people with diabetes, particularly with regard to the frequency of injections, concordance with therapies, requirement to self-monitor capillary glucose, effect on weight and risk of hypoglycaemia.	Thank you for your comment. Please note that following a discussion of the stakeholder comments received at consultation this research recommendation has been removed.
Primary Care	Guideline	034	015 +	Why has the guideline update not reviewed the evidence regarding CKD?	Thank you for your comment. The renal benefits of using SGLT2 inhibitors in people with type 2 diabetes and CKD

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Diabetes Society (PCDS)				Although we are aware that this has been reviewed in NG203, clinicians may be unaware of the link between different guidelines and their importance in managing type 2 diabetes. The more complicated the guidance (and the process of navigating it) is, the less likely clinicians are to follow it as intended.	have been assessed in a separate piece of work that has recently been out for stakeholder consultation and was published in November 2021. The final recommendations on renal and cardiovascular benefits will be brought together in a single updated guideline document when this current work on cardiovascular benefits is published in 2022.
Primary Care Diabetes Society (PCDS)	Guideline	042	008 + 016	"The evidence that was reviewed in this update was limited to the cardiovascular benefits of GLP-1 mimetics and the committee agreed that this was only generalisable to people with high risk of developing cardiovascular disease or with congestive heart failure or established atherosclerotic cardiovascular disease" Response: 1. It seems extraordinary that the committee did not undertake a review of the evidence regarding the effectiveness of GLP-1 RAs in terms of glycaemic control. In addition, we would have also recommended reviewing the evidence in terms of weight reduction. 2. Lack of HbA1c data in the modelling for the newer GLP1RA agents will have significant impact in primary care. A lot of our diabetes management in primary care is still hinged on HbA1c reduction and this is still an integral part of QOF. Basing the updates of NG28 on modelling on CV risk reduction alone will create significant confusion over the clinical use of GLP1-RAs in primary care. 3. Effect of obesity and overweight issues in with people with T2DM is under-estimated in the modelling. Therefore, the clinical benefits of weight loss associated with GLP-1RAs is also not adequately captured. Over 90% of people with T2DM are obese or overweight. 4. The modelling is based on data from cardiovascular outcome trials (CVOTs). The CVOTs predominately included patients at high-risk/established CVD, but 70 to 80 percent of the patients in primary care are not in this category; therefore, the generalisation of these results to the primary care population will be inappropriate. Additionally, the CVOTs were all very different	Thank you for your comment. 1., 2., and 3. You are correct that the model does not contain every outcome that could potentially be of interest for modelling adults with type 2 diabetes. However, the committee agreed these were the most important outcomes for assessing the additional cardiovascular and other benefits associated with drug treatment for type 2 diabetes, for the majority of the type 2 diabetes population. The committee agreed the cardiovascular outcome trials were the most appropriate data source to assess cardiovascular benefits of these drugs, being powered to specifically detect differences in hard outcomes, rather than only surrogate outcomes. The committee noted these studies were not representative of the full population of people with type 2 diabetes, but agreed this was a lesser limitation than the need to extrapolate from surrogate endpoints to cardiovascular outcomes, particularly given the findings from those studies suggesting these surrogate extrapolations are often not very robust. They also agreed that taking data on weight and hypoglycaemic events from these cardiovascular outcome trials was the most appropriate approach, in order to match the data used for cardiovascular event rates. For hypoglycaemic events, the approach taken is broadly in line with that taken in many other evaluations in diabetes, attaching costs and quality of life outcomes to the incidence of severe hypoglycaemic events, as these are the ones that make the most difference to a person's life. For changes in weight, it was noted it was important not to double count the impact of changes, as the effects on cardiovascular

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				in baseline characteristics and durations of follow-up, as evidenced in the differential event rates in control arms of the studies. Therefore, treating patients as the same, and as similar to our primary care patients, is not clinically appropriate. 5. It is unclear why the update generalises GLP-1 RAs as a class and does not recommend them for CV risk reduction in type 2 diabetes even though there are differences in the MACE achievements of the various drugs in the class (e.g. lixisenatide and exenatide were not associated with CV benefit). The same argument was not made with SGLT2is, even though ertugliflozin did not demonstrate benefits in the primary outcome in VERTIS. 6. It seems to me [SS] that in the modelling they did not adjust the HRs. Ignoring the fact that the CVOTs differ significantly in terms of research design, endpoint definitions and participants, these HRs are highly improbable to be equivalent across therapies.	outcomes should already be captured in the outcomes of those trials. It was therefore agreed that the most appropriate approach was to only include the direct quality of life gains associated with reductions in weight, with the other benefits captured through the cardiovascular event data. The committee noted that if anything the approach taken in the guideline may overestimate the benefits of weight reduction, as some of the estimated quality of life gains may be the result of avoided cardiovascular events, but it was agreed to be the best data source available. There are of course other benefits that could have been considered as part of the modelling, including renal (or other microvascular) outcomes, or additional benefits directly related to improved glycaemic control, but the committee considered these to be of lower priority than those included in the model. They also noted that it would not be appropriate for any modelling approach to simply look at benefits on different outcomes from different trials or data sources, and assume those benefits are additive, and therefore increase the cost-effectiveness of drugs when included together. They noted that in many circumstances these benefits are not additive, and which benefits are likely to be realised may depend on the individual characteristics of the people included in studies. As an example, in the separate evaluation of SGLT2 inhibitors for people with CKD and type 2 diabetes, SGLT2 inhibitors were found to significantly improve renal outcomes, but this is a population in which a large benefit would not be expected for glycaemic control (hence why these agents were not originally licensed for use in people with impaired renal function). It should also be noted that it is not the case that only additional outcomes beneficial to drug therapy were excluded from the modelling. As an example, adverse events related to drug treatment (excluding hypoglycaemia) were not included as part of the analysis. As a number of the

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					analyses in the guideline explicitly compare the addition of new treatments (for example, using 3 drugs versus 2) rather than simply switching drugs, it would be expected that inclusion of adverse events would decrease the cost-effectiveness for any additional treatments, as they would add to the adverse event burden. Therefore, whilst it is likely there would be differences found in the results of the cost-effectiveness analysis were a different set of outcomes to be included, it is not clear in which direction the results would change for any given agent, and whether they would become more or less cost-effective. 4 The committee noted that the trials all recruited people with established cardiovascular (CV) disease and a proportion also included people with high CV risk, but no prior CV event. They agreed that there was highest certainty that the results of the NMAs, the economic model and any CV benefits identified applied to people with established CV disease and that the uncertainty increased as the populations in the model became more removed from this group. They also noted that the CVOTs mainly contained participants who had been diagnosed with type 2 diabetes between 6 and 15 years ago on average, depending on the trial, and very few participants were likely to have been on metformin alone. However, they agreed it was likely that any CV protection should also be available to people with type 2 diabetes who were at an earlier stage of the treatment pathway, and it would be appropriate to allow them access to drugs with CV benefits if they had established CVD or were judged to be at high risk of developing CVD irrespective of the duration of their diabetes. In addition, the committee observed that individuals who are diagnosed with type 2 diabetes have often had the condition for several years already.

					5. Thank you for your comment. The committee reviewed the stakeholder comments but decided to continue treating SGLT2 inhibitors (SGLT2i) as a class for the following reasons: • There was a degree of uncertainty around whether there were real differences in cardiovascular (CV) benefits between the SGLT2i based on the clinical trial evidence and results from the NMAs. o Firstly, for hospitalisation for heart failure, the SGLT2i empagliflozin, canagliflozin, and dapagliflozin produced a clinically meaningful reduction compared with placebo in the random effects NMA model. However, in the sensitivity analyses using a fixed effect model ertugliflozin also showed a clinically meaningful reduction compared to placebo, which reflects the original clinical trial data. The NMA results could not differentiate between the SGLT2i for this outcome. o Secondly, for the 3 point MACE outcome, only canagliflozin and empagliflozin produced a statistically significant reduction compared to placebo but the SGLT2i could not be differentiated from each other in the NMA. o Thirdly for all cause and CV mortality empagliflozin showed a clinically meaningful reduction compared to placebo and the other SGLT2i, but the remaining SGLT2i could not be differentiated from each other or placebo in the NMA. o Fourthly, for non-fatal MI and non-fatal stroke the NMAs could not differentiate between empagliflozin, canagliflozin, ertugliflozin and placebo. The data for dapagliflozin was reported differently and could not be included in the NMAs. From the clinical trial data dapagliflozin could not be differentiated from

					placebo for MI and was not meaningfully different from placebo for stroke. ○ Finally, only dapagliflozin showed a clinically meaningful improvement in severe hypoglycaemia compared to placebo but the remaining SGLT2i could not be differentiated from each other and placebo in the NMA. • There was also a degree of uncertainty around the cost-effectiveness of individual SGLT2i in the economic modelling. Although only dapagliflozin was cost-effective at a threshold of £20,000/quality-adjusted life year (QALY) across all model scenarios and CV risk groups it could not be differentiated from the other SGLT2i in the NMA apart from for the all-cause and CV mortality outcomes where it was clinically meaningfully worse than empagliflozin. The ranking of ICERs for the other SGLT2i varied across model scenarios and risk groups. The committee agreed that there was sufficient uncertainty in the economic modelling (caused in turn by uncertainty in the underlying clinical data) to mean that they were not sufficiently confident that these different ICERs represented true underlying differences in cost-effectiveness, as opposed to simply random variation in the results between different SGLT2 trials. • Taking the cost-effectiveness and clinical results into account the committee decided against only recommending dapagliflozin and instead made recommendations for the SGLT2i as a class. However, they recognised that there was a greater degree of uncertainty around the CV benefit associated with ertugliflozin because, depending on the choice of model used in the NMA, it did not consistently show a clinically meaningful reduction in hospitalisation for heart failure compared to placebo, unlike empagliflozin, canagliflozin and dapagliflozin. It was also not statistically significantly better than placebo for the 3-point MACE outcome unlike canagliflozin and empagliflozin. The committee therefore recommended SGLT2i with proven

					CV benefit because this wording would enable the prescribers to select a particular drug from within the SGLT2 class if they thought this was clinically justified based on the individual characteristics of their patient, whilst future proofing the recommendation should additional evidence or new SGLT2s be made available. As per the recommendation on choosing drug treatment, once the clinical circumstances and needs of the person with type 2 diabetes, including their need for CV protection, have been taken into account, if 2 drugs in the same class are suitable for that individual then the prescriber is still expected to choose the option with the lowest acquisition cost to help use NHS resources wisely. Please see evidence review A for more a more detailed explanation of the analyses that were carried out and the committee's discussion of the results. In the NICE health economic analyses, when looking at GLP-1 mimetics as a class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of £20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the

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					intervention as an effective use of NHS resources will specifically take account of the following factors." and • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis." Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within

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					class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors. 6. You are correct that unadjusted hazard ratios were used in the analysis. In the absence of individual patient data, the committee agreed that there were no established methods for adjusting these data that could be conducted that would increase their confidence in the effect estimated. In particular, they noted that standard MAIC analyses required access to the individual patient data from at least some of the trials in the analysis, and as such data were not available to them, they agreed no such analyses could be robustly undertaken.
Roche Diagnostics Limited	Evidence review A	046	052	<u>The budget impact is unknown</u> The committee agreed that 'the cost impact of using dapagliflozin as first-line therapy in place of metformin would be substantial, with a significant opportunity cost to the NHS' and therefore 'metformin should remain the standard of care first-line drug treatment for newly, or recently, diagnosed adults with type 2 diabetes'. However, the cost impact of the proposed treatment prioritisation (metformin first-line, 'offer' SGLT2 inhibitors to established CVD and 'consider' for high-risk) is unknown. We propose that a formal cost impact analysis is conducted and presented to the committee before any final decision is made. This is important as the 'established CVD' and 'high risk' groups defined in the draft guideline represents the majority of the T2D population (McGurnaghan et al 2019, Read et al 2018) and high initial costs would potentially be unmanageable across primary care and lead to large	Thank you for your comment. NICE is undertaking a resource impact assessment of the draft recommendations in preparation for finalisation of the guideline update. This includes consideration of the sizes of the populations that would be covered by the SGLT2 inhibitor recommendations for people with established cardiovascular disease (CVD) and high risk of CVD. The committee have access to this document and do take resource impact into account when finalising the recommendations. The committee agreed that the use of SGLT2 inhibitors for people with established CVD or those at high risk of developing CVD would be costly and could lead to the implementation challenges you have highlighted. However, they agreed that since these drugs are clinically and cost-effective for this population in terms of CV protective benefits

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				regional differences and inequalities in the use of SGLT2 inhibitors (Whyte et al 2019). *References* Whyte MB, Hinton W, McGovern A, van Vlymen J, Ferreira F, Calderara S, Mount J, Munro N, de Lusignan S. Disparities in glycaemic control, monitoring, and treatment of type 2 diabetes in England: A retrospective cohort analysis. PLoS Med. 2019 Oct 7;16(10):e1002942 Read SH, van Diepen M, Colhoun HM, Halbesma N, Lindsay RS, McKnight JA, McAllister DA, Pearson ER, Petrie JR, Philip S, Sattar N, Woodward M, Wild SH; Scottish Diabetes Research Network Epidemiology Group. Performance of Cardiovascular Disease Risk Scores in People Diagnosed With Type 2 Diabetes: External Validation Using Data From the National Scottish Diabetes Register. Diabetes Care. 2018 Sep;41(9):2010-2018 McGurnaghan S, Blackbourn LAK, Mocevic E, Haagen Panton U, McCrimmon RJ, Sattar N, Wild S, Colhoun HM. Cardiovascular disease prevalence and risk factor prevalence in Type 2 diabetes: a contemporary analysis. Diabet Med. 2019 Jun;36(6):718-725	it is worth recommending them and facilitating work to overcome implementation challenges by providing a resource impact assessment tool. This document will be made available on the guideline website to help local and national commissioning bodies with their decision making. In addition, SGLT2s are already being used in this population in some areas based on other national or international guidance and so the resource impact may be less than anticipated.
Roche Diagnostics Limited	General	General	General	Limitations of the QRISK algorithm The draft guideline defines 'high risk' as a QRISK2 more than 10% in adults aged 40 and over or clinical judgement of an elevated lifetime risk of cardiovascular disease (defined as the presence of 1 or more cardiovascular risk factor in someone under 40). Whilst the QRISK2 algorithm is widely used within the NHS, we would like to highlight a couple of important limitations with its use. Firstly, as shown by Read et al (2018), the QRISK2 algorithm overestimates CVD risk in the T2D population. In this study, 87% of participants with T2D were calculated to be at risk over 5 years, however, only 10% experienced a CVD event over this timeframe.	Thank you for your comment. The committee deliberated over the definition of high risk of developing CV risk disease (high risk of future major adverse cardiovascular event such as an MI or stroke) to capture this population. They agreed that a QRISK2 score of >10% would be appropriate because this score takes into account most of the factors that were used to define this population in the economic model (and factors such as age, gender and ethnicity). They noted that QRISK2 is recommended for the assessment of CV risk in people with the 2 diabetes in the NICE guideline on NICE guideline on Cardiovascular disease: risk assessment and reduction, including lipid modification and is widely used and accepted in current general practice. Although other algorithms for assessing CVD risk exist, such as QRISK3,

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				Secondly, and even more importantly, the QRISK2 algorithm was developed and validated for the prediction of myocardial infarction (MI)/stroke, but not heart failure (HF) (Hippisley-Cox et al 2008). For this reason, Hippisley-Cox et al (2015) and others have developed separate risk algorithms for the prediction of HF rather than CVD, however these are not routinely used within the NHS. HF is the second most common serious CVD complication resulting from T2D (Einarson et al 2018) and survival rates in people with established HF are poor (Taylor et al, 2019). Importantly, HF is the first vascular presentation in 14% of all people with T2D, only marginally lower than peripheral arterial disease (the highest recorded at 16%) and higher than both stroke and MI (Shah et al 2015). The prevalence of HF is increasing and is more common in people with T2M than without (McAllister et al 2018). The risk of HF rises steeply with age and is highest in those with BMI > 30 kg/m^2 (Boonman-de Winter et al, 2012). In developed countries, the incidence of MI and stroke events in people with T2D, whilst high, appears to be decreasing (Gregg et al 2014). We strongly believe that the guideline should be built on a risk prediction strategy that is optimised for both CVD and HF, given the high prevalence and poor prognosis of the latter condition. Potential strategies are discussed below. Value of cardiac biomarkers 1) Risk prediction NT-proBNP is an excellent predictor of CVD including HF, when used alone or in combination with conventional risk factors, such as those used in risk scores such as QRISK. Malachias et al (2020) demonstrated that NT-proBNP alone had equal discrimination as multivariate models for CVD risk prediction, and the inclusion of NT-proBNP increased the predictive ability of such models. These findings have also been confirmed by the Natriuretic Peptides Studies Collaboration (2016), that found increased baseline NT-proBNP resulted in a risk ratio of 2 for a combination of CVD events and heart failure, with the addition of NT-	they are not in widespread use currently. Since a review of the evidence about the accuracy of such algorithms in comparison to each other and QRISK2 was not within the scope of this work, the committee agreed that QRISK2 was a pragmatic choice for assessing CV risk in people with type 2 diabetes. The method of assessment of CV risk was not within the scope of the type 2 diabetes update. This is covered in detail by the NICE guideline on Cardiovascular disease: risk assessment and reduction, including lipid modification. This guideline contains a recommendation for the use of QRISK2 to assess CVD risk in people with type 2 diabetes and this is why the committee refer to QRISK2. The type 2 diabetes committee are therefore unable to review the evidence you supplied on this topic and could not make the suggested recommendations for using NT-pro-BNP. However, we will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date. The NICE surveillance team also maintain a log of potentially relevant studies that are in progress for each guideline to enable them to quickly review new evidence for impact on that guideline. We will suggest that they add the Atherosclerosis Risk in Communities Study to this log.

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				proBNP to a model containing traditional risk factors again increased the discriminatory ability of the model. Ohkuma et al (2017), Neuhold et al (2011), Clodi et al (2012), Januzzi et al (2019), Prausmuller et al (2021) have all all shown that NT-proBNP alone or in addition to conventional risk factors improves a model's ability to better predict CVD/HF risk. Lastly, Welsh et al (2016) found that the inclusion of NT-proBNP into the QRISK score increased the C-statistic (P=0.005). The Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology and Japanese Heart Failure Society have recently updated the Universal Definition of Heart Failure (Bozkurt B et al 2021), which now specifically defines a pre-HF group (Stage B) within which there is a classification of those with elevated NT-proBNP levels but without current or prior symptoms or signs of HF. This subgroup of patients might be missed from the 'high risk' category defined in the draft guideline. It may also be of interest to the committee to know that research is underway at Brigham and Women's Hospital which will directly compare the utility of NT-proBNP with QRISK3 in identifying subsequent HF. This is a multicenter community registry (Atherosclerosis Risk in Communities Study). 2) Treatment optimisation Zelniker et al (2020) specifically looked at the treatment effect of dapagliflozin subgrouped by NT-proBNP. This paper was based on a secondary analysis of 14,565 patients from the DECLARE-TIMI 58 RCT and provides a breakdown of treatment effects based on NT-proBNP quartiles for dapagliflozin vs placebo. Importantly, the DECLARE-TIMI 58 study population closely matches the 'established CVD' and 'high-risk' populations defined in the current draft guidelines and has already been included within the evidence review. High NT-proBNP levels were associated with the greatest benefits from dapagliflozin, in terms of HF hospitalizations and CVD mortality. Moreover, as shown in the supporting information section of the paper (Figures S4, S6, S7, S9), those patients	

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				with an NT-proBNP baseline measurement below the median NT-proBNP level (75 pg/ml) or below a defined cut off of 125 pg/ml were found to gain little to no benefit from treatment based on the same outcomes (hazard ratio≈1 or ARR≈0 for 75pg/ml). Berg et al (2021) have recently published a similar analysis looking at biomarker-based risk prediction and subsequent treatment outcomes, albeit only focussing on HF hospitalisation. In this study a combination of NT-proBNP, hsTnT, and prior HF were used for risk prediction on a retrospective cohort of 13,000 patients taken from both SAVOR-TIMI 53 (derivation cohort) and DECLARE-TIMI 58 (validation cohort), both trials are already included within the review. The risk prediction tool showed good discriminatory ability with high c-indices in both cohorts (both >0.8). Most importantly the paper complements the finding of Zelniker et al, in that those identified at lowest risk, even when defined as high risk by traditional risk factors, see no benefit from treatment. In this paper 55% of the population were defined as low risk (that would likely be defined high risk under this guideline), and the treatment effect of dapagliflozin on this group produced a hazard ratio of 0.98 vs placebo for HF hospitalisation (ARR = 0.1%), while treatment in the highest risk group produced an HR of 0.72. <u>Proposed SGLT2 inhibitor prioritisation for 'high risk' patients</u> Given that i) the QRISK2 algorithm is not validated for HF, ii) NT-proBNP has excellent predictive performance for CVD/HF and iii) NT-proBNP identifies those 'high risk' patients that are most likely to benefit from SGLT2 inhibitor treatment (in terms of reducing CVD/HF outcomes), we propose the following prioritisation for SGLT2 inhibitor treatment (from 1 to 3): 1) In patients with T2D and established CVD - *offer* metformin and SGLT2 inhibitors 2) In patients with T2D and without established CVD - *offer* SGLT2 inhibitor treatment patient at high risk who also have a high NT-proBNP	

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				3) In all patients with T2D and at high risk - *offer* SGLT2 inhibitor treatment irrespective of NT-proBNP Adopting this approach and including an 'offer' instead of a 'consider' recommendation for a subgroup within the 'high risk' category, would support integrated care systems (ICS) in managing the roll out of SGLT2 inhibitors, whilst helping to prevent regional differences in uptake and associated inequalities, something we believe is likely with the current 'consider' recommendation. This strategy would ensure prioritisation of SGLT2 inhibitor treatment for patients with established CVD or at the highest risk of CVD/HF (and the most likely to benefit from treatment) and reduce the initial impact on NHS budgets. Importantly, a number of leading international experts have proposed frameworks based on prioritising SGLT2 inhibitor treatment by NT-proBNP (Sattar et al 2021 and Verma et al 2019). We have not proposed a specific NT-proBNP cut-off, but Zelniker et al (2020) highlight two candidates. One is 125pg/ml, this cut-off has been validated in a large number of risk prediction studies, and is included in international guidelines, such as the 2021 ESC Guidelines, to aid in the diagnosis of HF in non-acute settings. Findings from Zelniker et al suggest that using this cut off would result in the high risk population being reduced by around two-thirds. This would potentially enable a manageable and widespread uptake of SGLT2 inhibitors with no geographical variation in care. However, Zelniker et al did find that those with NT-proBNP <125pg/ml still experienced some benefit from treatment (HR<1), albeit a smaller treatment effect than the >125pg/ml group. The second possible cut-off could be the median NT-proBNP concentration from the Zelinker et al paper, 75pg/ml. While this cut-off was defined in the DECLARE TIMI 58 RCT, one of the largest SGLT2 inhibitor trials to date, it has not been validated in a prospective cohort. The hazard ratio and absolute risk reduction for treatment vs placebo in those with <75pg/ml were 1 and 0% respectively. Using this cut-off would avoid treatment of half the high risk population with no clinical disutility. Using an NT-proBNP price of £28 (NICE CG187, Appendix M) and	

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				monthly SGLT2 inhibitor cost of £38, it would effectively dominate the current guidelines and produce cost savings after just two months. Wider system benefits The wholescale adoption of NT-proBNP as a risk prediction tool could also provide additional benefits to the wider health care system. If used within a risk prediction tool, abnormal levels of NT-proBNP in isolation could still be cause for concern, particularly when combined with signs or symptoms suggestive of HF, and increased monitoring or investigation could provide additional benefit to the patient. NT-proBNP testing is already routinely used within the NHS to aid in the diagnosis of acute and chronic HF. A retrospective cohort study of 22,085 participants with a new HF diagnosis in the UK showed that high baseline NT-proBNP is associated with increased HF-related hospitalisation and poor survival, indicating the importance of appropriate identification and initiation of effective therapy to prevent poor outcomes (Taylor et al 2021). *References* Read SH, van Diepen M, Colhoun HM, Halbesma N, Lindsay RS, McKnight JA, McAllister DA, Pearson ER, Petrie JR, Philip S, Sattar N, Woodward M, Wild SH; Scottish Diabetes Research Network Epidemiology Group. Performance of Cardiovascular Disease Risk Scores in People Diagnosed With Type 2 Diabetes: External Validation Using Data From the National Scottish Diabetes Register. Diabetes Care. 2018 Sep;41(9):2010-2018 Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, Minhas R, Sheikh A, Brindle P. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. BMJ. 2008 Jun 28;336(7659):1475-82 Hippisley-Cox J, Coupland C. Development and validation of risk	

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Roche Diagnostics Limited	General	General	General	Other cardioprotective therapies Whilst out of scope for the current review, we would like to bring NICE to the attention of two ongoing studies that are investigating the impact of cardioprotective treatments in the T2D population and ask that these are considered when the 'Type 2 diabetes in adults: management' guidelines are next updated: PONTIAC II trial: A multi-centre, international, RCT investigating the effect of beta blockers and RAS-inhibitor uptitration (guided by NT-proBNP measurements) on CVD events, in adults with T2D. https://clinicaltrials.gov/ct2/show/NCT02817360 ADOPT trial: A RCT based in Asia investigating the effect of intensified therapy using renin-angiotensin system (RAS) antagonists, beta-blockers and SGLT2 inhibitors for primary prevention of cardiovascular events, in adults with T2D at high risk of CVD (NT-proBNP >125pg/mL). https://clinicaltrials.gov/ct2/show/NCT04286399	Thank you for your comment. We will pass this information onto the NICE surveillance team who monitor ongoing trials.
Roche Diagnostics Limited	Health economic report	General	General	Comparators	Thank you for your comment. The purpose of the review was to evaluate the cost-effectiveness of treatments in reducing CV risk. This was initially evaluated in the total type 2

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				First line treatment (addition or replacement) with SGLT2 inhibitors in the total T2D population was found to be cost effective (ICER around £17k-18k/QALY), however the only comparator used was the current standard of care (metformin only). We believe the correct health economic methodology to assess the true incremental cost effectiveness ratio of SGLT2 inhibitors is to compare the following comparators all against one another in order of either cost or QALY (i.e. a fully incremental approach): Metformin only for all patients Metformin + SGLT2i for subgroup/metformin only for "low risk" population Metformin + SGLT2i for the total population	diabetic population, with the analysis extended to the high CV population as they are more likely to benefit from treatments reducing CV risks. It is important to consider the impact of alternative courses of action within a given population, and make recommendations for each population. Low risk populations were not specifically looked at in the analysis as they are less likely to benefit from reduced CV risks.
Royal College of General Practitioners	Guideline	General	General	Regarding the NICE draft guideline for Type 2 diabetes in adult: management, the Royal College of General Practitioners has reviewed the draft guideline along with our network of clinical advisors and are supportive of the update and welcome the clear treatments pathways laid out in the guideline. We believe this will be a very useful guideline for the management of patients with type 2 diabetes.	Thank you for your comment and support of these changes to the guideline.
Royal College of Nursing	Guideline	004	007 - 008	It is important to include an assessment of likely benefit from long term interventions – this places more focus on individualised care	Thank you for your comment. This section of the guideline on individualised care was not prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest existing recommendations needed amending.
Royal College of Nursing	Guideline	009	008	Beneficial to provide a graphic to explore individualised HbA1c targets with the person living with diabetes – alongside this is a need for the person to understand the long-term impact of HbA1c	Thank you for your comment and support. We agree that it is important for the person to make an informed decision in discussion with their diabetes team. The long term impact of higher HbA1c levels is discussed in the PDA which is linked from the guideline.
Royal College of Nursing	Guideline	011	021 - 022	The patient decision aid is a helpful addition, worthwhile embedding in this guidance	Thank you for your comment and support.
Royal College of Nursing	Guideline	014	011	Monitoring requirements – more detail needed here; in relation to potential hypoglycaemia etc?	Thank you for your comment. The committee discussed this comment but agreed that, as this is a general recommendation about factors to take into account when choosing treatments rather than one which is drug specific

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					and because monitoring may vary by the drug chosen and the individual's personal factors, that it would not be possible to provide further detail on monitoring in this recommendation.
Royal College of Nursing	Guideline	General	General	The associated algorithm for blood glucose lowering therapy in adults with type 2 diabetes https://www.nice.org.uk/guidance/ng28/resources/algorithm-for-blood-glucose-lowering-therapy-in-adults-with-type-2-diabetes-pdf-2185604173 will require amendment in view of these updated guidelines if this draft is implemented	Thank you for your comment. The existing algorithm is being stood down and replaced by the visual summaries. These were included in the consultation version of this guideline for comment and will be published at the same time.
Royal College of Physicians	Guideline	General	General	The RCP is grateful for the opportunity to respond to the above consultation. We would like to endorse the response submitted by the Association of British Clinical Diabetologists (ABCD)	Thank you for your comment.
Royal Free London NHS Foundation Trust	General	General	General	Since the original publication of NG28 in 2015 more potent GLP1-R agonists and higher dosages of GLP1-R agonists have become available which achieve greater weight loss and HbA1c reduction. These have not been evaluated by NICE.	Thank you for your comment. The original scope of the update to the drug treatment sections of NG28 was to fully update the treatment section of the guideline as your comment notes. However, once work on the topic commenced it was determined that updating evidence reviews and health economics for such a wide scope, within the resources available to NICE for this topic, would take an unacceptably lengthy period. Taking such an approach for this guideline update would have further delayed publication of updated treatment recommendations in this rapidly changing area. In view of the timescales involved and the appetite from the committee and stakeholders for an update within an acceptable time period, we worked with our committee members to identify the priority areas for this update. The committee members agreed that our initial focus should be on reviewing the evidence from trials looking at cardiovascular outcomes. This reflected the changing evidence base as a result of the significant investment in clinical trials to directly capture cardiovascular outcomes,

					feedback from stakeholders that assessing this evidence was a priority and the impact that this new evidence could have on recommendations for the treatment of people with diabetes. We therefore revised the scope to reflect this and carried out the current piece of work. The current NICE evidence review was focused on looking at cardiovascular benefits and therefore we included CV outcome trials (CVOT) for all currently licensed GLP-1 receptor agonists (GLP-1 RA). The doses used in the CVOTs were in the expected dose range approved by the committee as reflecting current clinical use (see tables 1 and 2 in the Evidence review document) We did not examine the effects of different doses for any drug as aggregated dose data was used for each trial where more than one dose was use. Weight was taken into account in the economic modelling. The committee agreed that taking data on weight from these cardiovascular outcome trials was the most appropriate approach, in order to match the data used for cardiovascular event rates. For changes in weight, it was noted it was important not to double count the impact of changes, as the effects on cardiovascular outcomes should already be captured in the outcomes of those trials. It was therefore agreed that the most appropriate approach was to only include the direct quality of life gains associated with reductions in weight, with the other benefits captured through the cardiovascular event data. The committee noted that if anything the approach taken in the guideline may overestimate the benefits of weight reduction, as some of the estimated quality of life gains may be the result of avoided cardiovascular events, but it was agreed to be the best data source available. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes

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					treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand.
Royal Free London NHS Foundation Trust	General	General	General	Not all SGLT2 inhibitors have published evidence of cardiovascular benefit in patients with congestive heart failure or established atherosclerotic cardiovascular disease. There is no evidence-based guidance on choice of SGLT2 inhibitor for these groups of patients.	Thank you for your comment. The committee reviewed the stakeholder comments but decided to continue treating SGLT2 inhibitors (SGLT2i) as a class for the following reasons: • There was a degree of uncertainty around whether there were real differences in cardiovascular (CV) benefits between the SGLT2i based on the clinical trial evidence and results from the NMAs. o Firstly, for hospitalisation for heart failure, the SGLT2i empagliflozin, canagliflozin, and dapagliflozin produced a clinically meaningful reduction compared with placebo in the random effects NMA model. However, in the sensitivity analyses using a fixed effect model ertugliflozin also showed a clinically meaningful reduction compared to placebo, which reflects the original clinical trial data. The NMA results could not differentiate between the SGLT2i for this outcome. o Secondly, for the 3 point MACE outcome, only canagliflozin and empagliflozin produced a statistically significant reduction compared to

					placebo but the SGLT2i could not be differentiated from each other in the NMA. ○ Thirdly for all cause and CV mortality empagliflozin showed a clinically meaningful reduction compared to placebo and the other SGLT2i, but the remaining SGLT2i could not be differentiated from each other or placebo in the NMA. ○ Fourthly, for non-fatal MI and non-fatal stroke the NMAs could not differentiate between empagliflozin, canagliflozin, ertugliflozin and placebo. The data for dapagliflozin was reported differently and could not be included in the NMAs. From the clinical trial data dapagliflozin could not be differentiated from placebo for MI and was not meaningfully different from placebo for stroke. ○ Finally, only dapagliflozin showed a clinically meaningful improvement in severe hypoglycaemia compared to placebo but the remaining SGLT2i could not be differentiated from each other and placebo in the NMA. • There was also a degree of uncertainty around the cost-effectiveness of individual SGLT2i in the economic modelling. Although only dapagliflozin was cost-effective at a threshold of £20,000/quality-adjusted life year (QALY) across all model scenarios and CV risk groups it could not be differentiated from the other SGLT2i in the NMA apart from for the all-cause and CV mortality outcomes where it was clinically meaningfully worse than empagliflozin. The ranking of ICERs for the other SGLT2i varied across model scenarios and risk groups. The committee agreed that there was sufficient uncertainty in the economic modelling (caused in turn by uncertainty in the underlying clinical data) to mean that they were not sufficiently confident that these different ICERs represented true underlying differences

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					in cost-effectiveness, as opposed to simply random variation in the results between different SGLT2 trials. • Taking the cost-effectiveness and clinical results into account the committee decided against only recommending dapagliflozin and instead made recommendations for the SGLT2i as a class. However, they recognised that there was a greater degree of uncertainty around the CV benefit associated with ertugliflozin because, depending on the choice of model used in the NMA, it did not consistently show a clinically meaningful reduction in hospitalisation for heart failure compared to placebo, unlike empagliflozin, canagliflozin and dapagliflozin. It was also not statistically significantly better than placebo for the 3-point MACE outcome unlike canagliflozin and empagliflozin. The committee therefore recommended SGLT2i with proven CV benefit because this wording would enable the prescribers to select a particular drug from within the SGLT2 class if they thought this was clinically justified based on the individual characteristics of their patient, whilst future proofing the recommendation should additional evidence or new SGLT2s be made available. As per the recommendation on choosing drug treatment, once the clinical circumstances and needs of the person with type 2 diabetes, including their need for CV protection, have been taken into account, if 2 drugs in the same class are suitable for that individual then the prescriber is still expected to choose the option with the lowest acquisition cost to help use NHS resources wisely. Please see evidence review A for more a more detailed explanation of the analyses that were carried out and the committee's discussion of the results.

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Royal Free London NHS Foundation Trust	General	General	General	Not all SGLT2 inhibitors have published evidence of cardiovascular benefit in patients at high risk of CVD. There is no evidence-based guidance on choice of SGLT2 inhibitor for this group.	Thank you for your comment. The committee reviewed the stakeholder comments but decided to continue treating SGLT2 inhibitors (SGLT2i) as a class for the following reasons: • There was a degree of uncertainty around whether there were real differences in cardiovascular (CV) benefits between the SGLT2i based on the clinical trial evidence and results from the NMAs. o Firstly, for hospitalisation for heart failure, the SGLT2i empagliflozin, canagliflozin, and dapagliflozin produced a clinically meaningful reduction compared with placebo in the random effects NMA model. However, in the sensitivity analyses using a fixed effect model ertugliflozin also showed a clinically meaningful reduction compared to placebo, which reflects the original clinical trial data. The NMA results could not differentiate between the SGLT2i for this outcome. o Secondly, for the 3 point MACE outcome, only canagliflozin and empagliflozin produced a statistically significant reduction compared to placebo but the SGLT2i could not be differentiated from each other in the NMA. o Thirdly for all cause and CV mortality empagliflozin showed a clinically meaningful reduction compared to placebo and the other SGLT2i, but the remaining SGLT2i could not be differentiated from each other or placebo in the NMA. o Fourthly, for non-fatal MI and non-fatal stroke the NMAs could not differentiate between empagliflozin, canagliflozin, ertugliflozin and placebo. The data for dapagliflozin was reported differently and could not be included in the NMAs. From the clinical trial data

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					committee therefore recommended SGLT2i with proven CV benefit because this wording would enable the prescribers to select a particular drug from within the SGLT2 class if they thought this was clinically justified based on the individual characteristics of their patient, whilst future proofing the recommendation should additional evidence or new SGLT2s be made available. As per the recommendation on choosing drug treatment, once the clinical circumstances and needs of the person with type 2 diabetes, including their need for CV protection, have been taken into account, if 2 drugs in the same class are suitable for that individual then the prescriber is still expected to choose the option with the lowest acquisition cost to help use NHS resources wisely. Please see evidence review A for more a more detailed explanation of the analyses that were carried out and the committee's discussion of the results.
Royal Free London NHS Foundation Trust	General	General	General	Patients with 'Established CVD' or 'High-Risk CVD' would benefit from a GLP-1R agonist with proven cardiovascular benefit, if SGLT2 inhibitors are not suitable or tolerated.	Thank you for your comment. Although there were a number of stakeholder comments asking for clarification of the treatment options for people with type 2 diabetes in whom SGLT2 inhibitors (SGLT2i) were contraindicated or not tolerated, there were no cardiovascular outcome trial style clinical trials identified that looked at the effectiveness of treatments for people at high cardiovascular (CV) risk in this population. The committee therefore used the evidence for effectiveness and cost effectiveness for other interventions from the same economic modelling scenarios as those looking at the cost- effectiveness of SGLT2i. The committee examined the cost-effectiveness evidence relating to GLP-1 mimetic treatment for people with type 2 diabetes and high cardiovascular risk. In the NICE health economic analyses, when looking at GLP-1 mimetics as a

					class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of £20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the intervention as an effective use of NHS resources will specifically take account of the following factors." and • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis." Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular

					mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors. In addition, the committee noted that there were differences in the clinical effectiveness of the 2 forms of semaglutide. Although the acquisition costs for injectable and oral semaglutide are similar they showed marked differences in cost-effectiveness in the economic analyses. This was caused by differences in the effect estimates for stroke, myocardial infarction and severe hypoglycaemia. From earlier discussions about the clinical evidence (see the discussion sections in the evidence review for more details) the committee had agreed that it was uncertain whether the observed differences in effect on all-cause mortality compared to placebo between the 2 forms of semaglutide were real and they therefore decided not to place undue weight on them. They had also noted that this uncertainty and any other differences in effects between the drugs for

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					other outcomes was probably due to wide 95% confidence intervals for many outcomes with these drugs, due to the smaller numbers of participants and events in the trials compared to other CVOTs The committee therefore agreed that they were unable to recommend injectable semaglutide for people with type 2 diabetes and high cardiovascular risk who were unable to take and SGLT2i. As a result, the committee noted that people with high CV risk who could not take metformin with an SGLT2i would be offered metformin alone at treatment initiation. If they were also unable to take metformin then the clinician would select another treatment from the remaining options, namely sulfonylureas, DPP-4s or pioglitazone, depending on the individual's clinical circumstances and preferences. The committee decided against listing the options for people with type 2 diabetes who were at high CV risk and could not take an SGLT2i because they thought that this was an unnecessary level of detail given that they could not recommend a GLP-1 mimetic in place of the SGLT2i, that the treatment options were therefore the same for these people as for the rest of the type 2 diabetes population and because apart from for metformin, the guideline does not include details of which drug to take if a particular drug is contraindicated or not tolerated but rather expects the prescriber to use their clinical judgment.
Royal Free London NHS Foundation Trust	General	General	General	Patients with type 2 diabetes benefit from joined-up shared decision making in their diabetes management in accordance with previous guidance from NICE on shared care decision making. The separation of the draft guidance for patients with type 2 diabetes and CKD into a different document is likely to confuse, particularly as the treatment of patients with type 2 diabetes should be holistic and take into consideration all relevant comorbidities. This approach risks patients with type 2 DM and CKD not being offered appropriate treatment to reduce cardiovascular risk and progression of renal disease.	Thank you for your comment. The renal benefits of using SGLT2 inhibitors in people with type 2 diabetes and CKD have been assessed in a separate piece of work that has recently been out for stakeholder consultation and was published in November 2021. The final recommendations on renal and cardiovascular benefits will be brought together in a single updated guideline document when this current work on cardiovascular benefits is published in 2022.

Consultation on draft guideline - Stakeholder comments table
01/09/2021 – 14/10/2021

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Royal Free London NHS Foundation Trust	General	General	General	In its current form the draft guidance risks being difficult to translate into clinical practice and hence ignored by clinicians, as being already out of date at the time of publication. We believe there are significant evidence base updates that should be considered and a review of the scope of this guidance also taking into consideration the holistic treatment of patients with type 2 diabetes beyond the narrow window of CVOT trial data.	Thank you for your comment. The original scope of the update to the drug treatment sections of NG28 was to fully update the treatment section of the guideline as your comment notes. However, once work on the topic commenced it was determined that updating evidence reviews and health economics for such a wide scope, within the resources available to NICE for this topic, would take an unacceptably lengthy period. Taking such an approach for this guideline update would have further delayed publication of updated treatment recommendations in this rapidly changing area. In view of the timescales involved and the appetite from the committee and stakeholders for an update within an acceptable time period, we worked with our committee members to identify the priority areas for this update. The committee members agreed that our initial focus should be on reviewing the evidence from trials looking at cardiovascular outcomes. This reflected the changing evidence base as a result of the significant investment in clinical trials to directly capture cardiovascular outcomes, feedback from stakeholders that assessing this evidence was a priority and the impact that this new evidence could have on recommendations for the treatment of people with diabetes. We therefore revised the scope to reflect this carried out the current piece of work. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted.

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					This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand. The committee have reviewed stakeholder comments related to person centeredness and holistic care. They have ensured that the recommendation on choosing drug treatments includes taking the persons needs and preferences into account when choosing a drug treatment and that the eviewing treatment recommendationincludes revisiting diet and lifestyle measures when reviewing care. The committee believe that given the revised scope of the update they have made evidence-based recommendations taking into account the need to prioritise the important information from the cardiovascular outcome trials. Although they recognise the need for a fuller update of this section of the guideline as soon as practicable. The surveillance team at NICE monitor whether guidelines are up to date. The surveillance process includes reacting to events at any time after guideline publication (for example, publication of a key study) as well as a standard check every 5 years. Stakeholders can help with this process by letting us know which parts of the guideline stakeholders believe out-of-date and why during scope consultations. As these are evidence-based guidelines it is useful if stakeholders can provide links to important evidence sources that they believe would necessitate an update of a particular area of the guideline. We can then pass these references onto the NICE surveillance team for evaluation and a decision about whether an update is justified.

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Royal Free London NHS Foundation Trust	Guideline	018	General	Visual Summary 2 - SGLT2 inhibitors have been positioned as joint first-line therapy for patients with congestive heart failure or established atherosclerotic cardiovascular disease while in the visual summary these two groups of patients are denoted by 'Established CVD'. The definition of this group should be more clearly stated in the visual summary. SGLT2 inhibitors are recommended to be *considered* as joint first-line for patients at high-risk of CVD (as defined by QRISK2 > 10% in adults aged >= 40 years or the presence of one or more CVD risk factors if aged < 40 years). This is denoted as 'High-risk CVD' in visual summary. The definition of this group should be more clearly stated in the visual summary. It is unclear how the term 'considered' is expected to be interpreted by clinicians.	Thank you for your comment. The groups have been defined as in the guideline and definitions of 'high risk' and ASCVD have been added to the visual summaries.
Royal Free London NHS Foundation Trust	Guideline	019	General	Visual Summary 4 - In the table 'Choosing medicines for type 2 diabetes' there is an generalised statement for GLP-1 to 'avoid or use with caution' which does not apply to dulaglutide, liraglutide or semaglutide which are licenced to eGFR ≥15 ml/min.	Thank you for your comment. The content in the table has been updated for specific medicines rather than for medicine classes.
Royal Free London NHS Foundation Trust	Guideline	General	General	Visual Summary 1-4 - The visual summary splits the guidance into 4 panels, which do not flow coherently together and may confuse. It is critical that the guidance for CKD in type 2 diabetes is integrated into the visual summary.	Thank you for your comment. The visual summaries have now been grouped together and a link to the CKD recommendations has been added.
Royal Free London NHS Foundation Trust	Health Economic Report	General	General	The health economic analysis was restricted to 16 Cardiovascular Outcome Trials (CVOTs) asking the question 'Which pharmacological therapies are most effective at providing cardiovascular and other benefits in addition to blood glucose control in people with type 2 diabetes?'. This approach does not take into account patient perspectives for those patients wanting higher priority in reducing risk of hypoglycaemia, promotion of weight loss or frailty. Shared care decision making should allow patients to state their economic and clinical perspective priorities which may not always be cardiovascular risk reduction especially for CVD patients who have now been revascularised or optimised for heart failure. For such patients mobility is a key priority enabled through weight loss.	Thank you for your comment**.** You are correct that the model does not contain every outcome that could potentially be of interest for modelling adults with type 2 diabetes. However, the committee agreed these were the most important outcomes for assessing the additional cardiovascular and other benefits associated with drug treatment for type 2 diabetes, for the majority of the type 2 diabetes population. The committee agreed the cardiovascular outcome trials were the most appropriate data source to assess cardiovascular benefits of these drugs, being powered to specifically detect differences in hard outcomes, rather than only surrogate outcomes. The committee noted these studies were not representative of the full population of people with type 2 diabetes, but agreed this was a lesser

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					limitation than the need to extrapolate from surrogate endpoints to cardiovascular outcomes, particularly given the findings from those studies suggesting these surrogate extrapolations are often not very robust. They also agreed that taking data on weight and hypoglycaemic events from these cardiovascular outcome trials was the most appropriate approach, in order to match the data used for cardiovascular event rates. For hypoglycaemic events, the approach taken is broadly in line with that taken in many other evaluations in diabetes, attaching costs and quality of life outcomes to the incidence of severe hypoglycaemic events, as these are the ones that make the most difference to a person's life. For changes in weight, it was noted it was important not to double count the impact of changes, as the effects on cardiovascular outcomes should already be captured in the outcomes of those trials. It was therefore agreed that the most appropriate approach was to only include the direct quality of life gains associated with reductions in weight, with the other benefits captured through the cardiovascular event data. The committee noted that if anything the approach taken in the guideline may overestimate the benefits of weight reduction, as some of the estimated quality of life gains may be the result of avoided cardiovascular events, but it was agreed to be the best data source available.
Royal Free London NHS Foundation Trust	Health Economic Report	General	General	CVOTs are designed to produce glycaemic equipoise between the active agent and control or placebo arms, to be able to gauge cardiovascular harm whilst maintaining a balanced HbA1c between control and active groups. This approach does not lend itself to detecting glycaemic superiority of the treatment in comparison to placebo. CVOT trials may not accurately estimate the true benefit of the active agent as the potential benefits of HbA1c lowering are confounded by escalation of standard care.	Thank you for your comment. You are correct that the model does not contain every outcome that could potentially be of interest for modelling adults with type 2 diabetes. However, the committee agreed these were the most important outcomes for assessing the additional cardiovascular and other benefits associated with drug treatment for type 2 diabetes, for the majority of the type 2 diabetes population. The committee agreed the cardiovascular outcome trials were the most appropriate data source to assess

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				Therefore CVOTs will not accurately estimate the potential long-term benefits of improved glycaemia with GLP-1R agonists on microvascular and macrovascular complications. The cost effectiveness analysis has ignored the additional benefits which would be achieved in the real-world through glycaemic lowering, particularly in patients with high baseline HbA1c. In addition the health benefits associated with reduction in body weight will be underestimated by the model not accounting for mobility improvements with weight loss. We have data that achieving mobility goals of certain step counts (4400 steps a day for women) achieve considerable additional CV risk reduction. Lee I, Shiroma EJ, Kamada M, Bassett DR, Matthews CE, Buring JE. Association of step volume and intensity with all-cause mortality in older women. *JAMA Intern Med*. Published online May 29, 2019. https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2734709 .	cardiovascular benefits of these drugs, being powered to specifically detect differences in hard outcomes, rather than only surrogate outcomes. The committee noted these studies were not representative of the full population of people with type 2 diabetes, but agreed this was a lesser limitation than the need to extrapolate from surrogate endpoints to cardiovascular outcomes, particularly given the findings from those studies suggesting these surrogate extrapolations are often not very robust. They also agreed that taking data on weight from these cardiovascular outcome trials was the most appropriate approach, in order to match the data used for cardiovascular event rates. For changes in weight, it was noted it was important not to double count the impact of changes, as the effects on cardiovascular outcomes should already be captured in the outcomes of those trials. It was therefore agreed that the most appropriate approach was to only include the direct quality of life gains associated with reductions in weight, with the other benefits captured through the cardiovascular event data. The committee noted that if anything the approach taken in the guideline may overestimate the benefits of weight reduction, as some of the estimated quality of life gains may be the result of avoided cardiovascular events, but it was agreed to be the best data source available. There are of course other benefits that could have been considered as part of the modelling, including renal (or other microvascular) outcomes, or additional benefits directly related to improved glycaemic control, but the committee considered these to be of lower priority than those included in the model. They also noted that it would not be appropriate for any modelling approach to simply look at benefits on different outcomes from different trials or data sources, and assume those benefits are additive, and

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					therefore increase the cost-effectiveness of drugs when included together. They noted that in many circumstances these benefits are not additive, and which benefits are likely to be realised may depend on the individual characteristics of the people included in studies. As an example, in the separate evaluation of SGLT2 inhibitors for people with CKD and type 2 diabetes, SGLT2 inhibitors were found to significantly improve renal outcomes, but this is a population in which a large benefit would not be expected for glycaemic control.
Royal Free London NHS Foundation Trust	Health Economic Report	General	General	CVOT trials continue to show curves diverging at trial end, which means that conservative models will underestimate the benefit beyond the trial period.	Thank you for your comment. While the curves may diverge towards the end of the period, the treatment effects applied in the model are calculated by taking into consideration the events occurring during the course of the trial period. Hence the treatment effects applied beyond the trial period are not only defined by the what happened towards the end of the trial period, but by the events which happened during the couse of the trial period.
Royal Free London NHS Foundation Trust	Health Economic Report	General	General	The modelling applied an unadjusted point estimate of the hazard ratio for cardiovascular events from the CVOTs to a UKPDS-2 model. There was significant heterogeneity in the populations studied in trials which is likely to limit the validity of direct comparisons of cost effectiveness and introduce an uncertainty that should be acknowledged.	Thank you for your comment. You are correct that unadjusted hazard ratios were used in the analysis. In the absence of individual patient data, the committee agreed that there were no established methods for adjusting these data that could be conducted that would increase their confidence in the effect estimated. They noted that simply having populations at different risk levels in different trials would not be a source of bias in the results, as this should not impact on the relative effects estimated in the trials and subsequently used to populate the model. A concern would only arise if there were systematic differences between the trials in characteristics that would affect relative (and not just absolute) treatment effectiveness and, while the data did not allow the committee to completely rule out this possibility,

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					there were not clear clinical reasons they were aware of to suspect that such a pattern would exist. Nonetheless, the committee agreed the between trial heterogeneity was a source of uncertainty in the analysis, and considered this as part of their decision-making, as detailed in the committee discussion-section of the evidence review. In particular, they noted this uncertainty was one factor leading towards making class level recommendations, rather than interpreting relatively small overall differences in cost-effectiveness between drugs within the same class as clinically meaningful. They also noted that uncertainty would in general lead towards making weaker rather than stronger recommendations, and therefore any factors that led them to be more uncertain would lead to a smaller number of treatment options being recommended as cost-effective, rather than a larger number of options. It is also worth noting that while point estimates were used for base case analysis, the uncertainty around these estimates were considered in the probabilistic sensitivity analysis, where the treatment decisions did not change from the base case analysis.
Royal Free London NHS Foundation Trust	Health Economic Report	General	General	The economic parameter endpoints and narrow clinical perspective should be widened for consultation of expert patient groups keen on obesity management and mobility enhancement. A greater emphasis post COVID on weight management is needed and relegating therapies with proven weight reduction and cardiovascular benefits may need greater weight in economic models. In essence whilst we appreciate the considerable acknowledgement of models towards SGLT2 inhibitors, there remains a place for GLP1 agonists with proven cardiovascular benefit, for those patients intolerant or unsuited to SGLT2 inhibitors.	Thank you for your comment. The way the data on weight and BMI from the included cardiovascular outcome trials was reported was very variable and, in most cases, not comparable. The data was therefore not included in the clinical review findings, but weight was taken into consideration for the economic modelling as follows. For changes in weight, it was noted it was important not to double count the impact of changes in the economic model, as the effects on cardiovascular outcomes should already be captured in the outcomes of those trials. It was therefore agreed that the most appropriate approach was to only include the direct quality of life gains associated with reductions in weight, with the other benefits captured

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					through the cardiovascular event data. The committee noted that if anything the approach taken in the economic model may overestimate the benefits of weight reduction, as some of the estimated quality of life gains may be the result of avoided cardiovascular events, but it was agreed to be the best data source available. A scenario analysis was also run in the model, looking at people with a BMI of over 30, to see if the conclusions of the analysis changed. Across these different scenarios, the committee were confident that GLP-1 agonists remained an intervention that was not cost-effective (including in a population unable to use SGLT-2 inhibitors), and therefore agreed they could not expand the recommendations for their use, over and above those already included in the previous version of the guidance.
Ruddington Medical centre	Guideline	010	General	Figure - This is an ambiguous statement which is open to misinterpretation. Which health issues are being referred here? Patient can have T2D along with CVD and CKD. There is likely to higher cardiac and renal events if patient is managed with higher target HBIAC as shown by analysis of UKPDS data	Thank you for your comment. Recommendation 1.6.9 says that one reason for considering relaxing the HbA1c target would be if the person has significant comorbidities. Please also see the NICE guideline on multimorbidity (NG56). The wording in the PDA was chosen to convey this on non-technical language. The PDA and visual analogue scale are intended as tools that can be used if appropriate to support discussion between healthcare professional and person with diabetes, and promote a shared understanding.
Ruddington Medical centre	Guideline	010	General	In the figure- "I have lots of health issues as well as my diabetes is a scenario where HBAIC may be better"- This is an ambiguous statement which is open to misinterpretation. Which health issues are being referred here? Patient can have T2D along with CVD and CKD. There is likely to higher cardiac and renal events if patient is managed with higher target HBIAC as shown by analysis of UKPDS data.	Thank you for your comment. Recommendation 1.6.9 says that one reason for considering relaxing the HbA1c target would be if the person has significant comorbidities. Please also see the NICE guideline on multimorbidity(NG56). The wording in the PDA was chosen to convey this in non-technical language. The PDA and visual analogue scale are intended as tools that can be used if appropriate to support discussion between healthcare professional and person with diabetes, and promote a shared understanding.

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Ruddington Medical centre	Guideline	020	021 - 022	what would be advice if SGLT2 inhibitor is contra-indicated or patient is intolerant-Is it not a scenario where alternative classes of medications which have shown evidence for protection in patients with established atherosclerotic cardiovascular disease be recommended?	Thank you for your comment. Although there were a number of stakeholder comments asking for clarification of the treatment options for people with type 2 diabetes in whom SGLT2 inhibitors (SGLT2i) were contraindicated or not tolerated, there were no cardiovascular outcome trial style clinical trials identified that looked at the effectiveness of treatments for people at high cardiovascular (CV) risk in this population. The committee therefore used the evidence for effectiveness and cost effectiveness for other interventions from the same economic modelling scenarios as those looking at the cost- effectiveness of SGLT2i. The committee examined the cost-effectiveness evidence relating to GLP-1 mimetic treatment for people with type 2 diabetes and high cardiovascular risk. In the NICE health economic analyses, when looking at GLP-1 mimetics as a class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of £20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the intervention as an effective use of NHS resources will specifically take account of the following factors." And

					• "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis." Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use

					other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors. In addition, the committee noted that there were differences in the clinical effectiveness of the 2 forms of semaglutide. Although the acquisition costs for injectable and oral semaglutide are similar they showed marked differences in cost-effectiveness in the economic analyses. This was caused by differences in the effect estimates for stroke, myocardial infarction and severe hypoglycaemia. From earlier discussions about the clinical evidence (see the discussion sections in the evidence review for more details) the committee had agreed that it was uncertain whether the observed differences in effect on all-cause mortality compared to placebo between the 2 forms of semaglutide were real and they therefore decided not to place undue weight on them. They had also noted that this uncertainty and any other differences in effects between the drugs for other outcomes was probably due to wide 95% confidence intervals for many outcomes with these drugs, due to the smaller numbers of participants and events in the trials compared to other CVOTs. The committee therefore agreed that they were unable to recommend injectable semaglutide for people with type 2 diabetes and high cardiovascular risk who were unable to take an SGLT2i. As a result, the committee noted that people with high CV risk who could not take the recommended dual therapy of metformin and SGLT2, because they are unable to take the SGLT2, would be offered metformin alone at treatment initiation. If they were also unable to take metformin then the clinician would select another treatment from the remaining options, namely sulfonylureas, DPP-4s or pioglitazone, depending on the individual's clinical circumstances and preferences. The committee decided against listing the options for people with

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					type 2 diabetes who were at high CV risk and could not take an SGLT2i because they thought that this was an unnecessary level of detail given that they could not recommend a GLP-1 mimetic in place of the SGLT2i, that the treatment options were therefore the same for these people as for the rest of the type 2 diabetes population and because, apart from for metformin, the guideline does not include details of which drug to take if a particular drug is contraindicated or not tolerated but rather expects the prescriber to use their clinical judgment. The committee wanted to keep the pathway as simple as possible and they agreed that it would not be possible to do this if alternative options were provided every time a drug was not contradicted or not tolerated. However, they agreed that it was appropriate to have recommendations for metformin being contradicted or not tolerated because this is the drug that the majority of people would take as first-line therapy.
Ruddington Medical centre	Guideline	020	021 - 022	"If they have or develop congestive heart failure or established atherosclerotic cardiovascular disease, offer an SGLT2 inhibitor"- what would be advice if SGLT2 inhibitor is contra-indicated or patient is intolerant-Is it not a scenario where alternative classes of medications which have shown evidence for protection in patients with established atherosclerotic cardiovascular disease be recommended?	Thank you for your comment. Although there were a number of stakeholder comments asking for clarification of the treatment options for people with type 2 diabetes in whom SGLT2 inhibitors (SGLT2i) were contraindicated or not tolerated, there were no cardiovascular outcome trial style clinical trials identified that looked at the effectiveness of treatments for people at high cardiovascular (CV) risk in this population. The committee therefore used the evidence for effectiveness and cost effectiveness for other interventions from the same economic modelling scenarios as those looking at the cost- effectiveness of SGLT2i. The committee examined the cost-effectiveness evidence relating to GLP-1 mimetic treatment for people with type 2 diabetes and high cardiovascular risk. In the NICE health economic analyses, when looking at GLP-1 mimetics as a class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to

					recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of £20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the intervention as an effective use of NHS resources will specifically take account of the following factors." And • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis." Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable

					semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors. In addition, the committee noted that there were differences in the clinical effectiveness of the 2 forms of semaglutide. Although the acquisition costs for injectable and oral semaglutide are similar they showed marked differences in cost-effectiveness in the economic analyses. This was caused by differences in the effect estimates for stroke, myocardial infarction and severe hypoglycaemia. From earlier discussions about the clinical evidence (see the discussion sections in the evidence review for more details) the committee had agreed that it was uncertain whether the observed differences in effect on all-cause mortality compared to placebo between the 2 forms of semaglutide were real and they therefore decided not to place undue weight on them. They had also noted that this uncertainty and any other differences in effects between the drugs for other outcomes was probably due to wide 95% confidence

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					intervals for many outcomes with these drugs, due to the smaller numbers of participants and events in the trials compared to other CVOTs. The committee therefore agreed that they were unable to recommend injectable semaglutide for people with type 2 diabetes and high cardiovascular risk who were unable to take an SGLT2i. As a result, the committee noted that people with high CV risk who could not take the recommended dual therapy of metformin and SGLT2, because they are unable to take the SGLT2, would be offered metformin alone at treatment initiation. If they were also unable to take metformin then the clinician would select another treatment from the remaining options, namely sulfonylureas, DPP-4s or pioglitazone, depending on the individual's clinical circumstances and preferences. The committee decided against listing the options for people with type 2 diabetes who were at high CV risk and could not take an SGLT2i because they thought that this was an unnecessary level of detail given that they could not recommend a GLP-1 mimetic in place of the SGLT2i, that the treatment options were therefore the same for these people as for the rest of the type 2 diabetes population and because, apart from for metformin, the guideline does not include details of which drug to take if a particular drug is contraindicated or not tolerated but rather expects the prescriber to use their clinical judgment. The committee wanted to keep the pathway as simple as possible and they agreed that it would not be possible to do this if alternative options were provided every time a drug was not contradicted or not tolerated. However, they agreed that it was appropriate to have recommendations for metformin being contradicted or not tolerated because this is the drug that the majority of people would take as first-line therapy.

Consultation on draft guideline - Stakeholder comments table
01/09/2021 – 14/10/2021

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Ruddington Medical centre	Guideline	038	002, 003, 004 + 005	Is there any evidence behind this conclusion? All patients with Type 2 diabetes are subject to regular renal monitoring as a part of their annual diabetes review and a part of review when any new medication is initiated to judge its effectiveness	Thank you for your comment. The committee discussed the stakeholder comments about the renal impact of SGLT2 inhibitors (SGLT2i). They agreed that the existing recommendation was unclear and potentially confusing because it gave no indication of the frequently or when the monitoring should take place. They also recognised that although SGT2i can have a negative effect on renal function this is usually a small reduction in function and not a reason to stop taking the SGLT2i. Taking these points into account the committee have now removed this draft recommendation.
Ruddington Medical centre	Guideline	038	002, 003, 004 + 005	"Because of the relatively recent introduction of SGLT2 inhibitors, the committee were concerned that drug-induced renal damage could become widespread if monitoring is not carried out appropriately"-Is there any evidence behind this conclusion? All patients with Type 2 diabetes are subject to regular renal monitoring as a part of their annual diabetes review and a part of review when any new medication is initiated to judge its effectiveness. This statement has the potential of promoting that SGLT2 inhibitors can be nephrotoxic rather than renal protective for general population rather than be limited to specific subgroups.	Thank you for your comment. The committee discussed the stakeholder comments about the renal impact of SGLT2 inhibitors (SGLT2i). They agreed that the existing recommendation was unclear and potentially confusing because it gave no indication of the frequently or when the monitoring should take place. They also recognised that although SGT2i can have a negative effect on renal function this is usually a small reduction in function and not a reason to stop taking the SGLT2i. Taking these points into account the committee have now removed this draft recommendation.
Ruddington Medical centre	Health economic report	General	General	NICE have concluded that GLP1RAs as a class are not cost effective for reducing cardiovascular risk and have not therefore recommended their use in the pathway for diabetes patients with high CV risk or established CVD. The data in the economic model was limited to assessment of cardiovascular outcome trial data only and did not account for the totality of efficacy data of newer GLP-1RAs published since 2012. Lot of cardiovascular data both for SGLT2 and GLP-1 class has been generated outside CVOTs trials.	Thank you for your comment. You are correct that the model does not contain every outcome that could potentially be of interest for modelling adults with type 2 diabetes. However, the committee agreed these were the most important outcomes for assessing the additional cardiovascular and other benefits associated with drug treatment for type 2 diabetes, for the majority of the type 2 diabetes population. The committee agreed the cardiovascular outcome trials were the most appropriate data source to assess cardiovascular benefits of these drugs, being powered to specifically detect differences in hard outcomes, rather than only surrogate outcomes. The committee noted these studies were not representative of the full population of people with type 2 diabetes, but agreed this was a lesser

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					limitation than the need to extrapolate from surrogate endpoints to cardiovascular outcomes, particularly given the findings from those studies suggesting these surrogate extrapolations are often not very robust. There are of course other benefits that could have been considered as part of the modelling, including renal (or other microvascular) outcomes, or additional benefits directly related to improved glycaemic control, but the committee considered these to be of lower priority than those included in the model. They also noted that it would not be appropriate for any modelling approach to simply look at benefits on different outcomes from different trials or data sources, and assume those benefits are additive, and therefore increase the cost-effectiveness of drugs when included together. They noted that in many circumstances these benefits are not additive, and which benefits are likely to be realised may depend on the individual characteristics of the people included in studies.
Ruddington Medical centre	Health economic report	General	General	By limiting the scope of update to assessment of cardiovascular benefit only and clearly ignoring the weight loss benefits which can be achieved by GLP1 and SGLT2 class, the resulting guideline appears disjointed and could add confusion rather than clarity to individualised treatment decision-making. Weight loss has been identified as an intervention which has been recommended both in primary and secondary prevention of Cardiovascular disease. Achieving weight loss entirely by lifestyle modification has been difficult to achieve in clinical practice by significant proportion of patients suffering from Type 2 diabetes.	Thank you for your comment. While you are correct that the model does not contain every outcome that could potentially be of interest for modelling adults with type 2 diabetes, the model does account for differences in weight (and its subsequent impact on quality of life) and differences in hypoglycaemic events, in addition to differences in CV outcomes. The committee agreed these were the most important outcomes for assessing the additional cardiovascular and other benefits associated with drug treatment for type 2 diabetes, for the majority of the type 2 diabetes population. The committee agreed the cardiovascular outcome trials were the most appropriate data source to assess cardiovascular benefits of these drugs, being powered to specifically detect differences in hard outcomes, rather than only surrogate outcomes. The committee noted these

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					studies were not representative of the full population of people with type 2 diabetes, but agreed this was a lesser limitation than the need to extrapolate from surrogate endpoints to cardiovascular outcomes, particularly given the findings from those studies suggesting these surrogate extrapolations are often not very robust. They also agreed that taking data on weight from these cardiovascular outcome trials was the most appropriate approach, in order to match the data used for cardiovascular event rates. It was noted it was important not to double count the impact of changes, as the effects on cardiovascular outcomes should already be captured in the outcomes of those trials. It was therefore agreed that the most appropriate approach was to only include the direct quality of life gains associated with reductions in weight, with the other benefits captured through the cardiovascular event data. The committee noted that if anything the approach taken in the guideline may overestimate the benefits of weight reduction, as some of the estimated quality of life gains may be the result of avoided cardiovascular events, but it was agreed to be the best data source available. A scenario analysis was also run in the model, looking at people with a BMI of over 30, to see if the conclusions of the analysis changed. Across these different scenarios, the committee were confident that GLP-1 agonists remained an intervention that was not cost-effective, and therefore agreed they could not expand the recommendations for their use, over and above those already included in the previous version of the guidance."
Ruddington Medical centre	Health economic report	General	General	**Economic position-** NICE have concluded that GLP1RAs as a class are not cost effective for reducing cardiovascular risk and have not therefore recommended their use in the pathway for diabetes patients with high CV risk or established CVD. The data in the economic model was limited to assessment of cardiovascular outcome trial data only and did not account for the totality of efficacy data of newer GLP-1RAs published since 2012.	Thank you for your comment. While you are correct that the model does not contain every outcome that could potentially be of interest for modelling adults with type 2 diabetes, the model does account for differences in weight (and its subsequent impact on quality of life) and differences in hypoglycaemic events, in addition to differences in CV

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				Lot of cardiovascular data both for SGLT2 and GLP-1 class has been generated outside CVOTs trials. By limiting the scope of update to assessment of cardiovascular benefit only and clearly ignoring the weight loss benefits which can be achieved by GLP1 and SGLT2 class, the resulting guideline appears disjointed and could add confusion rather than clarity to individualised treatment decision-making. Weight loss has been identified as an intervention which has been recommended both in primary and secondary prevention of Cardiovascular disease. Achieving weight loss entirely by lifestyle modification has been difficult to achieve in clinical practice by significant proportion of patients suffering from Type 2 diabetes.	outcomes.. The committee agreed these were the most important outcomes for assessing the additional cardiovascular and other benefits associated with drug treatment for type 2 diabetes, for the majority of the type 2 diabetes population. The committee agreed the cardiovascular outcome trials were the most appropriate data source to assess cardiovascular benefits of these drugs, being powered to specifically detect differences in hard outcomes, rather than only surrogate outcomes. The committee noted these studies were not representative of the full population of people with type 2 diabetes, but agreed this was a lesser limitation than the need to extrapolate from surrogate endpoints to cardiovascular outcomes, particularly given the findings from those studies suggesting these surrogate extrapolations are often not very robust. They also agreed that taking data on weight from these cardiovascular outcome trials was the most appropriate approach, in order to match the data used for cardiovascular event rates. It was noted it was important not to double count the impact of changes, as the effects on cardiovascular outcomes should already be captured in the outcomes of those trials. It was therefore agreed that the most appropriate approach was to only include the direct quality of life gains associated with reductions in weight, with the other benefits captured through the cardiovascular event data. The committee noted that if anything the approach taken in the guideline may overestimate the benefits of weight reduction, as some of the estimated quality of life gains may be the result of avoided cardiovascular events, but it was agreed to be the best data source available
South Asian Health	General	General	General	He visual summaries are very useful for sharing and reviewing the guidance. The general impression is that the current format is complicated	Thank you for your comment. The approach to pulling together guideline recommendations in a visual form is a proof of concept. We will be continually reviewing our

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Foundation UK				and needs to be simplified further. Eg BMJ 2015, Infographic, Management of type 2 diabetes .	processes and will be updating the visual summaries based on changes to recommendations and following feedback from stakeholders and users.
South Asian Health Foundation UK	Guideline	016	025	1.7.13 - There is mention of volume depletion with SGLT2i and recommended that monitoring of renal function is required. The volume depletion is minimal for most patients and more relevant in older adults and those on diuretics. This can be made clear. Moreover, it is not clear how frequently or when the monitoring should take place. Further, there may be practical difficulties arrange monitoring and is likely to place additional burden on general practice. The SmPC on Empa, as an example, which states: Monitoring of renal function - Assessment of renal function is recommended as follows: - Prior to empagliflozin initiation and periodically during treatment, i.e. at least yearly Can the advice around this be reviewed?	Thank you for your comment. The committee discussed the stakeholder comments about the renal impact of SGLT2 inhibitors (SGLT2i). They agreed that the existing recommendation was unclear and potentially confusing because it gave no indication of the frequency or when the monitoring should take place. They also recognised that although SGT2i can have a negative effect on renal function this is usually a small reduction in function and not a reason to stop taking the SGLT2i. Taking these points into account the committee have now removed this draft recommendation.
South Asian Health Foundation UK	Guideline	017	004	1.7.14 - The guidance focuses on the risk of DKA which is a rare complication. While highlighting the risk of DKA is important, it would be good to see mention of more common side effects like the genitourinary infections.	Thank you for your comment. Following stakeholder consultation, the committee agreed that adding all the links proposed to additional safety issues was inappropriate because the guideline is the not intended to cover all the safety advice that should be taken into account when prescribing drug treatments and some of the suggested safety events were quite rare. In order to keep the guideline as simple and easy to follow as possible, the committee only included some key points regarding the safety of SGLT2 inhibitors because they are not widely used in practice yet in some areas and the new recommendations will greatly increase the number of people who are eligible to take them. Prescribers are expected to consult MHRA alerts, the BNF and summary of product characteristics (SPC) for more comprehensive safety information.
South Asian Health Foundation UK	Guideline	018	General	Visual summary 2 - The visual summary does not show the positioning of GLP-1 agonists use in patients with High risk CVD. The omission of GLP-1 is surprising considering the proven and emerging benefits of longer acting LP-1 agonists for cardiovascular protection. It is our opinion that GLP-1 agonists must be included as a therapeutic option in patients with high risk or established CVD.	Thank you for your comment. GLP-1 mimetics are not a first line treatment option and are included in 'treatment options where further interventions are needed'.

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South Asian Health Foundation UK	Guideline	019	General	Visual summary 4 - This is a useful visual summary but could be improved by adding additional columns that show CVD and reno-protection.	Thank you for your comment. We have shown that the SGLT2 inhibitors should be considered first line in people with a high risk of CVD or established ASCVD or HF in the visual summaries. We have added other considerations to the choosing medicines table for before treatment is initiated and have included the factors the committee felt were the most important, including renal and hepatic impairment and contraindications.
South Asian Health Foundation UK	Guideline	022	019	1.7.21 - The guidance '*Do not offer GLP-1 mimetic therapy to adults with type 2 diabetes 20 solely for cardiovascular risk reduction'* completely ignores the strong evidence of cardiovascular protection offered by GLP-1 agonists particularly with long acting once weekly preparations. The benefits of GLP-1 agonists can be particularly significant in minority ethnic groups such as south Asians who are known to have high cardiovascular risk. While we acknowledge economic modelling of these benefits is lacking, the benefits of long acting GLP-1 agonists independent of glucose control needs to be acknowledged. As such the guidance needs to be modified to reflect the scientific evidence of benefits of GLP-1agonists.	Thank you for your comment. The committee have taken stakeholder comments into account and agreed to remove the recommendation about not using GLP1-mimetic therapy solely for cardiovascular risk reduction in people with type 2 diabetes). Upon reviewing the recommendation, the committee agreed that it was inappropriate to make a decision about treatment choice based solely on a single factor (cardiovascular risk) and that, as detailed in the recommendation on choosing drug treatments, multiple factors should be taken into account instead. The committee reviewed the stakeholder comments regarding the use of GLP-1 mimetics and examined the updated economic evidence relating to GLP-1 mimetic treatment for people with type 2 diabetes and high cardiovascular risk. In the NICE health economic analyses, when looking at GLP-1 mimetics as a class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable semaglutide because this

					GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of £20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the intervention as an effective use of NHS resources will specifically take account of the following factors." and • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis." Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable

					semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors. In addition, the committee noted that there were differences in the clinical effectiveness of the 2 forms of semaglutide. Although the acquisition costs for injectable and oral semaglutide are similar they showed marked differences in cost-effectiveness in the economic analyses. This was caused by differences in the effect estimates for stroke, myocardial infarction and severe hypoglycaemia. From earlier discussions about the clinical evidence (see the discussion sections in the evidence review for more details) the committee had agreed that it was uncertain whether the observed differences in effect on all-cause mortality compared to placebo between the 2 forms of semaglutide were real and they therefore decided not to place undue weight on them. They had also noted that this uncertainty and any other differences in effects between the drugs for other outcomes was probably due to wide 95% confidence intervals for many outcomes with these drugs, due to the smaller numbers of participants and events in the trials compared to other CVOTs . Due to the higher level of uncertainty surrounding the cost-effectiveness of the GLP-1 mimetics as a class compared to

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					the SGLT2 inhibitors, the committee considered whether to recommend injectable semaglutide for people at high cardiovascular risk in whom an SGLT2 is contraindicated or not tolerated. However, taking into account the uncertainty in the cost-effectiveness and clinical effectiveness the committee decided against recommending injectable semaglutide for this population.
South Asian Health Foundation UK	Guideline	022	021	1.7.22 - The arbitrary cut off of a BMI of 35kg/m^2 for consideration of GLP-1agonists is a concern given the non-glycaemic benefits such as weight loss for most patients. Although allowance is made for use in lower BMI range in certain ethnic groups, this high cut off essentially disadvantages a number of patients who can benefit with early use of GLP-1 agonists rather than use sulfonylurea and insulin which cause weight gain.	Thank you for your comment The original scope of the update to the drug treatment sections of NG28 was to fully update the treatment section of the guideline. However, once work on the topic commenced it was determined that updating evidence reviews and health economics for such a wide scope, within the resources available to NICE for this topic, would take an unacceptably lengthy period. Taking such an approach for this guideline update would have further delayed publication of updated treatment recommendations in this rapidly changing area. In view of the timescales involved and the appetite from the committee and stakeholders for an update within an acceptable time period, we worked with our committee members to identify the priority areas for this update. The committee members agreed that our initial focus should be on reviewing the evidence from trials looking at cardiovascular outcomes. This reflected the changing evidence base as a result of the significant investment in clinical trials to directly capture cardiovascular outcomes, feedback from stakeholders that assessing this evidence was a priority and the impact that this new evidence could have on recommendations for the treatment of people with diabetes. We therefore revised the scope to reflect this and carried out the current piece of work. The committee are unable to make any changes to this recommendation because the evidence they looked at was judged only to be generalisable to people who were at high

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					risk of developing cardiovascular disease or who had established cardiovascular disease and this recommendation on GLP-1 use is not specific for those populations. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand.
South Asian Health Foundation UK	Guideline	023	005	1.7.23 - We acknowledge this is 2015 guidance. However, we would like to stress the need to review this advice as the cardiovascular benefits clearly over ride these considerations and although some patients may demonstrate benefits on either weight or HbA1c alone the degree of changes in these parameters would still be of considerable benefit to patients.	Thank you for your comment. Thank you for your comment. The recommendations covering triple therapy with GLP-1 was not updated as part of the current work. The committee are unable to make any changes to this recommendation because although this recommendation was within the scope of the update the evidence included in the review was judged only to be generalisable to people who were at high risk of developing cardiovascular disease or who had established cardiovascular disease. Consultation recommendation 1.7.23 does not apply to the high cardiovascular risk population and therefore the committee did not amend it. The committee reviewed the stakeholder comments regarding the use of GLP-1 mimetics and examined the updated economic evidence relating to GLP-1 mimetic

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					treatment for people with type 2 diabetes and high cardiovascular risk. In the NICE health economic analyses, when looking at GLP-1 mimetics as a class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of £20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the intervention as an effective use of NHS resources will specifically take account of the following factors." And • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis."

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					Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors. In addition, the committee noted that there were differences in the clinical effectiveness of the 2 forms of semaglutide. Although the acquisition costs for injectable and oral semaglutide are similar they showed marked differences in cost-effectiveness in the economic analyses. This was

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					caused by differences in the effect estimates for stroke, myocardial infarction and severe hypoglycaemia. From earlier discussions about the clinical evidence (see the discussion sections in the evidence review for more details) the committee had agreed that it was uncertain whether the observed differences in effect on all-cause mortality compared to placebo between the 2 forms of semaglutide were real and they therefore decided not to place undue weight on them. They had also noted that this uncertainty and any other differences in effects between the drugs for other outcomes was probably due to wide 95% confidence intervals for many outcomes with these drugs, due to the smaller numbers of participants and events in the trials compared to other CVOTs. Due to the higher level of uncertainty surrounding the cost-effectiveness of the GLP-1 mimetics as a class compared to the SGLT2 inhibitors, the committee considered whether to recommend injectable semaglutide for people at high cardiovascular risk in whom an SGLT2 is contraindicated or not tolerated. However, taking into account the uncertainty in the cost-effectiveness and clinical effectiveness the committee decided against recommending injectable semaglutide for this population.
South Asian Health Foundation UK	Guideline	024	General	Visual summary 3 - As mentioned previously in comment 3, the positioning of GLP-1 agonists as an option after triple oral therapy essentially ignores the CV benefits of this class of the drug .The guidance as it is depicted is therefore outdated and needs revision to keep in with the emerging evidence. The visual summary also does not show the therapeutic choices in patients with renal impairment and at risk of progression of kidney disease. There is reference to NICE CKD guidelines, but it would be good to include the recommended therapeutic options for prevention and progression of diabetic kidney disease in the visual summary. The guidance on 1.7.16 should also be updated accordingly to highlight the	Thank you for your comment. The committee reviewed the stakeholder comments regarding the use of GLP-1 mimetics and examined the updated economic evidence relating to GLP-1 mimetic treatment for people with type 2 diabetes and high cardiovascular risk. In the NICE health economic analyses, when looking at GLP-1 mimetics as a class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with

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				renal protection offered by SGLT2i particularly Canagliflozin and Dapagliflozin for which there is compelling evidence.	a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of £20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the intervention as an effective use of NHS resources will specifically take account of the following factors." and • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis." Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable

					this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors. In addition, the committee noted that there were differences in the clinical effectiveness of the 2 forms of semaglutide. Although the acquisition costs for injectable and oral semaglutide are similar they showed marked differences in cost-effectiveness in the economic analyses. This was caused by differences in the effect estimates for stroke, myocardial infarction and severe hypoglycaemia. From earlier discussions about the clinical evidence (see the discussion sections in the evidence review for more details) the committee had agreed that it was uncertain whether the observed differences in effect on all-cause mortality compared to placebo between the 2 forms of semaglutide were real and they therefore decided not to place undue weight on them. They had also noted that this uncertainty and any other differences in effects between the drugs for other outcomes was probably due to wide 95% confidence intervals for many outcomes with these drugs, due to the

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					smaller numbers of participants and events in the trials compared to other CVOTs. Due to the higher level of uncertainty surrounding the cost-effectiveness of the GLP-1 mimetics as a class compared to the SGLT2 inhibitors, the committee considered whether to recommend injectable semaglutide for people at high cardiovascular risk in whom an SGLT2 is contraindicated or not tolerated. However, taking into account the uncertainty in the cost-effectiveness and clinical effectiveness the committee decided against recommending injectable semaglutide for this population. In the absence of the GLP-1s being cost-effective treatments for people with high CV risk or established cardiovascular disease, the existing 2015 recommendations for when to use GLP-1s were retained. The renal benefits of using SGLT2 inhibitors in people with type 2 diabetes and CKD have been assessed in a separate piece of work that has recently been out for stakeholder consultation and was published in November 2021. The final recommendations on renal and cardiovascular benefits will be brought together in a single updated guideline document when this current work on cardiovascular benefits is published in 2022. The CKD recommendations are situated in the section on CKD in the type 2 diabetes guideline with a cross reference from the drug treatment section.
South Asian Health Foundation UK	Guideline	General	General	The guidelines quite rightly emphasize the aspect of individualisation. However, there is opportunity to define this individualisation better. For instance it is well acknowledged that therapeutic choices should reflect the overall health of the patients and the accompanying co-morbidities. Choice of therapy based on phenotypic characteristics eg obese type 2 vs non obese type 2 diabetes, ethnicity and CVD and renal risk can be a better way to highlight the individualisation and determine therapy choice.	Thank you for your comment. The recommendations in the current version of the guideline do contain options to individualise treatment options for the groups of people you mention in your comment. The renal benefits of using SGLT2 inhibitors in people with type 2 diabetes and CKD have been assessed in a separate piece of work that has been out for stakeholder consultation and was published in November 2021. The final

					recommendations on renal and cardiovascular benefits will be brought together in a single updated guideline document when this current work on cardiovascular benefits is published in 2022. The committee agreed with the need to produce guidance to help promote personalised treatment. The original scope of this work covered additional groups of interest including people with renal impairment, people in specific ethnic groups, adults aged 65 years and older, as well as people in specific cardiovascular risk groups. It aimed to fully update the drug treatment sections of the NG28 guideline. However, once work on the topic commenced it was determined that updating evidence reviews and health economics for such a wide scope, within the resources available to NICE for this topic, would take an unacceptably lengthy period. Taking such an approach for this guideline update would have further delayed publication of updated treatment recommendations in this rapidly changing area. In view of the timescales involved and the appetite from the committee and stakeholders for an update within an acceptable time period, we worked with our committee members to identify the priority areas for this update. The committee members agreed that our initial focus should be on reviewing the evidence from trials looking at cardiovascular outcomes. This reflected the changing evidence base as a result of the significant investment in clinical trials to directly capture cardiovascular outcomes, feedback from stakeholders that assessing this evidence was a priority and the impact that this new evidence could have on recommendations for the treatment of people with diabetes. We therefore revised the scope to reflect this and carried out the current piece of work. The committee made recommendations for people with established cardiovascular disease and those at high risk of developing cardiovascular disease using data from the

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					Cardiovascular outcome trials. In addition, the amended 2015 recommendation on drug treatment choice takes comorbidities and clinical and personal needs into account to stress the need to tailor treatment to the individual. To help the prescriber do this additional information has been provided as part of a visual summary, including factors such as whether the drug class is associate with weight gain or loss or is weight neutral. We recognise this does not compensate for the change in scope, but the decision to restrict the scope to cardiovascular benefits was a pragmatic one to try to ensure we could complete a useful piece of work in a shorter period of time to meet stakeholder needs. However, the recommendations for treatment with GLP-1s have been retained unaltered from the 2015 version of the guideline and these include specific recommendations based on BMI and ethnicity. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs.
St Helens & Knowsley Teaching	General	General	General	I have no specific comments about your questions (above) except that the guideline appears to be likely to greatly increase SGLT2 inhibitor use and this may have significant resource implications, for example, in additional monitoring (renal function and ketones), in additional costs if patients and	Thank you for your comment. NICE is undertaking a resource impact assessment of the draft recommendations in preparation for finalisation of the guideline update. This includes consideration of the sizes of the populations that

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Hospitals NHS Trust				carers are to be supplied with and trained in the use of ketone testing, in additional support when patients and carers are unsure about the results of said monitoring tests, in additional resources to support the suspension and resumption of these drugs as recommended and in additional resources when patients receiving these drugs have other hospital encounters for example for elective surgery. Laminated and wall-mounted visuals are very useful so I would support separate PDFs.	would be covered by the SGLT2 inhibitor recommendations for people with established cardiovascular disease (CVD) and high risk of CVD. This document will be made available on the guideline website. The visual summaries and PDA will be made available as PDFs on the guideline website.
St Helens & Knowsley Teaching Hospitals NHS Trust	Guideline	004	007	R1.1.1 '…their likelihood of benefiting from or being harmed by long-term interventions.'	Thank you for your comment. This recommendation was not within the scope of the current update. The change in wording was part of the process of refreshing the recommendations. The current wording has been retained as it implies consideration of harms as part of the decision making process and this recommendation was not within the scope of the ones the committee could edit.
St Helens & Knowsley Teaching Hospitals NHS Trust	Guideline	010	001	Figure 1 Your target HbA1c: weighing it up. This is a useful decision aid. 'I'm not concerned about the chance of getting side effects from medicines' might be better as 'I'm willing to risk getting side effects from medicines.' Have these statements been thoroughly evaluated for face validity etc – if not, it is a missed opportunity to optimise the patient-friendliness of the aid.	Thank you for your comment and support. The PDA and figure 1 have been developed with people with lived experience of type 2 diabetes, and have been amended in the light of stakeholder comments (including the part you highlight). We would support further evaluation of the PDA and visual analogue scale in practice and we are planning to collate feedback on the PDA and VAS when published.
St Helens & Knowsley Teaching Hospitals NHS Trust	Guideline	011 - 012	020 - 030, 002 - 003	Excellent improvement – this is very important.	Thank you for your comment.
St Helens & Knowsley Teaching Hospitals NHS Trust	Guideline	014	008	1.7.1 'effectiveness of the drug treatments in terms of metabolic response and cardiovascular and renal protection.'	Thank you for your comment. Following committee discussion of stakeholder comments the recommendation on choosing drug treatments has been amended to include consideration of cardiovascular and renal protection (third bullet).
St Helens & Knowsley Teaching	Guideline	022	019	1.7.21 This statement is inappropriate unless there is a similar statement for all other agents discussed. In the context of this type 2 diabetes guideline, none of the agents has a licence to be used solely for	Thank you for your comment. The committee have taken stakeholder comments into account and agreed to remove the recommendation about not using GLP1-mimetic therapy

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Hospitals NHS Trust				cardiovascular risk reduction, they're glucose-lowering agents with additional benefits.	solely for cardiovascular risk reduction in people with type 2 diabetes. Upon reviewing the recommendation, the committee agreed that it was inappropriate to make a decision about treatment choice based solely on a single factor (cardiovascular risk) and that, as detailed in the recommendation on choosing drug treatments, multiple factors should be taken into account instead.
St Helens & Knowsley Teaching Hospitals NHS Trust	Guideline	025	022 - 028	1.7.9 What about patients with established renal disease – should there not be a similar statement recommending SGLT2 inhibitor alone?	Thank you for your comment. The renal benefits of using SGLT2 inhibitors in people with type 2 diabetes and CKD have been assessed in a separate piece of work that has recently been out for stakeholder consultation and was published in November 2021. The final recommendations on renal and cardiovascular benefits will be brought together in a single updated guideline document when this current work on cardiovascular benefits is published in 2022. The CKD recommendations are situated in the section on CKD in the type 2 diabetes guideline with a cross reference from the drug treatment section.
St Helens & Knowsley Teaching Hospitals NHS Trust	Guideline	General	General	Why is there not a recommendation to consider adding a GLP receptor agonist with proven cardiovascular benefit in patients at high risk of or with established CVD who are unable to take or tolerate an SGLT2 inhibitor? Patients broadly understand CV risk, but may have very specific fears e.g. stroke – it would be helpful if the guidance could recommend the most appropriate agent to prevent specific elements of CVD if they differ between agents and if this is possible.	Thank you for your comment. Although there were a number of stakeholder comments asking for clarification of the treatment options for people with type 2 diabetes in whom SGLT2 inhibitors (SGLT2i) were contraindicated or not tolerated, there were no cardiovascular outcome trial style clinical trials identified that looked at the effectiveness of treatments for people at high cardiovascular (CV) risk in this population. The committee therefore used the evidence for effectiveness and cost effectiveness for other interventions from the same economic modelling scenarios as those looking at the cost- effectiveness of SGLT2i. The committee examined the cost-effectiveness evidence relating to GLP-1 mimetic treatment for people with type 2 diabetes and high cardiovascular risk. In the NICE health economic analyses, when looking at GLP-1 mimetics as a class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of

					being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of £20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the intervention as an effective use of NHS resources will specifically take account of the following factors." and • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis." Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable

					semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors. In addition, the committee noted that there were differences in the clinical effectiveness of the 2 forms of semaglutide. Although the acquisition costs for injectable and oral semaglutide are similar they showed marked differences in cost-effectiveness in the economic analyses. This was caused by differences in the effect estimates for stroke, myocardial infarction and severe hypoglycaemia. From earlier discussions about the clinical evidence (see the discussion sections in the evidence review for more details) the committee had agreed that it was uncertain whether the observed differences in effect on all-cause mortality compared to placebo between the 2 forms of semaglutide were real and they therefore decided not to place undue weight on them. They had also noted that this uncertainty and any other differences in effects between the drugs for other outcomes was probably due to wide 95% confidence

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					intervals for many outcomes with these drugs, due to the smaller numbers of participants and events in the trials compared to other CVOTs. The committee therefore agreed that they were unable to recommend injectable semaglutide for people with type 2 diabetes and high cardiovascular risk who were unable to take and SGLT2i. As a result, the committee noted that people with high CV risk who could not take metformin with an SGLT2i would be offered metformin alone at treatment initiation. If they were also unable to take metformin then the clinician would select another treatment from the remaining options, namely sulfonylureas, DPP-4s or pioglitazone, depending on the individual's clinical circumstances and preferences. The committee decided against listing the options for people with type 2 diabetes who were at high CV risk and could not take an SGLT2i because they thought that this was an unnecessary level of detail given that they could not recommend a GLP-1 mimetic in place of the SGLT2i, that the treatment options were therefore the same for these people as for the rest of the type 2 diabetes population and because apart from for metformin, the guideline does not include details of which drug to take if a particular drug is contraindicated or not tolerated but rather expects the prescriber to use their clinical judgment. The committee wanted to keep the pathway as simple as possible, and they agreed that it would not be possible to do this if alternative options were provided every time a drug was not contradicted or not tolerated. However, they agreed that it was appropriate to have recommendations for metformin being contradicted or not tolerated because this is the drug that the majority of people would take as first-line therapy. Given the focus on looking at treatments reducing all CV risks, the current economic model looks at the cost-effectiveness of these treatments in both the total diabetic

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					population, and across three other subgroups which have varying levels of high cardio vascular risk (the definitions of which are listed in section 3.1 in the economic report). A cost-effectiveness analysis looking at a population at risk of only one particular CV outcome such as stroke was thought to be inappropriate as the risk factors contributing towards stroke will likely contribute towards other CV events as well, hence resulting in populations similar to the three subgroups modelled in our analysis. The committee were therefore unable to make separate recommendations for people at risk of stroke, as a population as risk of stroke is likely to be at risk of other CV events as well
St Helens & Knowsley Teaching Hospitals NHS Trust	Guideline	General	General	There is no indication in this guideline of the relative efficacy (or speed) for lowering HbA1c of the different agents – is this not important for clinicians trying to help patients choose the most appropriate agent? For example, a patient awaiting surgery delayed by a high HbA1c might choose a different drug if it means they are likely to get their surgery earlier.	Thank you for your comment. Unfortunately, the guideline cannot cover every clinical situation and is intended to cover routine general treatment of type 2 diabetes. The evidence review did not cover the relative efficacy or speed of HbA1c lowering of different agents because this was not prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest this addition.
St Helens & Knowsley Teaching Hospitals NHS Trust	Guideline	General	General	The relative effectiveness of different agents (being used primarily for glycaemic control) to induce weight loss is critically important to many patients – should this not be reviewed and included?	Thank you for your comment. The way the data on weight and BMI from the included cardiovascular outcome trials was reported was very variable and, in most cases, not comparable. The data was therefore not included in the clinical review findings, but weight was taken into consideration for the economic modelling as follows. For changes in weight, it was noted it was important not to double count the impact of changes in the economic model, as the effects on cardiovascular outcomes should already be captured in the outcomes of those trials. It was therefore agreed that the most appropriate approach was to only include the direct quality of life gains associated with reductions in weight, with the other benefits captured through the cardiovascular event data. The committee noted that if anything the approach taken in the economic model may overestimate the benefits of weight reduction, as some of the estimated quality of life gains may be the result of

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					avoided cardiovascular events, but it was agreed to be the best data source available. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking these into account we have decided that a full update of this section of the guideline is warranted. However, this is expected to take some time to complete due to the size of the evidence base. Before development begins there will be another scoping exercise to ensure that we are able to meet stakeholder needs.
St Helens & Knowsley Teaching Hospitals NHS Trust	Scope	General	General	Working with patients and carers, clinicians try to use best available, contemporary evidence to agree individualised diabetes management plans. These plans invariably attempt to balance multiple evidence-based therapeutic targets with individual patient factors e.g. blood sugar balance, fear of hypoglycaemia, concerns about weight and weight gain (and desire for weight loss) and cardiovascular risk. Six years after the last iteration of NG28, it is disappointing to see that NICE has significantly curtailed its proposed scope and only reviewed evidence in certain limited areas of care. A wider scope and more comprehensive review would make the guideline more useful, more credible and more apposite to real world consultations. This guidelines is excessively CVOT focussed.	Thank you for your comment. The original scope of the update to the drug treatment sections of NG28 was to fully update the treatment section of the guideline as your comment notes. However, once work on the topic commenced it was determined that updating evidence reviews and health economics for such a wide scope, within the resources available to NICE for this topic, would take an unacceptably lengthy period. Taking such an approach for this guideline update would have further delayed publication of updated treatment recommendations in this rapidly changing area. In view of the timescales involved and the appetite from the committee and stakeholders for an update within an acceptable time period, we worked with our committee members to identify the priority areas for this update. The committee members agreed that our initial focus should be on reviewing the evidence from trials looking at cardiovascular outcomes. This reflected the changing evidence base as a result of the significant investment in

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					clinical trials to directly capture cardiovascular outcomes, feedback from stakeholders that assessing this evidence was a priority and the impact that this new evidence could have on recommendations for the treatment of people with diabetes. We therefore revised the scope to reflect this carried out the current piece of work. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand.
Sussex Community Foundation NHS Trust	Guideline	006	008 - 010	With the rise in the use of nutritionist and other alternative titles, who do not have the same regulation and potentially standards of educational rigor/training. Should we not specify state registered dietitian or nurse with appropriate competencies ?	Thank you for your comment. The section of the guideline covering dietary advice and bariatric was not prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest existing recommendations needed amending. The surveillance team at NICE monitor whether guidelines are up to date. The surveillance process includes reacting to events at any time after guideline publication (for example, publication of a key study) as well as a standard check every 5 years. Stakeholders can help with this process by letting us know which parts of the guideline stakeholders believe out-of-date and why during scope consultations. As these are evidence-based guidelines it is useful if stakeholders can

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					provide links to important evidence sources that they believe would necessitate an update of a particular area of the guideline. We can then pass these references onto the NICE surveillance team for evaluation and a decision about whether an update is justified.
Sussex Community Foundation NHS Trust	Guideline	006 - 007	General	Given the results of the Direct and Droplet trials and multiple bariatric surgery trials should we not have considerably stronger advice on remission in diabetes and the positive long term effects of bariatric surgery on many people with Type 2 diabetes in addition to pointing towards another guideline	Thank you for your comment. The section of the guideline covering dietary advice and bariatric surgery was not prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest existing recommendations needed amending.
Sussex Community Foundation NHS Trust	Guideline	008	003 - 009	It would be sensible given the increased prevalence of peripheral vascular disease to have a note on this with a link to appropriate guideline, similarly for Atrial fibrillation and heart failure.	Thank you for your comment. The section of the guideline covering antiplatelet therapy was not prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest existing recommendations needed amending.
Sussex Community Foundation NHS Trust	Guideline	011	027 - 030	The risk of severe hypoglycaemia in Type 2 diabetes relates very much to the choice of medication much more than the demographic of the patient. I think this needs to be rephrased – are we really saying those who drive or operate machinery should by rote have a higher A1c ?	Thank you for your comment. We have removed reference to driving from the visual analogue scale (the PDA text retains the words '. some [hypos] can cause people to feel dizzy or faint and, they might need help from someone else to treat the hypo. There are special rules for some drivers who have diabetes – talk to your diabetes team to see if they affect you.'). In addition, the PDA now makes clearer that 'Some medicines are more likely to cause hypos than others.' .
Sussex Community Foundation NHS Trust	Guideline	012	001 - 002	Intensive management needs to be defined. It would be sensible also to add Life limiting co-morbidities	Thank you for your comment. The figure relates to reasons for thinking about relaxing the HbA1c target mentioned in recommendation 1.6.9. The guideline did not consider any new evidence on this topic as it was out of scope of the current update so it is not possible to include disease duration per se, but it does include life expectancy ('thinking about my age and my health overall') and multimorbidity ('health issues apart from my diabetes').
Sussex Community Foundation NHS Trust	Guideline	012	012 - 015	The need to strongly encourage adherence with the DVLA legal requirements would be a good change here.	Thank you for your comment. The section of the guideline covering self-monitoring of blood glucose was not prioritised at the scoping stage as no evidence was identified in the

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					surveillance review to suggest existing recommendations needed amending.
Sussex Community Foundation NHS Trust	Guideline	012	020 - 021	It is not just operating machinery that needs to be taken into account. Any person taking an oral medication that increases their risk of hypoglycaemia must have the ability to test their glucose levels.	Thank you for your comment. The section of the guideline covering self-monitoring of blood glucose was not prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest existing recommendations needed amending.
Sussex Community Foundation NHS Trust	Guideline	014	028 - 029	This is really good to see assessment of Cardiovascular status – be great to see more detail	Thank you for your comment. Since this guideline is focused on type 2 diabetes management rather than assessing cardiovascular status we have been unable to add the requested additional detail to the recommendations, although there is a little more detail in the rationale and evidence review discussion section. Please refer to NICE's guideline on cardiovascular disease: risk assessment and reduction, including lipid modification.
Sussex Community Foundation NHS Trust	Guideline	015	003	Should we not be using Qrisk 3	Thank you for your comment. The committee deliberated over the definition of high risk of developing CV risk disease (high risk of future major adverse cardiovascular event such as an MI or stroke) to capture this population. They agreed that a QRISK2 score of >10% would be appropriate because this score takes into account most of the factors that were used to define this population in the economic model (and factors such as age, gender and ethnicity. They noted that QRISK2 is recommended for the assessment of CV risk in people with the 2 diabetes in the NICE guideline on NICE guideline on Cardiovascular disease: risk assessment and reduction, including lipid modification and is widely used and accepted in current general practice. Although other algorithms for assessing CVD risk exist, such as QRISK3, they are not in widespread use currently. Since a review of the evidence about the accuracy of such algorithms in comparison to each other and QRISK2 was not within the scope of this work, the committee agreed that QRISK2 was a pragmatic choice for assessing CV risk in people with type 2 diabetes.

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Sussex Community Foundation NHS Trust	Guideline	015	020	Why not offer instead of consider ?	Thank you for your comment. The recommendation covering use of modified release metformin was not within the scope of this update. The current committee did not review any evidence on this topic.This topic was not prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest existing recommendations needed amending.
Sussex Community Foundation NHS Trust	Guideline	015 - 016	General	There appears to be no mention of GLP-1 analogue therapy in those with Atherosclerotic heart disease. This is very surprising and will make the guideline significantly less useful in clinical practice. Given that DPP-4 inhibitors have no evidence in improving CV outcome it is concerning they appear to have such a prominent place in the guideline. The lack of focus also on renal outcomes where again there is evidence for GLP-1 analogue appears shortsighted, as well as the positive weight loss which again is ignored.	Thank you for your comment. The committee reviewed the stakeholder comments regarding the use of GLP-1 mimetics and examined the updated economic evidence. In the NICE health economic analyses, when looking at GLP-1 mimetics as a class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of £20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the intervention as an effective use of NHS resources will specifically take account of the following factors." and • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above."

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					One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis." Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors.

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					Due to the higher level of uncertainty surrounding the cost-effectiveness of the GLP-1 mimetics as a class compared to the SGLT2 inhibitors, the committee considered whether to recommend injectable semaglutide for people at high cardiovascular risk in whom an SGLT2 is contraindicated or not tolerated. However, taking into account the uncertainty in the cost-effectiveness and clinical effectiveness the committee decided against recommending injectable semaglutide for this population The DPP-4 inhibitors remain an option in the pathway for glycaemic control those without established ASCVD, heart failure and not at increased risk of cardiovascular disease, as well as for those for whom SGLT2 inhibitors are contraindicated or not tolerated. The alternative treatment options are listed alphabetically, and it is not our intention to promote one over another where there are a list of options. We expect that the clinician will pick the best option based on the needs of their individual patient and we hope that the additional information in the visual will help them do so. The renal benefits of using SGLT2 inhibitors in people with type 2 diabetes and CKD have been assessed in a separate piece of work that has recently been out for stakeholder consultation and was published in November 2021. The final recommendations on renal and cardiovascular benefits will be brought together in a single updated guideline document when this current work on cardiovascular benefits is published in 2022.
Sussex Community Foundation NHS Trust	Guideline	017	010 – 011	There needs to be advice re other fasting states eg surgery	Thank you for your comment. The recommendation which included sick day rules was reviewed following stakeholder comments and the bullet point on sick day rules has now been removed as the committee agreed it would be inconsistent to present this information for one class of drugs but not any others. They expected that sick day rules and

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					other safety related advice would be discussed with the individual with type 2 diabetes as part of the decision-making process regarding drug choice and wanted to keep the guidance as simple and clear as possible.
Sussex Community Foundation NHS Trust	Guideline	019	General	Visual summary 4 - It is perplexing that all the GLP-1 analogues are presented as equal with no differentiation as to CV outcome data. It is concerning that advice to use with caution or avoid in renal impairment is there.	Thank you for your comment. The content in the table has been updated for specific medicines rather than for medicine classes.
Sussex Community Foundation NHS Trust	Guideline	022 - 023	019 - 008	It feels a significant missed opportunity to continue to relegate to GLP-1 analogue therapy to a very discrete group of patients particularly when their inherent risk of hypoglycaemia is low and some of them have positive CV and renal outcomes. As well as weight loss and in many patients comparable glucose lowering to basal insulin. To continue to require weight loss andHbA1c reduction of 11mmol/mol or more without reference to CV benefits appears most surprising	Thank you for your comment. The committee reviewed the stakeholder comments regarding the use of GLP-1 mimetics and examined the updated economic evidence relating to GLP-1 mimetic treatment for people with type 2 diabetes and high cardiovascular risk. In the NICE health economic analyses, when looking at GLP-1 mimetics as a class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of £20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the intervention as an effective use of NHS resources will specifically take account of the following factors." and • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement

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					about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis." Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use

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					other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors. In addition, the committee noted that there were differences in the clinical effectiveness of the 2 forms of semaglutide. Although the acquisition costs for injectable and oral semaglutide are similar they showed marked differences in cost-effectiveness in the economic analyses. This was caused by differences in the effect estimates for stroke, myocardial infarction and severe hypoglycaemia. From earlier discussions about the clinical evidence (see the discussion sections in the evidence review for more details) the committee had agreed that it was uncertain whether the observed differences in effect on all-cause mortality compared to placebo between the 2 forms of semaglutide were real and they therefore decided not to place undue weight on them. They had also noted that this uncertainty and any other differences in effects between the drugs for other outcomes was probably due to wide 95% confidence intervals for many outcomes with these drugs, due to the smaller numbers of participants and events in the trials compared to other CVOTs. Due to the higher level of uncertainty surrounding the cost-effectiveness of the GLP-1 mimetics as a class compared to the SGLT2 inhibitors, the committee considered whether to recommend injectable semaglutide for people at high cardiovascular risk in whom an SGLT2 is contraindicated or not tolerated. However, taking into account the uncertainty in the cost-effectiveness and clinical effectiveness the committee decided against recommending injectable semaglutide for this population.

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					In the absence of the GLP-1s being cost-effective treatments for people with high CV risk or established cardiovascular disease, the existing 2015 recommendations for when to use GLP-1s were retained. These apply to the general population of people with type 2 diabetes. Since no new non- cardiovascular outcome trial evidence regarding the benefits of GLP-1s was included in this review the committee were unable to amend or rewrite the 2015 criteria for GLP-1 use in this current update. When these recommendations were made in 2015 these criteria were used because of the lack of cost-effectiveness of this treatment for most people. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand.
Sussex Community Foundation NHS Trust	Guideline	023	013	Choosing box - In the reviewing and changing treatments box it is difficult to fully understand the logic employed by recommended "stopping medicines that have not worked" without defining this further. Given that Type 2 diabetes is a progressive condition are we not in danger of promoting avoidable glycaemic burden by encouraging switching if not at target ? Perhaps looking at specifying a level above target where switching unlikely to work would be a better approach.	Thank you for your comment. This wording has been amended to include 'stop medicines that have had no impact on glycaemic control or weight'.

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Sussex Community Foundation NHS Trust	Guideline	024	General	It is concerning that it appears the evidence for CV protection with GLP-1 analogue therapy appears to be ignored	Thank you for your comment. The committee reviewed the stakeholder comments regarding the use of GLP-1 mimetics and examined the updated economic evidence relating to GLP-1 mimetic treatment for people with type 2 diabetes and high cardiovascular risk. In the NICE health economic analyses, when looking at GLP-1 mimetics as a class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of £20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the intervention as an effective use of NHS resources will specifically take account of the following factors." and • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending

					a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis." Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors. In addition, the committee noted that there were differences in the clinical effectiveness of the 2 forms of semaglutide. Although the acquisition costs for injectable and oral semaglutide are similar they showed marked differences in

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					cost-effectiveness in the economic analyses. This was caused by differences in the effect estimates for stroke, myocardial infarction and severe hypoglycaemia. From earlier discussions about the clinical evidence (see the discussion sections in the evidence review for more details) the committee had agreed that it was uncertain whether the observed differences in effect on all-cause mortality compared to placebo between the 2 forms of semaglutide were real and they therefore decided not to place undue weight on them. They had also noted that this uncertainty and any other differences in effects between the drugs for other outcomes was probably due to wide 95% confidence intervals for many outcomes with these drugs, due to the smaller numbers of participants and events in the trials compared to other CVOTs. Due to the higher level of uncertainty surrounding the cost-effectiveness of the GLP-1 mimetics as a class compared to the SGLT2 inhibitors, the committee considered whether to recommend injectable semaglutide for people at high cardiovascular risk in whom an SGLT2 is contraindicated or not tolerated. However, taking into account the uncertainty in the cost-effectiveness and clinical effectiveness the committee decided against recommending injectable semaglutide for this population. In the absence of the GLP-1s being cost-effective treatments for people with high CV risk or established cardiovascular disease, the existing 2015 recommendations for when to use GLP-1s were retained.
Sussex Community Foundation NHS Trust	Guideline	026	General	There is nothing on assessment of hypoglycaemic awareness for people living with Type 2 diabetes that are on insulin. A short reminder regarding frailty would be good.	Thank you for your comment. The section of the guideline covering insulin-based treatments was not prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest existing recommendations needed amending. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced

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					evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs.
Sussex Community Foundation NHS Trust	Guideline	031	General	Despite a considerable section devoted to erectile dysfunction there is nothing with regards to female sexual dysfunction	Thank you for your comment. The section of the guideline covering managing complications was not prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest existing recommendations needed amending. We will however raise this point with surveillance to enable them to determine whether this topic should be covered by future guideline updates.
Sussex Community Foundation NHS Trust	Guideline	038	001 - 005	It is concerning that it appears the committee are stating that there may be widespread drug-induced renal damage for a class of drug where the evidence consistently appears to be the opposite. Without substantial changes this may reduce prescribing of SGLT-2 inhibitors unnecessarily particularly in primary care, and lead to unnecessary cessation following a small (and expected) change in eGFR/ creatinine post initiation More detailed guidance about renal function post SGLT-2 inhibitor commencement would surely be sensible eg https://cjasn.asnjournals.org/content/16/8/1278	Thank you for your comment. The committee discussed the stakeholder comments about the renal impact of SGLT2 inhibitors (SGLT2i). They agreed that the existing recommendation was unclear and potentially confusing because it gave no indication of the frequently or when the monitoring should take place. They also recognised that although SGT2i can have a negative effect on renal function this is usually a small reduction in function and not a reason to stop taking the SGLT2i. Taking these points into account the committee have now removed this draft recommendation.
Sussex Community Foundation NHS Trust	Guideline	039	005 - 007	It is not clear why the committee believe that the addition of SGLT-2 inhibition more prominently is likely to have a substantial resource impact. If this is the view it surely needs explanation	Thank you for your comment. The committee thought that by recommending SGLT2 inhibitors earlier in the treatment pathway and by widening the groups of people who can access them to people with established cardiovascular disease and those with a high risk of developing cardiovascular disease this this would lead to more people being prescribed these drugs. Currently the technology

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					appraisals only allow them to be prescribed to a more limited group of people who meet the criteria in the technology appraisals. Since a significant proportion of people with type 2 diabetes will either be at high risk of developing cardiovascular disease or have established cardiovascular disease already it is expected that the proportion of people taking an SGLT2 will increase greatly with associated costs. NICE is undertaking a resource impact assessment of the draft recommendations in preparation for finalisation of the guideline update. This includes consideration of the sizes of the populations that would be covered by the SGLT2 inhibitor recommendations for people with established cardiovascular disease (CVD) and high risk of CVD. This document will be available on the guideline website for commissioners to look at resource implications of these recommendations.
Sussex Community Foundation NHS Trust	Guideline	039	020 - 024	These sentences appear to contradict the resource concerns in lines 5-7 page 39. It is difficult to understand why the committee believe there will be an increase in renal function testing and if so in what circumstances do they recommend ?	Thank you for your comment. The committee discussed the stakeholder comments about the renal impact of SGLT2 inhibitors (SGLT2i). They agreed that the existing recommendation was unclear and potentially confusing because it gave no indication of the frequently or when the monitoring should take place. They also recognised that although SGT2i can have a negative effect on renal function this is usually a small reduction in function and not a reason to stop taking the SGLT2i. Taking these points into account the committee have now removed this draft recommendation.
Sussex Community Foundation NHS Trust	Guideline	042	General	It seems really surprising that the scope of this update did not look at clinical and cost-effectiveness in controlling glucose levels for GLP-1 analogue therapy. It feels a mistake that the benefits of GLP-1 analogue therapy appear to have been largely ignored and that no comparison with insulin was undertaken.	Thank you for your comment. You are correct that the model does not contain every outcome that could potentially be of interest for modelling adults with type 2 diabetes. However, the committee agreed these were the most important outcomes for assessing the additional cardiovascular and

					other benefits associated with drug treatment for type 2 diabetes, for the majority of the type 2 diabetes population. The committee agreed the cardiovascular outcome trials were the most appropriate data source to assess cardiovascular benefits of these drugs, being powered to specifically detect differences in hard outcomes, rather than only surrogate outcomes. The committee noted these studies were not representative of the full population of people with type 2 diabetes, but agreed this was a lesser limitation than the need to extrapolate from surrogate endpoints to cardiovascular outcomes, particularly given the findings from those studies suggesting these surrogate extrapolations are often not very robust. They also agreed that taking data on weight and hypoglycaemic events from these cardiovascular outcome trials was the most appropriate approach, in order to match the data used for cardiovascular event rates. For hypoglycaemic events, the approach taken is broadly in line with that taken in many other evaluations in diabetes, attaching costs and quality of life outcomes to the incidence of severe hypoglycaemic events, as these are the ones that make the most difference to a person's life. For changes in weight, it was noted it was important not to double count the impact of changes, as the effects on cardiovascular outcomes should already be captured in the outcomes of those trials. It was therefore agreed that the most appropriate approach was to only include the direct quality of life gains associated with reductions in weight, with the other benefits captured through the cardiovascular event data. The committee noted that if anything the approach taken in the guideline may overestimate the benefits of weight reduction, as some of the estimated quality of life gains may be the result of avoided cardiovascular events, but it was agreed to be the best data source available. There are of course other benefits that could have been considered as part of the modelling, including renal (or other

					microvascular) outcomes, or additional benefits directly related to improved glycaemic control, but the committee considered these to be of lower priority than those included in the model. They also noted that it would not be appropriate for any modelling approach to simply look at benefits on different outcomes from different trials or data sources, and assume those benefits are additive, and therefore increase the cost-effectiveness of drugs when included together. They noted that in many circumstances these benefits are not additive, and which benefits are likely to be realised may depend on the individual characteristics of the people included in studies. As an example, in the separate evaluation of SGLT2 inhibitors for people with CKD and type 2 diabetes, SGLT2 inhibitors were found to significantly improve renal outcomes, but this is a population in which a large benefit would not be expected for glycaemic control (hence why these agents were not originally licensed for use in people with impaired renal function). It should also be noted that it is not the case that only additional outcomes beneficial to drug therapy were excluded from the modelling. As an example, adverse events related to drug treatment (excluding hypoglycaemia) were not included as part of the analysis. As a number of the analyses in the guideline explicitly compare the addition of new treatments (for example, using 3 drugs versus 2) rather than simply switching drugs, it would be expected that inclusion of adverse events would decrease the cost-effectiveness for any additional treatments, as they would add to the adverse event burden. Therefore, whilst it is likely there would be differences found in the results of the cost-effectiveness analysis were a different set of outcomes to be included, it is not clear in which direction the results would change for any given agent, and whether they would become more or less cost-effective. The original scope of the update to the drug treatment sections of NG28 was to fully update the treatment section

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					of the guideline as your comment notes. However, once work on the topic commenced it was determined that updating evidence reviews and health economics for such a wide scope, within the resources available to NICE for this topic, would take an unacceptably lengthy period. Taking such an approach for this guideline update would have further delayed publication of updated treatment recommendations in this rapidly changing area. In view of the timescales involved and the appetite from the committee and stakeholders for an update within an acceptable time period, we worked with our committee members to identify the priority areas for this update. The committee members agreed that our initial focus should be on reviewing the evidence from trials looking at cardiovascular outcomes. This reflected the changing evidence base as a result of the significant investment in clinical trials to directly capture cardiovascular outcomes, feedback from stakeholders that assessing this evidence was a priority and the impact that this new evidence could have on recommendations for the treatment of people with diabetes. We therefore revised the scope to reflect this and carried out the current piece of work. Following the prioritisation of the outcome of cardiovascular benefit, insulin was no longer included in the review protocol as an intervention of interest because no cardiovascular outcome trials had been carried out for insulin. No evidence for combination treatment with GLP-1 and insulin or for insulin compared to other treatments was searched for or reviewed as part of this update and the committee were therefore unable to make any additions or changes the existing recommendations for these drugs. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we

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					have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand.
Sussex Community Foundation NHS Trust	Guideline	General	General	It would be really good to see some evidence based statements of the importance of management of glucose, weight, CV risk, Blood pressure at the beginning of the guideline and something on disease progression	Thank you for your comment. The sections of the guideline covering weight management, blood pressure and glucose management were not within the scope of this update. The committee did not review any evidence on these topics and were therefore unable to make the requested changes. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand..

Consultation on draft guideline - Stakeholder comments table
01/09/2021 – 14/10/2021

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Sussex Community Foundation NHS Trust	Health Economic report	008	035 - 037	The non-CVOT standard of care reported (Initial therapy – metformin, First intensification – metformin and sulfonylurea, Second intensification – metformin, sulfonylurea and NPH insulin) is now so far away from clinical practice in England as to no longer be fairly representative.	Thank you for your comment. The SoC arm and the treatments associated with it were designed using input from the committee to create a SoC arm which was representative of a contemporary UK setting given the evidence available. The SoC arm in the model was generated in order to provide a baseline rate of events to which the treatment effects from the evidence review could be applied. It is also worth noting that given the treatment effects of the considered alternatives are applied to the same SoC arm, any changes of this nature ot the SoC arm is unlikely to change the treatment decision (as it is primarily driven by treatment effects).
Sussex Community Foundation NHS Trust	Health Economic report	028	021	Semaglutide (injectable) is once weekly. Exenatide may be twice daily – once weekly depending on preparation.	Thank you for your comment. The model has been updated such that Semaglutide is treated as a once weekly injection. Exenatide was assumed as a once weekly injection, as this was thought to be the most common frequency used.
Sussex Community Foundation NHS Trust	Health Economic report	028 - 029	027, 001 - 002	We would question the time for insulin initiation and titration and would suspect this might be an underestimate. There is also no inclusion of patient time as being part of the health economic evaluation. In addition an increasing number of people living with Type 2 diabetes who require community nurse administration of insulin (we can provide data for Sussex), whilst these are perhaps less than 10 % of the total number of people with Type 2 diabetes taking insulin the Healthcare professional time is significant. We would estimate 20-30 minutes of healthcare professional time / patient / day would be reasonable. It is concerning that this ongoing use of healthcare professional time is not being taken into account	Thank you for your comment. Insulin initiation costs have been incorporated to the model with insulin initiation hours obtained through committee assumptions and the hourly costs of a Nurse obtained from the PSSRU Unit Costs of Health and Social Care 2020. The time spent by a Nurse as accounted for in the model was informed by the committee, considering what the national norm for this would be.
Sussex Community Foundation NHS Trust	Health economic report	General	General	There does not appear to be any analysis of the benefit of weight loss or gain on musculoskeletal outcomes. There does not appear to be any analysis of the benefit of weight loss or weight gain on the risk of common malignancies.	Thank you for your comment. As outlined in section 2.3.2.4 change in weight and BMI levels from baseline levels due to a particular treatment was incorporated into the analysis. For changes in weight, it was noted it was important not to double count the impact of changes, as the effects on cardiovascular outcomes should already be captured in the outcomes of those trials. It was therefore agreed that the most appropriate approach was to only include the direct

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					quality of life gains associated with reductions in weight, with the other benefits captured through the cardiovascular event data.
Total Diet & Meal Replacements (TDMR) Europe	General	General	General	Referring to other NICE Guidelines for weight management and dietary advice is problematic because some of these NICE guidelines are outdated and do not include the latest scientific research. *NICE Guideline CG189 on obesity: identification, assessment and management* and *Guideline PH53 on Weight management: lifestyle services for overweight or obese adults* were last updated in 2014, over seven years ago. Since then, a number of studies have shown the effectiveness of TDRs in tackling overweight and obesity, and type 2 diabetes. Public Health authorities are becoming increasingly aware of the effectiveness of TDRs for weight loss and the management of type 2 diabetes. NHS Scotland and NHS England have launched a programme supporting TDRs for obese people with type 2 diabetes. These pilots build on the approaches of the Diabetes Remission Clinical Trial (DiRECT), and the Doctor Referral of Overweight People to Low Energy total diet replacement Treatment (DROPLET) trial, reflecting the evidence bases developed by both of these trials. The DiRECT trial showed that a high proportion of people would engage with a total diet replacement weight loss programme for up to 20 weeks and that a good proportion maintained their weight loss and diabetes remission. [Lean MEJ, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster randomised trial. The Lancet. December 2017. https://doi.org/10.1016/S0140-6736(17)33102-1] [Lean MEJ, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Durability of primary care-led weight-management intervention for remission of type 2 diabetes: 2 year results of the DiRECT open-label, cluster-randomised trial. The Lancet Diabetes & Endocrinology. March 2019. https://doi.org/10.1016/S2213-8587(19)30068-3][Rehackova, L, Rodrigues, AM, Thom, G, et al. Participant experiences in the Diabetes REmission Clinical Trial (DiRECT). *Diabet Med*. 2021; 00:e14689. https://doi.org/10.1111/dme.14689]	Thank you for your comments. The section of the guideline covering dietary advice was not within the scope of this update. The current committee did not review any evidence on this topic and were therefore unable to amend the relevant recommendations. However, there is a large piece of work currently in progress to update the weight management guidelines. The scope of this work details which of the existing weight management guidelines are being updated and this includes the 2 guidelines you refer to. There is a relevant question in the scope on Individual-level approaches for prevention of excess weight, weight loss, and maintaining a healthier weight: 2.1 What is the effectiveness and cost effectiveness of total or partial diet replacements, intermittent fasting, plant-based and low-carbohydrate diets in achieving and maintaining weight loss in adults living with overweight or obesity?

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				The results of DROPLET showed that GP referrals to a commercial provider offering a weight loss and maintenance programme, based on TDR with individual behavioural support, led to an average weight loss of 10.7 kg after 1 year (7.2kg more than usual weight-loss programmes offered in primary care). This was associated with significant reductions in CVD risk. [Astbury NM, Aveyard P, Nickless A, Hood K, Corfield K, Lowe R, Jebb SA. Doctor Referral of Overweight People to Low Energy total diet replacement Treatment (DROPLET): pragmatic randomised controlled trial. Nuffield Department of Primary Care Health Sciences, University of Oxford, UK. August 2018. http://dx.doi.org/10.1136/bmj.k3760] There are other recent studies showing thepotential for TDRs to help people manage their weight and type 2 diabetes. The Prevention of diabetes through lifestyle Intervention and population studies in Europe and around the World (PREVIEW) research team has presented results on weight maintenance over three years in over two thousand overweight people with pre-diabetes who begin their risk-reduction with an 800kcal/d TDR diet given with a behaviour change intervention. The overall mean weight loss after 8 weeks was 10.7 + 0.4kg (10.8% of body weight). After the initial weight loss period those who achieved 8% weight loss were entered into a randomised trial of higher and lower dietary protein intake, higher and lower dietary glycaemic index levels and higher and lower physical exercise activity intensity levels for three years. The results of the three year maintenance outcomes showed that both diets and both exercise strategies were equally effective for weight-loss maintenance. [Christensen P, Larsen TM, Westerterp-Plantenga M, Macdonald I, Alfredo Martinez J, Handjiev S, Poppitt S, et al. Men and women respond differently to rapid weight loss: Metabolic outcomes of multi-centre intervention study after a low-energy diet in 2500 overweight, individuals with pre-diabetes (PREVIEW). Diabetes, Obesity and Metabolism, A Journal of Pharmacology and Therapeutics. August 2018. https://doi.org/10.1111/dom/13466]	

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				MRPs should also be included under the guideline's dietary advice as a useful method to lose and manage weight. A systematic review and meta-analysis of the effectiveness MRPs shows that programmes incorporating MRPs as part of their dietary intervention resulted in greater weight loss at one year than those not incorporating MRPs. Specifically, those participants who had included MRPs in their diet had lost an additional 1.49 kg at one year compared with those participants whose diet did not include MRPs. The review also showed that this greater weight loss was maintained over the longer term with data being reported after four years showing a more significant degree of weight loss maintenance in participants who had undertaken programmes incorporating MRPs. [Astbury, NM, Piernas, C, Hartmann-Boyce, J, Lapworth, S, Aveyard, P, Jebb, SA. A systematic review and meta-analysis of the effectiveness of meal replacements for weight loss. *Obesity Reviews*. 2019; 20: 569– 587. https://doi.org/10.1111/obr.12816]	
Total Diet & Meal Replacements (TDMR) Europe	Guideline	006	007 - 023	1.3 - The guideline points to dietary and weight management advice as part of the lifestyle recommendations that should be provided for type 2 diabetes management. It however gives very general recommendations (1.3.3 to 1.3.5) and points to NICE guidelines on obesity and weight management (1.3.10) for more specific advice. This is a missed opportunity to provide adequate weight management and dietary recommendations to manage type 2 diabetes and should be addressed.	Thank you for your comment. The section of the guideline covering dietary advice and bariatric surgery was not prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest existing recommendations needed amending. The surveillance team at NICE monitor whether guidelines are up to date. The surveillance process includes reacting to events at any time after guideline publication (for example, publication of a key study) as well as a standard check every 5 years. Stakeholders can help with this process by letting us know which parts of the guideline stakeholders believe out-of-date and why during scope consultations. As these are evidence-based guidelines it is useful if stakeholders can provide links to important evidence sources that they believe would necessitate an update of a particular area of the guideline. We can then pass these references onto the NICE surveillance team for evaluation and a decision about whether an update is justified.

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Total Diet & Meal Replacements (TDMR) Europe	Guideline	General	General	Total Diet & Meal Replacements (TDMR) Europe is the European trade body for manufacturers and distributors of total diet replacements (TDRs) and meal replacements (MRPs), which provide weight loss and weight management programmes for the overweight and obese. TDRs, which include very low-calorie diets (VLCDs) and low calorie diets (LCDs), are specifically formulated programmes that are based around formula foods that replace the whole of the daily diet. These formula foods are nutritionally balanced with key vitamins, minerals, high quality protein, essential fats, and fibre, and are designed to replace conventional foods for a period to facilitate optimal weight loss. MRPs are products presented as a replacement for one or more meals of the daily diet. They are used alongside conventional food, as part of an energy restricted diet, to facilitate and maintain weight loss. TDMR Europe fully supports the proposal to update and replace *NICE guideline NG28 on Type 2 diabetes in adults: management*. We are deeply concerned, however, by NICE's decision not to review the evidence on dietary and weight management advice as part of the update of the guideline. TDMR Europe believes that the exclusion of the latest scientific research on weight management advice, and particularly dietary advice, is a missed opportunity in the light of the strong link between obesity and overweight and type 2 diabetes and the scientific evidence pointing to the effectiveness of TDRs for weight loss and type 2 diabetes management and remission.	Thank you for your comment and support of the new guidance. As you have noted, the section of the guideline covering dietary advice and bariatric surgery was not prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest existing recommendations needed amending. The current committee did not review any evidence on this topic and are therefore unable to make any new recommendations. The surveillance team at NICE monitor whether guidelines are up to date. The surveillance process includes reacting to events at any time after guideline publication (for example, publication of a key study) as well as a standard check every 5 years. Stakeholders can help with this process by letting us know which parts of the guideline stakeholders believe out-of-date and why during scope consultations. As these are evidence-based guidelines it is useful if stakeholders can provide links to important evidence sources that they believe would necessitate an update of a particular area of the guideline. We can then pass these references onto the NICE surveillance team for evaluation and a decision about whether an update is justified.
Total Diet & Meal Replacements (TDMR) Europe	Guideline	General	General	TDMR Europe urges NICE to reconsider its decision not to update the dietary and weight management advice within this guideline, and then to consider the evidence for inclusion of TDRs and MRPs in the weight management recommendations for the management of type 2 diabetes in adults.	Thank you for your comment. Please see our responses to your earlier comments as well. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder

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					comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs.
Training, Research and Education for Nurses in Diabetes (TREND)	General	General	General	Please consider 'Language Matters' document 2018 stop using 'patient' and refer to the self management by '**people with diabetes'**	Thank you for your comment. We have reviewed the guideline and the use of the term 'patient' was confined to the section on patient education and the patient decision aid. (PDA). As requested, we have removed the word patient from the education section. However, we have retained this word for the PDA because it is the recognised name for these decision aids and changing the name would risk causing confusion among stakeholders that could lead to reduced use of the tool in shared decision making.
Training, Research and Education for Nurses in Diabetes (TREND)	General	General	General	This guideline is **out of date** before it is even launched. It has missed clinical evidence from 2009 on clinical benefits of GLP-1 RA which is unethical and lacks validity. Clinicians working in the speciality of diabetes care will discount the National Guidance in favour of the Global Guidance which aims to validate the use of GLP-Ras both clinically and cost effectively. The health economic modelling is flawed. It is folly to exclude glucose reduction and weight reduction benefits of GLP-1 Ras for people with T2DM	Thank you for your comment. The original scope of the update to the drug treatment sections of NG28 was to fully update the treatment section of the guideline as your comment notes. However, once work on the topic commenced it was determined that updating evidence reviews and health economics for such a wide scope, within the resources available to NICE for this topic, would take an unacceptably lengthy period. Taking such an approach for this guideline update would have further delayed publication of updated treatment recommendations in this rapidly changing area. In view of the timescales involved and the appetite from the committee and stakeholders for an update within an acceptable time period, we worked with our committee members to identify the priority areas for this update. The committee members agreed that our initial focus should be on reviewing the evidence from trials looking at cardiovascular outcomes. This reflected the changing evidence base as a result of the significant investment in clinical trials to directly capture cardiovascular outcomes,

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					feedback from stakeholders that assessing this evidence was a priority and the impact that this new evidence could have on recommendations for the treatment of people with diabetes. We therefore revised the scope to reflect this and carried out the current piece of work. Whilst the economic model does not contain every outcome that could potentially be of interest for modelling adults with type 2 diabetes, the committee agreed that the outcomes included were the most important outcomes for assessing the additional cardiovascular and other benefits associated with drug treatment for type 2 diabetes, for the majority of the type 2 diabetes population. The committee agreed the cardiovascular outcome trials were the most appropriate data source to assess cardiovascular benefits of these drugs, being powered to specifically detect differences in hard outcomes, rather than only surrogate outcomes. The committee noted these studies were not representative of the full population of people with type 2 diabetes, but agreed this was a lesser limitation than the need to extrapolate from surrogate endpoints to cardiovascular outcomes, particularly given the findings from those studies suggesting these surrogate extrapolations are often not very robust. They also agreed that taking data on weight and hypoglycaemic events from these cardiovascular outcome trials was the most appropriate approach, in order to match the data used for cardiovascular event rates. For changes in weight, it was noted it was important not to double count the impact of changes, as the effects on cardiovascular outcomes should already be captured in the outcomes of those trials. It was therefore agreed that the most appropriate approach was to only include the direct quality of life gains associated with reductions in weight, with the other benefits captured through the cardiovascular event data. The committee noted that if anything the approach taken in

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					the guideline may overestimate the benefits of weight reduction, as some of the estimated quality of life gains may be the result of avoided cardiovascular events, but it was agreed to be the best data source available. There are of course other benefits that could have been considered as part of the modelling, including renal (or other microvascular) outcomes, or additional benefits directly related to improved glycaemic control, but the committee considered these to be of lower priority than those included in the model. They also noted that it would not be appropriate for any modelling approach to simply look at benefits on different outcomes from different trials or data sources, and assume those benefits are additive, and therefore increase the cost-effectiveness of drugs when included together. They noted that in many circumstances these benefits are not additive, and which benefits are likely to be realised may depend on the individual characteristics of the people included in studies. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand.

Type 2 diabetes in adults: management (update)

Consultation on draft guideline - Stakeholder comments table
01/09/2021 – 14/10/2021

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Training, Research and Education for Nurses in Diabetes (TREND)	Guideline	004	003	Point 1.1 - Individualised care – good point	Thank you for your comment.
Training, Research and Education for Nurses in Diabetes (TREND)	Guideline	009	008	Like the addition of figure 1 for people living with diabetes	Thank you for your comment.
Training, Research and Education for Nurses in Diabetes (TREND)	Guideline	013	014	1.7 - Consideration for SGLT2 in ASCVD / HFin line with ADA - Good	Thank you for your comment and support of these recommendations.
Training, Research and Education for Nurses in Diabetes (TREND)	Guideline	016	001	1.7.10 - Would have been good to add where Pio, DPPVs and SUs are not appropriate	Thank you for your comment. This recommendation details alternative treatments if metformin is contraindicated or not tolerated. This recommendation was retained unaltered from the 2015 version of the guideline. The committee wanted to keep the pathway as simple as possible, and they agreed that it would not be possible to do this if alternative options were provided every time a drug was not contradicted or not tolerated. However, they agreed that it was appropriate to have recommendations for metformin being contradicted or not tolerated because this is the drug that the majority of people would take as first-line therapy.

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Training, Research and Education for Nurses in Diabetes (TREND)	Guideline	018		Vis Sum 2 - Would like to see GLP-1s included	Thank you for your comment. GLP-1 mimetics are not a first line treatment option and are included in the visual summary for where further interventions are needed.
Training, Research and Education for Nurses in Diabetes (TREND)	Guideline	021	015	1.7.17 - The outdated step-wise intro of meds leads to clinical inertia	Thank you for your comment. The committee agreed that it is good clinical practice (except in emergencies) to introduce new drugs separately to assess the effectiveness and tolerability of each drug. It is unclear how else you would establish the effectiveness or problems with each component of therapy if they are not started in a step-wise fashion. This is aimed at reducing the risk of clinical inertia delaying the introduction of further drug treatments.
Training, Research and Education for Nurses in Diabetes (TREND)	Guideline	022	021	1.7.22 - Introduces a GLP-1 RA only if triple therapy is unsuccessful- it should be started much earlier – why wait for CVD to take hold **Do not** recommend that GLP1s are not used until the BMI is > 35	Thank you for your comment. The committee reviewed the stakeholder comments regarding the use of GLP-1 mimetics and examined the updated economic evidence relating to GLP-1 mimetic treatment for people with type 2 diabetes and high cardiovascular risk. In the NICE health economic analyses, when looking at GLP-1 mimetics as a class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of

					£20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the intervention as an effective use of NHS resources will specifically take account of the following factors." and • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis." Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within

					class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors. In addition, the committee noted that there were differences in the clinical effectiveness of the 2 forms of semaglutide. Although the acquisition costs for injectable and oral semaglutide are similar they showed marked differences in cost-effectiveness in the economic analyses. This was caused by differences in the effect estimates for stroke, myocardial infarction and severe hypoglycaemia. From earlier discussions about the clinical evidence (see the discussion sections in the evidence review for more details) the committee had agreed that it was uncertain whether the observed differences in effect on all-cause mortality compared to placebo between the 2 forms of semaglutide were real and they therefore decided not to place undue weight on them. They had also noted that this uncertainty and any other differences in effects between the drugs for other outcomes was probably due to wide 95% confidence intervals for many outcomes with these drugs, due to the smaller numbers of participants and events in the trials compared to other CVOTs. Due to the higher level of uncertainty surrounding the cost-effectiveness of the GLP-1 mimetics as a class compared to the SGLT2 inhibitors, the committee considered whether to recommend injectable semaglutide for people at high cardiovascular risk in whom an SGLT2 is contraindicated or not tolerated. However, taking into account the uncertainty in the cost-effectiveness and clinical effectiveness the

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					committee decided against recommending injectable semaglutide for this population. In the absence of the GLP-1s being cost-effective treatments for people with high CV risk or established cardiovascular disease, the existing 2015 recommendations for when to use GLP-1s were retained. These apply to the general population of people with type 2 diabetes. Since no new non- cardiovascular outcome trial evidence regarding the benefits of GLP-1s was included in this review the committee were unable to amend or rewrite the 2015 criteria for GLP-1 use in this current update. When these recommendations were made in 2015 these criteria were used because of the lack of cost-effectiveness of this treatment for most people.
Training, Research and Education for Nurses in Diabetes (TREND)	Guideline	023	005	1.7.23 - Even though said in 2015 – In the present age need to get rid of this: "Only continue GLP-1 mimetic therapy if the adult with type 2 6 diabetes has had a beneficial metabolic response (a reduction of at 7 least 11 mmol/mol [1.0%] in HbA1c **and** weight loss of at least 3% 8 of initial body weight in 6 months)". [2015) Goes against Global clinical guidance	Thank you for your comment. The recommendations covering triple therapy with GLP-1 was not updated as part of the current work. The committee are unable to make any changes to this recommendation because although this recommendation was within the scope of the update the evidence included in the review was judged only to be generalisable to people who were at high risk of developing cardiovascular disease or who had established cardiovascular disease. Consultation recommendation 1.7.23 does not apply to the high cardiovascular risk population and therefore the committee did not amend it. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted.

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					This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand.
Training, Research and Education for Nurses in Diabetes (TREND)	Guideline	024	General	Visual Sum 3 - Outdated regarding GLP-RAs	Thank you for your comment.
Training, Research and Education for Nurses in Diabetes (TREND)	Guideline	025	General	Visual Sum 4 - Info on SGLT2 confusing when related to renal impairment – needs to be specific This table is repeated on P 25	Thank you for your comment. We have now provided this information specific for individual medicines rather than medicine classes.
Training, Research and Education for Nurses in Diabetes (TREND)	Guideline	027 - 028	025 +	1.7.28 - Bullet 3 – "Consider, as an alternative to NPH insulin, using insulin detemir or insulin glargine" why not state Degludec here too. Saves cost of DN visit to administer BD doses	Thank you for your comment. The section of the guideline covering insulin-based treatment was not within the scope of this update. The committee did not review any evidence on this topic and were therefore unable to make the requested changes. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the

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					size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs..
UK Clinical Pharmacy Association (UKCPA)	Guideline	004	004	Rec 1.1.1 If you are going to include figure 1 in the body of the text, it might be best placed here (rather on page 10).	Thank you for your comment. We have decided to keep the visual analogue scale (figure 1) with the recommendations on blood glucose targets so that it is physically close to the recommendations to which it most closely relates. We hope this will be of most help to users of the guideline.
UK Clinical Pharmacy Association (UKCPA)	Guideline	006	007	1.3 We are concerned that this section of the guidance has not been updated to include remission. We appreciate that this is not a section highlighted for comment however with NHS England supporting the roll-out of remission programs we wanted to highlight our concern that this is not going to be supported by any recommendations from NICE.	Thank you for your comment. The section of the guideline covering dietary advice and bariatric surgery was not prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest existing recommendations needed amending. The surveillance team at NICE monitor whether guidelines are up to date. The surveillance process includes reacting to events at any time after guideline publication (for example, publication of a key study) as well as a standard check every 5 years. Stakeholders can help with this process by letting us know which parts of the guideline stakeholders believe out-of-date and why during scope consultations. As these are evidence-based guidelines it is useful if stakeholders can provide links to important evidence sources that they believe would necessitate an update of a particular area of the guideline. We can then pass these references onto the NICE surveillance team for evaluation and a decision about whether an update is justified.
UK Clinical Pharmacy Association (UKCPA)	Guideline	008	004	1.5.1 We are concerned that antiplatelet therapy has not been reviewed. Given the burden of cardiovascular disease on morbidity and mortality in people living with diabetes we had hoped this review would have looked at the new evidence and updated the recommendations accordingly.	Thank you for your comment. The section of the guideline covering antiplatelet therapy was not prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest existing recommendations needed amending. The surveillance team at NICE monitor whether guidelines are up to date. The surveillance process includes reacting to events at any time after guideline publication (for example,

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					publication of a key study) as well as a standard check every 5 years. Stakeholders can help with this process by letting us know which parts of the guideline stakeholders believe out-of-date and why during scope consultations. As these are evidence-based guidelines it is useful if stakeholders can provide links to important evidence sources that they believe would necessitate an update of a particular area of the guideline. We can then pass these references onto the NICE surveillance team for evaluation and a decision about whether an update is justified.
UK Clinical Pharmacy Association (UKCPA)	Guideline	009	006	We are concerned that Appendix A is not fit for purpose – in our opinion its length is unlikely to work in a clinical setting. It would not be suitable for those with low literacy or those with language barriers. Previous NICE guidance had a summary for patients on benefits vs risks of the different agents for glucose lowering. Could this document have a brief table summarising risks versus benefits for each agent? First sentence in the document states' if you have type 2 diabetes, you will have higher levels of glucose (sugar) in your blood.' This assumes that all people with T2DM have high glucose levels which is not the case. Should the words 'you will' be changed to 'you may'? Fifth bullet point down states 'taking a statin to manage your cholesterol if it is high'. The term 'high' is subjective. Could this statement be changed to be more reflective of the way we manage cardiovascular risk for example 'taking a statin' if relevant, to manage your cholesterol and reduce your cardiovascular risk. In addition, we now have a number of medications to reduce cardiovascular risk/cholesterol, not only statins. Last paragraph states that 'the lower you want to keep your blood glucose level, the more medicines you are likely to take. This also means that you are more likely to get side effects'. This statement could be seen as negative – it could be read that you will get side effects the more	Thank you for your comments. Both PDA and visual analogue scale (VAS) are tools that can be used if appropriate, neither is mandatory. During the clinical encounter the discussion can focus on the VAS. If the healthcare professional and person with diabetes do not want to go through the PDA during the consultation, it can be provided to support shared decision making either before or after the consultation, in line with the NICE guideline on shared decision making (NG197). The Flesch-Kincaid reading ease score suggests it will be understandable by people with a reading age of 11-13. This is in line with the NICE PDA standards. Information on the different blood glucose lowering drugs is now included in the guideline visual summary which can be used alongside the PDA. We have amended the sentence about blood glucose levels in people with type 2 diabetes and the reference to lipid management following your comment. The risk of side effects increases with increased numbers of medicines. It is one factor among many that needs to be considered. The first sentence you quote has been amended to say 'Aiming for a lower blood glucose target may mean

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				medicines you take, which is not necessarily the case. This could impact on both acceptance of additional medications and adherence of existing medications. Please can the language be used in this statement be reviewed?	you have to take more medicines'. As in the consultation version, the PDA balances that statement that taking more medicines may increase the risk of side effects by saying 'But not everyone will get side effects and they may not trouble you if they do happen. It is usually possible to change your medicines to ones that suit you better.' The committee considers this is fair, balanced and accurate.
UK Clinical Pharmacy Association (UKCPA)	Guideline	009	006	In addition, some people will have lower blood glucose levels through dietary interventions and minimal medications. The statement 'the lower you want to keep your blood glucose level, the more medicines you are likely to take' is not strictly true for all	Thank you for your comment. We have amended the PDA to say 'Aiming for a lower blood glucose target may mean you have to take more medicines'.
UK Clinical Pharmacy Association (UKCPA)	Guideline	009	007	Rec 1.6.5 – we felt that inclusion of some numerical values might help benchmark what you mean by 'a lower HbA1c target' and a 'higher HbA1c target' In other guidelines such as the ADA Standards of Care despite them using similar terms, qualification was made in other parts of the guidance with numerical targets. This will help a clinician balance the risk of hypoglycaemia vs. risk of sub optimal blood glucose control. If not this could lead to variation in care as people interpret their own target HbA1c levels- see examples of local guidance in the following links which have adapted the ADA target HbA1c diagram and ended up with different numerical values: https://www.hey.nhs.uk/wp/wp-content/uploads/2018/05/TYPE-2-DIABETES-HbA1c-TARGETS-v4-March-2018.pdf and https://www.hounslowccg.nhs.uk/media/116623/Diabetes-Individualising-HbA1c.pdf	Thank you for your comments. The starting point is the targets given in recommendations 1.6.7 and 1.6.8. The aim of the PDA is to support an individualised discussion between the healthcare professional and person with diabetes. The committee felt that putting specific target values in the PDA or visual analogue scale could be too restrictive and counter-productive to the aim of support shared decision making. They emphasised the need for dialogue that is tailored to the person's individual circumstances, preferences, goals and values.
UK Clinical Pharmacy Association (UKCPA)	Guideline	010		Figure 1 - We have concerns regarding this decision aid. Although we believe it is useful to highlight when to approach tighter glycaemic control with caution, we do feel that the questions being asked in this decision aid push everyone to less stringent control. We would ask this is reviewed. The two questions in particular that are an issue are 'I do not want to take any more medicines' 'I do not want side effects from medicines', We believe most people would probably say they feel they do not want any more medicines and that they do not want side effects.	Thank you for your comment. The figure is intended as a basis for discussion between the healthcare professional and the person with diabetes. Moreover, the choices are not binary but the visual analogue scale (VAS) enables the person to indicate the extent to which they agree with either statement. We agree that most people would wish to avoid side effects and not take unnecessary medicines. However, we hope that putting these considerations alongside others, such as life expectancy, will encourage discussions between the healthcare professional and person with diabetes to

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					support informed decision making and a better shared understanding of the issues at play. We have amended the PDA to highlight that the person needs to consider the relative importance of all the factors in the VAS and also consider if other things that are important to them.
UK Clinical Pharmacy Association (UKCPA)	Guideline	013	020	We would recommend that visual summary 1,2 and 3 are all combined into one algorithm. Visual summary 4 should be removed as it is likely to be out of date quickly and we don't believe it is value adding above what people could find in the BNF.	Thank you for your comment. We have combined the visual summaries. The approach to pulling together guideline recommendations in a visual form is a proof of concept. We will be continually reviewing our processes and will be updating the table based on changes to recommendations and following feedback from stakeholders and users.
UK Clinical Pharmacy Association (UKCPA)	Guideline	014	008	We are concerned throughout this guidance that renal protection is ignored. Should renal protection be added in here as well as cardiovascular protection (with reference to the appropriate guidance)? We understand that duplication avoidance is at play however holistic care demands that we consider these things as a collective.	Thank you for your comment. Following committee discussion of stakeholder comments the recommendation on choosing drug treatments has been amended to include consideration of cardiovascular and renal protection (third bullet). The renal benefits of using SGLT2 inhibitors in people with type 2 diabetes and CKD have been assessed in a separate piece of work that has recently been out for stakeholder consultation and was published in November 2021. The final recommendations on renal and cardiovascular benefits will be brought together in a single updated guideline document when this current work on cardiovascular benefits is published in 2022.
UK Clinical Pharmacy Association (UKCPA)	Guideline	014	013 - 014	We are concerned that the recommended 'lowest acquisition cost' SGLT2 is ertugliflozin with no compelling CV data	Thank you for your comment. We agree that the decision to prescribe a particular drug should not include consideration of treatment acquisition costs alone and it is for this reason that recommendation 1.7. 1 covers multiple factors to take into account when choosing drug treatments. These include the individual's clinical needs as well as their needs and preferences, monitoring licensing and safety issues. The point about lowest acquisition cost is intentionally the last bullet point and is only relevant if 2 drugs within the same class are appropriate having taken all the earlier points into account. This point not meant to be taken in isolation. The

					contents of this recommendation and the recommendation on reviewing treatments are intended to support personalised care by ensuring that the choice of drug is tailored to individual needs and circumstances. The committee reviewed the stakeholder comments but decided to continue treating SGLT2 inhibitors (SGLT2i) as a class for the following reasons: o There was a degree of uncertainty around whether there were real differences in cardiovascular (CV) benefits between the SGLT2i based on the clinical trial evidence and results from the NMAs. o Firstly, for hospitalisation for heart failure, the SGLT2i empagliflozin, canagliflozin, and dapagliflozin produced a clinically meaningful reduction compared with placebo in the random effects NMA model. However, in the sensitivity analyses using a fixed effect model ertugliflozin also showed a clinically meaningful reduction compared to placebo, which reflects the original clinical trial data. The NMA results could not differentiate between the SGLT2i for this outcome. o Secondly, for the 3 point MACE outcome, only canagliflozin and empagliflozin produced a statistically significant reduction compared to placebo but the SGLT2i could not be differentiated from each other in the NMA. o Thirdly for all cause and CV mortality empagliflozin showed a clinically meaningful reduction compared to placebo and the other SGLT2i, but the remaining SGLT2i could not be differentiated from each other or placebo in the NMA. o Fourthly, for non-fatal MI and non-fatal stroke the NMAs could not differentiate between empagliflozin, canagliflozin, ertugliflozin and placebo. The data for dapagliflozin was

					○ reported differently and could not be included in the NMAs. From the clinical trial data dapagliflozin could not be differentiated from placebo for MI and was not meaningfully different from placebo for stroke. ○ Finally, only dapagliflozin showed a clinically meaningful improvement in severe hypoglycaemia compared to placebo but the remaining SGLT2i could not be differentiated from each other and placebo in the NMA. ○ There was also a degree of uncertainty around the cost-effectiveness of individual SGLT2i in the economic modelling. Although only dapagliflozin was cost-effective at a threshold of £20,000/quality-adjusted life year (QALY) across all model scenarios and CV risk groups it could not be differentiated from the other SGLT2i in the NMA apart from for the all-cause and CV mortality outcomes where it was clinically meaningfully worse than empagliflozin. The ranking of ICERs for the other SGLT2i varied across model scenarios and risk groups. The committee agreed that there was sufficient uncertainty in the economic modelling (caused in turn by uncertainty in the underlying clinical data) to mean that they were not sufficiently confident that these different ICERs represented true underlying differences in cost-effectiveness, as opposed to simply random variation in the results between different SGLT2 trials. ○ Taking the cost-effectiveness and clinical results into account the committee decided against only recommending dapagliflozin and instead made recommendations for the SGLT2i as a class. However, they recognised that there was a greater degree of uncertainty around the CV benefit associated with ertugliflozin because, depending on the choice of model used in the NMA, it did not consistently show a clinically meaningful reduction in hospitalisation for heart failure compared to placebo, unlike empagliflozin, canagliflozin and dapagliflozin. It was also not statistically

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					significantly better than placebo for the 3-point MACE outcome unlike canagliflozin and empagliflozin. The committee therefore recommended SGLT2i with proven CV benefit because this wording would enable the prescribers to select a particular drug from within the SGLT2 class if they thought this was clinically justified based on the individual characteristics of their patient, whilst future proofing the recommendation should additional evidence or new SGLT2s be made available. As per the recommendation on choosing drug treatment, once the clinical circumstances and needs of the person with type 2 diabetes, including their need for CV protection, have been taken into account, if 2 drugs in the same class are suitable for that individual then the prescriber is still expected to choose the option with the lowest acquisition cost to help use NHS resources wisely. Please see evidence review A for more a more detailed explanation of the analyses that were carried out and the committee's discussion of the results.
UK Clinical Pharmacy Association (UKCPA)	Guideline	014	029	1.7.4 - the term 'congestive' heart failure is out of date. Consider just saying 'heart failure' or 'chronic heart failure as per NICE NG 106	Thank you for your comment. The committee discussed the stakeholder comments about the use of the term 'congestive' heart failure. They agreed that it would be inappropriate to change this to say symptomatic chronic heart failure with reduced ejection fraction because people with heart failure are a larger group of people than those with heart failure with reduced ejection fraction. In addition, the recommendations deliberately cover people with type 2 diabetes and heart failure to match the clinical and economic evidence. Based on stakeholder requests the committee decided to change congestive heart failure to chronic heart failure. This change was made because this term refers to the same population of people with heart failure as congestive heart failure does and it was thought that the

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					wider medical society will understand this term better because it is in wider use currently.
UK Clinical Pharmacy Association (UKCPA)	Guideline	015	001	1.7.4 - Please consider defining atherosclerotic disease. This may help people pick up under recognised high-risk cardiovascular disease states e.g. peripheral arterial disease	Thank you for your comment. The committee have now provided a definition of ASCVD in the Terms used in the guideline section. This definition includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, previous coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.
UK Clinical Pharmacy Association (UKCPA)	Guideline	015	010	1.7.5 - we would ask that the committee consider adding in that this should be done sequentially here (it appears further down and may be missed) and potentially to be very explicit about titrating metformin to maximum tolerated dose and to add in SGLT2 despite HbA1c/Blood glucose readings.	Thank you for your comment. Following stakeholder comments the committee have reworded this recommendation to emphasise the need introduce the SGLT2 inhibitor without delay once metformin is tolerated. This is aimed at reducing the risk of clinical inertia delaying the introduction of the SGLT2.
UK Clinical Pharmacy Association (UKCPA)	Guideline	015	011	There is concern over such a large inclusion criterion for dual therapy and cost implications/ prioritisation of the highest risk people. We would ask if the committee could consider revisiting this and defining e.g. very high risk and high-risk categories to try to enable primary care to take a structured approach to review. The DECLARE TIMI and CANVAS criteria may help with this. You could also consider looking at the EASD/ESC guidelines which define high/very high risk.	Thank you for your comment. The committee noted that the evidence showed cost-effectiveness of the SGLT2 inhibitors in the high risk and established cardiovascular disease populations modelled by the NICE economic model (please see the Evidence review document). The committee declined to amend the recommendations to cover very high risk and high-risk categories because they agreed that both groups should have access to the SGLT2s based on the results of the clinical and economic modelling. NICE is undertaking a resource impact assessment of the draft recommendations in preparation for finalisation of the guideline update. This includes consideration of the sizes of the populations that would be covered by the SGLT2 inhibitor recommendations for people with established cardiovascular disease (CVD) and high risk of CVD. The committee have access to this document and do take

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					resource impact into account when finalising the recommendations. The committee agreed that the use of SGLT2 inhibitors for people with established CVD or those at high risk of developing CVD would be costly and could lead to the implementation challenges you have highlighted. However, they agreed that since these drugs are clinically and cost-effective for this population in terms of CV protective benefits it is worth recommending them and facilitating work to overcome implementation challenges by providing a resource impact assessment tool. This document will be made available on the guideline website to help local and national commissioning bodies with their decision making. In addition, SGLT2s are already being used in this population in some areas based on other national or international guidance and so the resource impact may be less than anticipated. In the economic model, high CV risk populations were defined by either looking at the baseline characteristics, or by looking at their history of CV disease. The EASD guideline does define a very high risk population, but one of the conditions defining this is the condition of other target organ damage which we we are unable to identify in our baseline population (except for the eGFR condition). We have however included a combined High CV risk population which combined both the primary and secondary high CV risk populations (defined in section 3.1 in the economic report)
UK Clinical Pharmacy Association (UKCPA)	Guideline	016	010	1.7.11 – if Repaglinide is to be included still, we are concerned that the wording on this is confusing and would recommend that it is reworded to say 'Repaglinide is licenced as monotherapy or as dual therapy but only in combination with metformin'.	Thank you for your comment. Based upon stakeholder comments this recommendation regarding Repaglinide, is being stood down because stakeholder agreed that this treatment was not widely used in current practice.
UK Clinical Pharmacy	Guideline	016	016 - 019	The wider use of SGLT-2 inhibitors is supported, however, we would like to ensure that NICE highlights safety in this wide-ranging population of	Thank you for your comment. The committee were aware that the aim of very-low carbohydrate and ketogenic diets is

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Association (UKCPA)				eligible people living with type 2 diabetes. We recognise the risk of DKA associated with SGLT-2 inhibitors, however, the committee appears to be focused on low carbohydrate and ketogenic diets only. Low reserve of insulin secreting cells, low BMI or ketosis-prone diabetes should be considered (i.e., significant clinical features of insulin deficiency where we would not use an SGLT-2 inhibitor). Is there any reason why some risk factors have been chosen over others? Is there scope to add a prescribing decision aid around the SGLT-2i specifically focusing on risks versus benefits to highlight cohorts where benefits outweigh risks?	to replace dietary carbohydrate with fat with the specific intention of inducing a ketotic state. In people with type 2 diabetes taking an SGLT2 inhibitor (SGLT2i) this may increase the risk of diabetic ketoacidosis (DKA). DKA is a rare, but serious, complication in type 2 diabetes. The committee highlighted this risk because the SGLT2 inhibitors are comparatively new drugs and, in the committees' view, clinical experience with them is low in primary care in some areas, but the new recommendations are expected to greatly increase their use in this setting. Additionally, the summary of product characteristics (SmPC) for SGLT2i advise caution in people with restricted food intake in relation to ketosis. However, taking stakeholder comments into account, the committee have revised the wording to better reflect the need to check whether the individual would be at an increased risk of DKA if they take an SGLT2i rather than causative effect of such diets. They also included mention of several risk factors for DKA as examples, including the use of very-low carbohydrate and ketogenic diets. The list is not meant to be exhaustive but to highlight some risk factors that the committee thought were particularly important for prescribers to be aware of. The committee made an additional recommendation to highlight to the clinician that they should try to address any modifiable risk factors before starting SGLT2i treatment. This guideline already has a series of visual summaries to help the clinician with their prescribing decisions and with following the recommendations. It also has a PDA around blood glucose targets. Unfortunately, we are unable to provide additional decision support aids.
UK Clinical Pharmacy Association (UKCPA)	Guideline	016	020 – 023	The importance of checking for pregnancy or planning pregnancy is welcomed however this should not only be for SGLT-2 inhibitors alone, it should be included as a separate point and a routine question for type 2 diabetes **and** when prescribing any medication.	Thank you for your comment. The committee have included a link under the recommendation on choosing drug treatments to refer to the NICE guideline on Diabetes in pregnancy.

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UK Clinical Pharmacy Association (UKCPA)	Guideline	016	025	We note the importance of specific side effects with SGLT-2 inhibitors however would recommend adding in side effects linked to the three MHRA alerts currently published for SGLT-2 inhibitors: risk of DKA, fournier's gangrene and amputations. These are currently hidden on page 28, row 19 as a generic statement. If listing a side effect such as fluid volume depletion, we would welcome the advice that the patient should be counselled to ensure adequate hydration whilst taking SGLT-2 inhibitors and further details on renal parameters that would indicate cessation of therapy for example	Thank you for your comment. The committee agreed that expanding the safety recommendations to cover all the points suggested by stakeholders was unfeasible and was inappropriate because the guideline is the not intended to cover all the safety advice that should be taken into account when prescribing drug treatments and some of the suggested safety events were quite rare. In order to keep the guideline as simple and easy to follow as possible, the committee rewrote the safety recommendations to focus on some key points relating to the safety of SGLT2 inhibitors because they are not widely used in practice yet in some areas, and in particular may be unfamiliar to many clinicians in primary care, and the new recommendations will greatly increase the number of people who are eligible to take them. They removed some of the safety information that was in the consultation version of the guideline where it was not specific to SGLT2s, was not thought to be useful by stakeholders or was thought to be widely known. The committee agreed that prescribers are expected to consult MHRA alerts, the BNF and summary of product characteristics (SPC) for more comprehensive safety information. This is highlighted in the recommendation on choosing drug treatments which includes safety as one of the factors to take into account. The committee discussed the stakeholder comments about the renal impact of SGLT2 inhibitors (SGLT2i). They agreed that the existing recommendation was unclear and potentially confusing because it gave no indication of the frequency or when the monitoring should take place. They also recognised that although SGT2i can have a negative effect on renal function this is usually a small reduction in function and not a reason to stop taking the SGLT2i. Taking

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					these points into account the committee have now removed this draft recommendation. The committee declined to add information to the patient advice recommendation about ensuring adequate hydration because they would need to define what this what this meant and the amount of liquid a person needed to consume to be adequately hydrated would vary between individuals, depending on their clinical circumstances.
UK Clinical Pharmacy Association (UKCPA)	Guideline	016	027	1.7.13 - We would ask that you consider being explicit on monitoring. https://kdigo.org/wp-content/uploads/2020/10/KDIGO-2020-Diabetes-in-CKD-GL.pdf and https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf may help pull something cohesive together. Once explicit monitoring requirements are established, ensure these align with NICE SGLT2i in CKD guidance	Thank you for your comment. The committee discussed the stakeholder comments about the renal impact of SGLT2 inhibitors (SGLT2i. They agreed that the existing recommendation was unclear and potentially confusing because it gave no indication of the frequently or when the monitoring should take place. They also recognised that although SGT2i can have a negative effect on renal function this is usually a small reduction in function and not a reason to stop taking the SGLT2i. Taking these points into account the committee have now removed this draft recommendation.
UK Clinical Pharmacy Association (UKCPA)	Guideline	017	001 – 003	1.7.13 - We are concerned over the amount of cross referencing. This has to be a usable document.	Thank you for your comment. These cross references have been removed and a single cross reference to the section on CKD is included at the start of the initial treatment section on the guideline instead.
UK Clinical Pharmacy Association (UKCPA)	Guideline	017	006	1.7.14 - We are concerned that particularly in a primary care environment some of these terms may be misunderstood. Very low carb and ketogenic should be defined. There are additional lifestyle factors that could increase the risk of DKA e.g., drugs and alcohol. It would also be helpful to include the importance of hydration to prevent dehydration given the mechanism of action of these drugs.	Thank you for your comment. We have added a definition of very low carb and ketogenic diet to the terms used in this guideline. Following stakeholder comments at consultation the committee have amended the wording of the recommendation on things to check before starting the SGLT2 inhibitor to focus on whether the person is at increased risk of diabetic ketoacidosis (DKA) if they take an SGLT2 inhibitor. They have included some examples that, in the committee's view, could lead to increased risk, but this is not meant to be an exhaustive list. This is noted in the

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					rationale that accompanies the recommendation.The committee agreed that prescribers should consult the summary of product characteristics for further information. The committee made an additional recommendation to highlight to the clinician that they should try to address any modifiable risk factors before starting SGLT2i treatment. The committee declined to add information to the patient advice recommendation about ensuring adequate hydration because they would need to define what this what this meant and the amount of liquid a person needed to consume to be adequately hydrated would vary between individuals, depending on their clinical circumstances.
UK Clinical Pharmacy Association (UKCPA)	Guideline	017	008	1.7.14 - We would ask that the committee considers saying rather than 'to avoid DKA' perhaps 'to reduce risk of DKA' we feel this is more appropriate given the evidence	Thank you for your comment. The committee have amended the draft recommendation to 'Advise adults with type 2 diabetes who are taking an SGLT2 inhibitor about the need to minimise their risk of DKA by not starting a very low carbohydrate or ketogenic diet without discussing it with their healthcare professional, because they may need to suspend SGLT2 inhibitor treatment.'
UK Clinical Pharmacy Association (UKCPA)	Guideline	017	010	We welcome the addition of sick day rules for SGLT-2 inhibitors. Could these be expanded e.g. to include metformin, when to re-start, additional information regarding stopping for surgery – see 3.-Covid-19-Type-2-Sick-Day-Rules-Crib-Sheet-06042020.pdf (england.nhs.uk)	Thank you for your comment. The recommendation which included sick day rules was reviewed following stakeholder comments and the bullet point on sick day rules has now been removed as the committee agreed it would be inconsistent to present this information for one class of drugs but not any others.. They expected that sick day rules and other safety related advice would be discussed with the individual with type 2 diabetes as part of the decision-making process regarding drug choice and wanted to keep the guidance as simple and clear as possible. We have therefore been unable to include the additional information you suggested.

Consultation on draft guideline - Stakeholder comments table
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UK Clinical Pharmacy Association (UKCPA)	Guideline	017	012	Visual Summary 1 – we are concerned that any consideration of renal benefit has been excluded. We feel strongly that renal should be included in this document so people can start thinking holistically. First bullet point discusses person's individual clinical circumstances, preference and needs. Could bullet point 4 be incorporated given that the persons cardiovascular risk and status would be a clinical circumstance. If so, the first bullet point could read 'the person's individual clinical circumstances (including cardiovascular disease [CVD] risk and status) and their preferences and needs Should the last bullet point 'check adherence to diet and lifestyle' be the first bullet point given diet and lifestyle is the cornerstone of T2DM management We would suggest that the bullet point starting with 'stop medicines that have not worked or not tolerated' state 'check adherence and stop medicines that have not worked or are not tolerated'. If medicines have not worked as people are not taking them, we need to review medication adherence rather than stopping the medication and taking it out of future options due to being ineffective. We would then suggest the bullet point below starting with Optimise…. Given that adherence has already been covered in the bullet point above. We are also concerned about the comment 'think about switching…' as we need to be careful to highlight that benefit may be beyond glycaemia.	Thank you for your comment. The visual summaries have now been grouped together and a link to the CKD recommendations has been added to the visual summary. Thank you for your comment. The committee have reworded the recommendation on reviewing drug treatments following stakeholder consultation to make their intentions clearer. However, it decided not to amend the order of the bullets as the entire recommendation should be read before beginning to act on the points included in it. We have updated the bullets so they are more aligned with the guideline recommendations and have moved diet and lifestyle advice to the top as a separate box.
UK Clinical Pharmacy Association (UKCPA)	Guideline	018	001	We are concerned that this is not a usable algorithm at this time. We feel strongly that one algorithm should be produced for treatment. We felt that it may look like 1st line treatment is DPP4 etc due to placement of title. Colours are poor for visibility. Re-enforcing lifestyle, diet and the need for structured education would benefit from being included at each stage. The sequential adding of sglt2s may be missed. There is a line at the top which says to assess renal function as part of your initial assessment and then it is ignored through the rest of the algorithm. Bottom left hand side box, SLGT2 needs to be changed to SGLT2 Bottom left hand side box states The Guideline update recommends SGLT2i use in wider population than technology appraisals published before August 2021. Does this statement mean that all previous TA's are now superseded? However the guideline links to the TA's. This could be	Thank you for your comment. The approach to pulling together guideline recommendations in a visual form is a proof of concept. We will be continually reviewing our processes and will be updating the visual summaries based on changes to recommendations and following feedback from stakeholders and users. Treatment options are listed alphabetically and the choice of treatment should be based on the patients' values and preferences and clinical factors. We opted to keep the visual summaries for first line treatment and treatment if further interventions are needed separate because they would never apply to the same person at the same point in time. At the time of consultation, the CKD recommendations were not available. We have

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				made clearer. If this guideline accepts wider use, should the original TA's be superseded?	now linked to these from the visual summaries. The typo has been amended. The technology appraisals still apply for people who are not at a high risk of CVD, we have altered the visual to show that the TAs apply to the non-CV risk pathway.
UK Clinical Pharmacy Association (UKCPA)	Guideline	019	001	Visual summary 4 comes before 3	Thank you for your comment. This was intentional but the visual summaries have now been combined following feedback from users.
UK Clinical Pharmacy Association (UKCPA)	Guideline	019	001	Visual summary 4 – we are concerned this algorithm will be out of date very quickly and there is nothing here that cannot be found in the BNF and SPC as needed. There also inaccuracies and given people may use this as their sole resource of information, this is concerning. The table may be more useful if it incorporates a traffic light system, perhaps as a quick reference/overview e.g. dose and we would welcome a section being added to this table to highlight key side effects - this is partly been added for the MHRA alerts for SGLT-2i however not consistent for all e.g. MHRA alert is missing - GLP-1 receptor agonists: reports of diabetic ketoacidosis when concomitant insulin was rapidly reduced or discontinued - GOV.UK (www.gov.uk). Side effects such as risk of worsening retinopathy for those on insulin and existing retinopathy when starting semaglutide are key prescribing points to consider. Having some information that is missing or incorrect is a concern as some prescribers may use this table as a sole resource In renal impairment the DPP4 linagliptin needs no dose adjustment for renal impairment and a number of GLP-1 agonists can be used down to eGFR 15ml/min. Please elaborate how the combination with insulin impairs hypoglycaemic response; was this meant to say that individuals are at more at risk of hypoglycaemia in the presence of renal impairment? SGLT2 needs more specifics on hepatic impairment Consider adding that with sulphonylureas, short acting agents in this class would be preferred in renal impairment. What differentiated hypo risk for SUs as moderate vs. insulin high risk? Sulphonylureas can have severe hypoglycaemia and this can be of long duration and can require hospitalisation. A more useful visual summary that takes into account	Thank you for your comment. The approach to pulling together guideline recommendations in a visual form is a proof of concept. We will be continually reviewing our processes and will be updating the table based on changes to recommendations and following feedback from stakeholders and users. MHRA warnings have been removed as we would expect prescribers to consult the MHRA, BNF, and SPCs before prescribing. This contraindication, renal and hepatic content in the table has been updated for specific medicines rather than for medicine classes.

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				cardiovascular and renal effects for each drug class would be more useful such as that produced by ADA, S101 https://care.diabetesjournals.org/content/diacare/suppl/2019/12/20/43.Supplement_1.DC1/Standards_of_Care_2020.pdf **Contraindications** - For all drugs listed in the table, looking at the SPC's and BNF often the only contra-indication is hypersensitivity to the ingredients only. In reality we know that there are clinical contra-indications and some have been listed, however, others haven't e.g. pancreatitis is missing from GLP-1 analogues and DPP-4 inhibitors. Would it be appropriate to title this section contra-indications and cautions for use and add in further information? Information on use in pregnancy and breast feeding are also missing from this table. We would ask that this section is updated and made more comprehensive. Having some information that is missing or incorrect is a concern as some prescribers may use this table as a sole resource **Renal Impairment** – in addition to the inaccuracies already discussed above compatibility in dialysis or end stage renal disease is missing for all. We would ask that this table is updated in line with the licensing documents. Having some information that is missing or incorrect is a concern as some prescribers may use this table as a sole resource. Sulfonylureas – under this section, it states to avoid where possible if severe. A number of the summary of product characteristic documents (www.medicines.org.uk) state that they are contra-indicated in severe renal impairment, rather than 'avoid where possible' e.g. glimepiride Glimepiride 1 mg Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) and gliclazide - Diamicron 80mg Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) Please can this section be reviewed. Having some information that is missing or incorrect is a concern as some prescribers may use this table as a sole resource. Metformin- please could this section be updated with the dose adjustments that need to be made when eGFR is between 30-45ml/min which are outlined in the SPC - Glucophage 500 mg film coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) Please can this section be reviewed. Having some information that is	

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				missing or incorrect is a concern as some prescribers may use this table as a sole resource. **Hepatic Impairment** DPP-4 inhibitors – the information in the table is misleading as there are differences between the DDP-4 inhibitors. For example linagliptin states no dose adjustments needed, however, clinical experience is lacking in hepatic impairment - Trajenta 5 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk), sitagliptin states no dose adjustment mild-moderate and in severe, care to be exercised as studies on severe hepatic impairment are lacking JANUVIA 100mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk). Vildagliptin states not to be used in hepatic impairment - Galvus 50 mg Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk). Please can this section be reviewed. Having some information that is missing or incorrect is a concern as some prescribers may use this table as a sole resource GLP-1 analogues – this section states that there are no warnings on use of GLP-1 analogues in hepatic impairment. Please can this section be updated as this statement is not correct – for example for liraglutide, no dose adjustment is required for mild to moderate impairment, however, it is not recommended for severe impairment - Victoza 6 mg/ml solution for injection in pre-filled pen - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk), semaglutide – no dose adjustment in mild to moderate hepatic impairment, limited experience in severe therefore caution in use - Ozempic 1 mg solution for injection in pre-filled pen - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk), dulaglutide – no dose adjustment - TRULICITY 1.5 mg solution for injection in pre-filled pen - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) Please can this section be reviewed. Having some information that is missing or incorrect is a concern as some prescribers may use this table as a sole resource. Sulfonylureas – under this section, it states to avoid if severe. A number of the summary of product characteristic documents (www.medicines.org.uk) state that they are contra-indicated in severe hepatic impairment, rather than 'avoid where possible' e.g. glimepiride Glimepiride 1 mg Tablets -	

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				Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) and gliclazide - Diamicron 80mg Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) Please can this section be reviewed. Having some information that is missing or incorrect is a concern as some prescribers may use this table as a sole resource Metformin – the glucophage SPC states that metformin is contra-indicated in hepatic insufficiency - Glucophage 500 mg film coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk). SGLT-2i – the document states that caution is needed in severe hepatic impairment. The advice in the SPCs differ for example in dapagliflozin, it states it can be used with dose adjustments - Forxiga 10 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk). However in empagliflozin and canagliflozin it states not recommended Jardiance 10 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk), Invokana 100 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) Please can this section be reviewed. Having some information that is missing or incorrect is a concern. Some prescribers may use this table as a sole resource SGLT-2i – we welcome that the MHRA warnings on DKA and genital infections are noted here. The MHRA warning on lower limb amputations - SGLT2 inhibitors: updated advice on increased risk of lower-limb amputation (mainly toes) - GOV.UK (www.gov.uk) is not listed however is still a live MRA alert. We recognise that there is conflicting evidence around this. By omitting the MHRA alert, are NICE stating that this is no longer a concern and clinicians and patients do not need to discuss?	
UK Clinical Pharmacy Association (UKCPA)	Guideline	020	001	Reviewing drug treatments – at each review of T2DM, adherence to lifestyle and diet interventions should be assessed given that these interventions work synergistically with medications. We would ask that lifestyle and diet are added into the sections e.g., in line 6, could it state 'how to optimise their current treatment regimen (including non-pharmacological management)	Thank you for your comment. The committee added a reference to revisiting advice about diet and lifestyle to the reviewing recommendation in response to your request. The committee agreed that it is important to revisit advice about diet and lifestyle because part of this discussion is to ensure the person is supported with both non-pharmacological and pharmacological interventions to improve their current health and prognosis.

Consultation on draft guideline - Stakeholder comments table
01/09/2021 – 14/10/2021

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UK Clinical Pharmacy Association (UKCPA)	Guideline	020	005	We would suggest that the bullet point starting with 'stopping medicines that have not worked or not tolerated' state 'check adherence and stop medicines that have not worked or are not tolerated'. If medicines have not worked as people are not taking them, we need to review medication adherence rather than stopping the medication and taking it out of future options due to being ineffective. We would then suggest removing 'adherence to existing medication' in the bullet point below given that adherence has already been covered in the bullet point above	Thank you for your comment. The committee have reworded the recommendation on reviewing drug treatments following stakeholder consultation to bring the points about optimising current treatment regimens, including checking adherence, to the top. They decided against making your suggested changes as they agreed that checking adherence was a key component to facilitate optimising the current regimen. The point about stopping medicines is now directly below this one.
UK Clinical Pharmacy Association (UKCPA)	Guideline	021	017	1.7.18 we are concerned that 'monotherapy' is not the correct word when most people will be on dual therapy if following the guidance by this point	Thank you for your comment. Although people with established cardiovascular disease or a high risk of developing cardiovascular disease will probably be taking dual therapy by this stage, some people will still be assessed as lower risk and be taking monotherapy (or may have declined dual therapy). The draft recommendation on adding further treatment applies to this population. There is another draft recommendation that covers additional treatment options for people who already on more than one drug.
UK Clinical Pharmacy Association (UKCPA)	Guideline	021	019	1.7.18 We are concerned about the introduction of a new term 'individually agreed threshold'. We are concerned that this is not a term that makes sense in the context of this guideline given that earlier in the guideline you have set a threshold of 58mmol/mol for escalation from monotherapy. No guidance has been given on what this threshold is in relation to individualised targets.	Thank you for your comment. The term 'individually agreed threshold' has been retained from the 2015 version of this guideline. The section of the guideline covering targets was not within the scope of this update and the committee are therefore unable to change this terminology. However, the new update does contain a PDA to help with setting personalised targets.
UK Clinical Pharmacy Association (UKCPA)	Guideline	022	019	1.7.21 The evidence shows vascular protection with GLP-1RA therapy and therefore the statement 1.7.21 can be misleading. While we do not advocate GLP-1RA use solely for vascular protection, agents in this class should be considered in those with inadequate glycaemic control and high cardiovascular risk in the absence of contraindications.	Thank you for your comment. The committee have taken stakeholder comments into account and agreed to remove the recommendation about not using GLP1-mimetic therapy solely for cardiovascular risk reduction in people with type 2 diabetes. Upon reviewing the recommendation, the committee agreed that it was inappropriate to make a decision about treatment choice based solely on a single factor (cardiovascular risk) and that, as detailed in the

					recommendation on choosing drug treatments, multiple factors should be taken into account instead. The committee reviewed the stakeholder comments regarding the use of GLP-1 mimetics and examined the updated economic evidence relating to GLP-1 mimetic treatment for people with type 2 diabetes and high cardiovascular risk. In the NICE health economic analyses, when looking at GLP-1 mimetics as a class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of £20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the intervention as an effective use of NHS resources will specifically take account of the following factors." and • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending

					a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis." Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors. In addition, the committee noted that there were differences in the clinical effectiveness of the 2 forms of semaglutide. Although the acquisition costs for injectable and oral semaglutide are similar they showed marked differences in cost-effectiveness in the economic analyses. This was

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					caused by differences in the effect estimates for stroke, myocardial infarction and severe hypoglycaemia. From earlier discussions about the clinical evidence (see the discussion sections in the evidence review for more details) the committee had agreed that it was uncertain whether the observed differences in effect on all-cause mortality compared to placebo between the 2 forms of semaglutide were real and they therefore decided not to place undue weight on them. They had also noted that this uncertainty and any other differences in effects between the drugs for other outcomes was probably due to wide 95% confidence intervals for many outcomes with these drugs, due to the smaller numbers of participants and events in the trials compared to other CVOTs. Due to the higher level of uncertainty surrounding the cost-effectiveness of the GLP-1 mimetics as a class compared to the SGLT2 inhibitors, the committee considered whether to recommend injectable semaglutide for people at high cardiovascular risk in whom an SGLT2 is contraindicated or not tolerated. However, taking into account the uncertainty in the cost-effectiveness and clinical effectiveness the committee decided against recommending injectable semaglutide for this population.
UK Clinical Pharmacy Association (UKCPA)	Guideline	023	013	We are concerned that visual summary 1 has been included again. Is this supposed to be in the document twice?	Thank you for your comment. This was intentional but the visual summaries have now been combined following feedback from users.
UK Clinical Pharmacy Association (UKCPA)	Guideline	024	General	Visual summary 3. We are concerned that this is not fit for purpose at this time. No differentiation is made to medications that have CV risk vs. CV safe. Repeating the list of Tas for SGLT2s for dual and triple therapy is cumbersome and adds to confusion. Also why are two of the Tas listed in the insulin box? If the patient is not at high CVD risk and on metformin only, you would move on to the disease progression flow chart. It is not clear which combinations NICE are recommending without clicking into each of the TA documents. In the previous algorithm, the language used for SGLT-2i is 'offer' and 'consider'. In the metformin monotherapy	Thank you for your comment. The approach to pulling together guideline recommendations in a visual form is a proof of concept. We will be continually reviewing our processes and will be updating the visual summaries based on changes to recommendations and following feedback from stakeholders and users.

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				scenario for those not at high CVD risk, the language reverts back to a TA and uses the words 'may be an option'. For this cohort, are NICE stating that we should be using a DPP-4i, pioglitazone or sulfonylurea over a SGLT-2i and follow the TA's for SGLT-2i? The flow charts could be clearer. The algorithm is less clear on use of triple oral therapies and beyond. The disease progression flow chart may be better set out as a flow chart cascading downwards rather than sideways. **It would be more helpful if options were detailed as first, second and third line options/intensification as per previous guidance**. Insulin is mentioned as an option to 'consider' when dual therapy has not controlled HbA1c. What about as third or fourth line? The algorithm suggests insulin should only be considered when dual therapy has not achieved the persons individualised target. Please can insulin be detailed in the algorithm as per the narrative on pages 26-28 The bottom box states 'switch or add treatments from different drug classes up to triple therapy (dual therapy if metformin contra-indicated). Is the guidance stating that quadruple therapy (triple oral plus GLP-1 analogue) is not recommended? If so, please state this Bottom box states The Guideline update recommends SGLT2i use in wider population than technology appraisals published before August 2021. Does this statement mean that all previous TA's are now superseded? However the guideline links to the TA's. This is confusing. Could this be made clearer? If this guideline accept wider use, should the original TA's not be superseded? Technology Appraisal for empagliflozin for dual therapy and triple therapy should read (and link to) TA336 and not 366. The different SGLT-2i are listed in different orders, should this be consistent i.e. alphabetically, in order of TA number, or other? Dapagliflozin TA 418 does not include insulin. Empagliflozin (TA 336) does include insulin, however, is not listed as an option here. Please can this section be reviewed to ensure the correct options are listed	Dapagliflozin TA288 does include insulin and has been linked in this section. Empagliflozin has now also been listed as an option with insulin. The visual summary reflects the guideline recommendations in that people would be offered a DPP4, pioglitazone, or a sulfonylurea second line. The Tas are included as they are options for some people. We have opted to link to the Tas rather than write out the TA recommendations to keep the summary clear and to one side of A4. We are not recommending that DPP4s, pioglitazone, and sulfonylureas are used in preference to SGLT2s. Where the TA recommendations apply, these should be considered as part of shared decision making alongside the other options. The purpose of the visual summaries is to summarise the recommendations in the drug treatment section of the guideline. If prescribers opted to try three oral medicines before insulin and it did not work, we would assume that they would then try insulin. We feel this does not need to be stated in the visual as we did not receive any other stakeholder comments about this. The GLP mimetic recommendation states that triple therapy, including a GLP-mimetic should be used and this has been reflected in the visual summary. The word 'antidiabetic' has been removed from the visual summaries.

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				The term 'antidiabetic' drugs is used. Given the NHS England language matters document, please could this language be reviewed. Given the evidence for cardiovascular risk reduction, should these agents not be classified as third line for those with existing CVD and those at high risk of CVD?	
UK Clinical Pharmacy Association (UKCPA)	Guideline	024	General	We are concerned that you do seem to have included the circumstance of 'straight to insulin' in your algorithm	Thank you for your comment. Rescue therapy for symptomatic hyperglycaemia has been moved to the top of the visual summaries.
UK Clinical Pharmacy Association (UKCPA)	Guideline	024	General	It should be highlighted that in some circumstances SGLT2 may be continued even when their glucose lowering effect is marginal e.g. HF, CKD.	Thank you for your comment. Wording has been added to the prescribing guidance to make it clear that SGLT2s may be continued in these circumstances.
UK Clinical Pharmacy Association (UKCPA)	Guideline	027	025	1.7.28 consider adding something in about insulin biosimilars or most cost effective choices	Thank you for your comment. The section of the guideline covering insulin-based treatments was not prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest existing recommendations needed amending. However, we have been able to add recommendations covering the points you have raised to this section. These were drafted as part of the diabetes type 1 update on this topic but were judged to be equally relevant to this guideline.
UK Clinical Pharmacy Association (UKCPA)	Guideline	029	002	We are concerned that the section on gastroparesis covers an extremely niche area of practice and that this section may be out of date with its drug recommendations. If we are going to look at all connecting co-morbidities should we be including other complications e.g. peripheral neuropathy, dental care etc.	Thank you for your comment. The section of the guideline covering managing complications was not prioritised at the scoping stage as no evidence was identified in the surveillance review to suggest existing recommendations needed amending.
UK Clinical Pharmacy Association (UKCPA)	Guideline	033	001	We are concerned about the use of the word 'clinical judgement' but then it appears to be well defined. Does this need further judgement?	Thank you for your comment. The committee have agreed that this did not require further explanation as it is, as stated in the comment, well defined.
UK Clinical Pharmacy Association (UKCPA)	Guideline	034	009	What do you mean by long term outcomes?	Thank you for your comment. The research recommendation covering long-term outcomes associated with blood glucose lowering agents has been reviewed by the committee and has been stood down. The committee believe that the

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					longer-term outcomes (cardiovascular benefits) have been established by the CV outcome trials included in this update.
UK Clinical Pharmacy Association (UKCPA)	Guideline	034	013	We would like the committee to consider if meglitinides should feature in a research recommendation when they are so infrequently used in practice.	Thank you for your comment. The recommendation covering long-term outcomes associated with blood glucose lowering agents has been reviewed by the committee and has been stood down. The committee believe that the longer-term outcomes (cardiovascular benefits) have been established by the CV outcome trials included in this update. Additionally, the committee were aware that meglitinides are now infrequently used (when compared to 2015 when the research recommendation was initially made).
UK Clinical Pharmacy Association (UKCPA)	Guideline	037	015 - 017	We also felt that the possibility of wrong diagnosis should be first on the list of things to explore if someone has presented with a DKA on these medications.	Thank you for your comment. While the committee agree that misdiagnosis might occur the scope of the guideline is for adults with confirmed diagnosis of type 2 diabetes.
UK Clinical Pharmacy Association (UKCPA)	Guideline	038	005	We feel that the monitoring needs clear guidance. We are concerned that primary care will not know how to make this decision. L/S BP needs to be added in addition to renal function especially if they are co-commitment diuretics.	Thank you for your comment. The committee discussed the stakeholder comments about the renal impact of SGLT2 inhibitors (SGLT2i). They agreed that the existing recommendation was unclear and potentially confusing because it gave no indication of the frequently or when the monitoring should take place. They also recognised that although SGT2i can have a negative effect on renal function this is usually a small reduction in function and not a reason to stop taking the SGLT2i. Taking these points into account the committee have now removed this draft recommendation.
UK Clinical Pharmacy Association (UKCPA)	Guideline	042	008 - 015	We are very concerned that the full metabolic benefits of GLP-1 therapy has not been captured, given the narrow focus on part of their effect. There is a great need for a full review of GLP-1 mimetics, which would capture glycaemic and other metabolic benefits. We would appreciate the committee also ensuring there is no confusion given some of these medications can be used for weight loss alone e.g. saxenda and ensure any technology appraisals align. The guidance doesn't address the needs of those with diabetes (including when HbA1c at/near target) and severe obesity and who are in tier 3 obesity service and heading towards consideration for bariatric surgery. Access to GLP-1 treatment, including	Thank you for your comment. 1. You are correct that the model does not contain every outcome that could potentially be of interest for modelling adults with type 2 diabetes. However, the committee agreed these were the most important outcomes for assessing the additional cardiovascular and other benefits associated with drug treatment for type 2 diabetes, for the majority of the type 2 diabetes population. The committee agreed the cardiovascular outcome trials were the most appropriate data source to assess cardiovascular benefits of these

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				the higher doses of GLP-1 should probably be more readily available i.e. not having to have fulfilled the criteria of "triple therapy with metformin + 2 others ineffective, not tolerated or contra-indicated" …. Where for example if these individuals had pre-diabetes they would be eligible (i.e. NICE guidance for Saxenda). In the ADA/EASD consensus statement they have a pathway for those with a compelling need for weight reduction.	drugs, being powered to specifically detect differences in hard outcomes, rather than only surrogate outcomes. The committee noted these studies were not representative of the full population of people with type 2 diabetes but agreed this was a lesser limitation than the need to extrapolate from surrogate endpoints to cardiovascular outcomes, particularly given the findings from those studies suggesting these surrogate extrapolations are often not very robust. They also agreed that taking data on weight and hypoglycaemic events from these cardiovascular outcome trials was the most appropriate approach, in order to match the data used for cardiovascular event rates. For hypoglycaemic events, the approach taken is broadly in line with that taken in many other evaluations in diabetes, attaching costs and quality of life outcomes to the incidence of severe hypoglycaemic events, as these are the ones that make the most difference to a person's life. For changes in weight, it was noted it was important not to double count the impact of changes, as the effects on cardiovascular outcomes should already be captured in the outcomes of those trials. It was therefore agreed that the most appropriate approach was to only include the direct quality of life gains associated with reductions in weight, with the other benefits captured through the cardiovascular event data. The committee noted that if anything the approach taken in the guideline may overestimate the benefits of weight reduction, as some of the estimated quality of life gains may be the result of avoided cardiovascular events, but it was agreed to be the best data source available. There are of course other benefits that could have been considered as part of the modelling, including renal (or other microvascular) outcomes, or additional benefits directly related to improved glycaemic control, but the committee considered these to be of lower priority than those included in the model. They also noted that it would not be

					appropriate for any modelling approach to simply look at benefits on different outcomes from different trials or data sources, and assume those benefits are additive, and therefore increase the cost-effectiveness of drugs when included together. They noted that in many circumstances these benefits are not additive, and which benefits are likely to be realised may depend on the individual characteristics of the people included in studies. As an example, in the separate evaluation of SGLT2 inhibitors for people with CKD and type 2 diabetes, SGLT2 inhibitors were found to significantly improve renal outcomes, but this is a population in which a large benefit would not be expected for glycaemic control (hence why these agents were not originally licensed for use in people with impaired renal function). It should also be noted that it is not the case that only additional outcomes beneficial to drug therapy were excluded from the modelling. As an example, adverse events related to drug treatment (excluding hypoglycaemia) were not included as part of the analysis. As a number of the analyses in the guideline explicitly compare the addition of new treatments (for example, using 3 drugs versus 2) rather than simply switching drugs, it would be expected that inclusion of adverse events would decrease the cost-effectiveness for any additional treatments, as they would add to the adverse event burden. Therefore, whilst it is likely there would be differences found in the results of the cost-effectiveness analysis were a different set of outcomes to be included, it is not clear in which direction the results would change for any given agent, and whether they would become more or less cost-effective. 2. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder

					comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand. 3. The scope of this update only included evidence for cardiovascular benefit of drug treatments used in the management of type 2 diabetes (see the Evidence review document for details). The only identified CV outcome trial evidence for Liraglutide was from the LEADER trial which used a dose up to 1.8 mg per day. Higher doses of Liraglutide up to 3 mg per day can be prescribed as an adjunct in weight management but no cardiovascular outcome trial evidence was found for the higher daily dose, which also does not currently have a licensed indication for type 2 diabetes management, and so no recommendation for use of a higher dose could be made by the committee. Appropriate cross-referencing to all applicable technology appraisals has been made in the guideline. 4. The NICE guideline has a separate section, which was out-of-scope for this update, on dietary advice and bariatric surgery (section 1.3 of the Guideline document). This contains a link to the NICE guideline on Obesity: identification, assessment and management which contains recommendations for use of Pharmacological interventions in obesity. 5. The committee were aware of the ADA guidance, but their decisions were made according to the NICE guideline manual and took into account the evidence relevant to our review question. Although the NICE guidance may differ to the guidance provided by ADA, the committee were confident that their recommendations reflected the evidence

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					they reviewed and their clinical judgement. It is of particular importance to note that the NICE guideline used an original economic model as the basis to recommend the most clinically and cost-effective options while the ADA guidance did not systematically take cost-effectiveness into account.
UK Clinical Pharmacy Association (UKCPA)	Guideline	043	001 - 003	Was there no evidence for Insulin vs. GLP-1 already? If there is some evidence of comparisons, then why was economic modelling not possible? what cost would a GLP-1 have to be to come out cost effective?	Thank you for your comment. Please note that following stakeholder comments at consultation this research recommendation has been removed. The economic evaluation concentrated on comparing treatment reducing CV risks as reported by cardiovascular outcome trials. This is in line with the treatments considered in the evidence review, and insulin therapy alone was not one of these treatments. Furthermore, the economic analysis was designed to estimate the incremental cost per QALY gained at the list price of the drug, in line with NICE processes, and threshold analyses were not conducted to determine at which point any particular treatment would become cost-effective for a given parameter.
UK Clinical Pharmacy Association (UKCPA)	Guideline	045	015 - 020	We believe that a full review should be completed ASAP. There are many elements of this guideline that are not up to date and are not appropriately tying together as a result.	NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand.
UK Clinical Pharmacy	Questions on	General	General	Q1 - Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why.	Thank you for your comment and this information.

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Association (UKCPA)	comments form			*For places following the Portsmouth super six model of care, most people living with type 2 diabetes will be managed in a primary care setting. This guideline for most purposes will therefore be a primary care guideline.*	
UK Clinical Pharmacy Association (UKCPA)	Questions on comments form	General	General	Q2 - Would implementation of any of the draft recommendations have significant cost implications? *Yes. If populations eligible for SGLT2s are rigorously searched for and there is primary care staffing that will allow review and initiation this will be a large overspend.*	Thank you for your comment and this information.
UK Clinical Pharmacy Association (UKCPA)	Questions on comments form	General	General	Q3 - What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or examples of good practice.) *The main challenge of this document is going to be the fact that it does not represent expert practice. There are already localities that have adopted the ADA/EASD guidelines either in totality or in part. With the guidelines being so far removed from these, particularly in relation to the GLP-1 agonists and the failure to update so many facets of the guideline where current thinking has progressed, we are going to be left in a situation where a postcode lottery to best care will develop. We need these guidelines to be updated in full and for them to reflect current thinking and practice. We are very concerned that this has not happened.*	Thank you for your response. The committee were aware of the ADA guidance, but their decisions were made according to the NICE guideline manual and took into account the evidence relevant to our review question. Although the NICE guidance may differ to the guidance provided by ADA, the committee were confident that their recommendations reflected the evidence they reviewed and their clinical judgement. It is of particular importance to note that the NICE guideline used an original economic model as the basis to recommend the most clinically and cost-effective options while the ADA guidance did not systematically take cost-effectiveness into account. The committee are comprised of diabetes experts and in their opinion the recommendations for SGLT2s for people with high CV risk or establishd CVD are in line with current best practice. They recognised that ideally if the SGLT2 inhibitors were contraindicated or not tolerated that GLP-1s would be an alternative option for these people. However, these drugs were not cost-effrective as a class or individually for people in these CV risk groups and so the committe could not recommend them in this current update. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
					of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. In the meantime, the new recommendations for people with high CV risk, which have been amended based on stakeholder comments, will stand.
UK Clinical Pharmacy Association (UKCPA)	Questions on comments form	General	General	Q4 - Should the recommendation for treatment options for people with type 2 diabetes in whom metformin is contraindicated / not tolerated after treatment initiation be retained or stood down? We propose retaining the recommendations for treatment initiation for these people but standing down recommendation 1.7.20 covering later treatment options. Do you agree or disagree and why? *We think in general that a logical flow to recommendations needs to be developed to make this a more usable document.*	Thank you for your response. We have tried to simplify the recommendations and order them to give a logical flow. However, we recognise that some people may find it easier to work from our visual summary document.
UK Clinical Pharmacy Association (UKCPA)	Questions on comments form	General	General	Q5 - What do you think about the positioning of the visuals alongside the recommendations they summarise? Please explain your response. *We did not feel the visual summaries needed to be in the main body of the text. Most people in primary care will only use the visual summary and refer to main text if clarification is needed.*	Thank you for your comment. Based on stakeholder responses, and to test the proof of concept of integrating guideline recommendations into a visual summary, we have kept the visual summaries alongside the recommendations and as a separate PDF.
UK Clinical Pharmacy Association (UKCPA)	Questions on comments form	General	General	Q6 - Would the visual summaries in general help in your day-to-day practice? Please explain in your response how they would or would not help. *We did not find these visual summaries to be useful but an updated visual summary which covers everything on one side of A4 would be perfect and very useful for practice.*	Thank you for your comment. The approach to pulling together guideline recommendations in a visual form is a proof of concept. We will be continually reviewing our processes and will be updating the visual summaries based on changes to recommendations and following feedback from stakeholders and users. We realise that it would be useful to fit everything on one side of A4 but it was not possible to included all of the relevant information in a readable format. We have separated the visual summaries into 'first line treatment' and 'treatment options when further interventions are needed' to improve flow and readability.
UK Clinical Pharmacy	Questions on	General	General	Q7 - We have also included a pdf version of all the visuals within a single document. Is this pdf needed as well as the visuals included in the	Thank you for your comment. Based on consultation feedback, we have opted to keep the visuals in the guideline and as a separate PDF.

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Association (UKCPA)	comments form			guideline document? Please explain your response. *We would prefer to just have the pdf. See above*	
UK Clinical Pharmacy Association (UKCPA)	Questions on comments form	General	General	Q8 - Do you think the visual summaries could be improved or made more useful? Please explain your response. *Yes. We believe we have covered most of the issues with this in the main feedback. We would have expected to see something like the ADA/EASD algorithm.*	Thank you for your comment. The approach to pulling together guideline recommendations in a visual form is a proof of concept. We will be continually reviewing our processes and will be updating the visual summaries based on changes to recommendations and following feedback from stakeholders and users.
Wirral University Teaching Hospital NHS Foundation Trust	Guideline	019	General	Visual Summary 4 - The pathway is not patient focussed. It does not stratify which drugs to use for patients who have obesity, frail and which to avoid if they have heart failure or which can cause hypoglycaemia. It groups pioglitazone, DDPIV inhibitors and sulphonylurea into one box and does not give guidance what to use and when and what to watch out for.	Thank you for your comment. The committee agreed with the need to produce guidance to help promote personalised treatment. The original scope of the update to the drug treatment sections of the NG28 guideline was to fully update the treatment section of the guideline. However, once work on the topic commenced it was determined that updating evidence reviews and health economics for such a wide scope, within the resources available to NICE for this topic, would take an unacceptably lengthy period. Taking such an approach for this guideline update would have further delayed publication of updated treatment recommendations in this rapidly changing area. In view of the timescales involved and the appetite from the committee and stakeholders for an update within an acceptable time period, we worked with our committee members to identify the priority areas for this update. The committee members agreed that our initial focus should be on reviewing the evidence from trials looking at cardiovascular outcomes. This reflected the changing evidence base as a result of the significant investment in clinical trials to directly capture cardiovascular outcomes, feedback from stakeholders that assessing this evidence was a priority and the impact that this new evidence could have on recommendations for the treatment of people with diabetes. We therefore revised the scope to reflect this and carried out the current piece of work.

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Wirral University Teaching Hospital NHS Foundation Trust	Guideline	022	021	1.7.22 - The pathway mentions lower BMI values for Asians but does not give a value for GLP-1 analogue	Thank you for your comment. NICE has reviewed the stakeholder comments regarding the change of scope and the reduced evidence base that we have included for the current update of the type 2 diabetes treatment pathway. We maintain that the approach we took was appropriate given the time constraints and the high priority given to the work looking at cardiovascular benefits of drug treatments. However, taking the stakeholder comments into account we have decided that a fuller update of the drug treatment section of the guideline is warranted. This is expected to take some time to complete due to the size of the evidence base. Before development begins there will be a scoping exercise to ensure that we are able to meet stakeholder needs. We expect that the recommendation mentioned will be covered by this work.
Wirral University Teaching Hospital NHS Foundation Trust	Guideline	024 022	General	Visual Summary 3 - 1.7.22 - The pathway places GLP-1 analogues too low down. There is no recognition of the recent GLP-1 Cardiovascular Outcome Trials (CVOT) demonstrating improved outcomes and the role it plays in reducing cardiovascular events.	Thank you for your comment. The committee reviewed the stakeholder comments regarding the use of GLP-1 mimetics and examined the updated economic evidence relating to GLP-1 mimetic treatment for people with type 2 diabetes and high cardiovascular risk. In the NICE health economic analyses, when looking at GLP-1 mimetics as a class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of

					£20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the intervention as an effective use of NHS resources will specifically take account of the following factors." and • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis." Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within

					class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors. In addition, the committee noted that there were differences in the clinical effectiveness of the 2 forms of semaglutide. Although the acquisition costs for injectable and oral semaglutide are similar they showed marked differences in cost-effectiveness in the economic analyses. This was caused by differences in the effect estimates for stroke, myocardial infarction and severe hypoglycaemia. From earlier discussions about the clinical evidence (see the discussion sections in the evidence review for more details) the committee had agreed that it was uncertain whether the observed differences in effect on all-cause mortality compared to placebo between the 2 forms of semaglutide were real and they therefore decided not to place undue weight on them. They had also noted that this uncertainty and any other differences in effects between the drugs for other outcomes was probably due to wide 95% confidence intervals for many outcomes with these drugs, due to the smaller numbers of participants and events in the trials compared to other CVOTs. Due to the higher level of uncertainty surrounding the cost-effectiveness of the GLP-1 mimetics as a class compared to the SGLT2 inhibitors, the committee considered whether to recommend injectable semaglutide for people at high cardiovascular risk in whom an SGLT2 is contraindicated or not tolerated. However, taking into account the uncertainty in the cost-effectiveness and clinical effectiveness the

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
					committee decided against recommending injectable semaglutide for this population. In the absence of the GLP-1s being cost-effective treatments for people with high CV risk or established cardiovascular disease, the existing 2015 recommendations for when to use GLP-1s were retained.
Wirral University Teaching Hospital NHS Foundation Trust	Guideline	024	General	Visual Summary 3 - The majority of our Type 2 patients are overweight or obese. So why are medications that do not improve weight loss or actually causes weight loss recommended before GLP-1 analogues which do improve weight loss and improve cardiovascular outcomes	Thank you for your comment. The committee reviewed the stakeholder comments regarding the use of GLP-1 mimetics and examined the updated economic evidence relating to GLP-1 mimetic treatment for people with type 2 diabetes and high cardiovascular risk. In the NICE health economic analyses, when looking at GLP-1 mimetics as a class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of £20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the intervention as an effective use of NHS resources will specifically take account of the following factors." and • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of

					NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis." Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors.

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Wirral University Teaching Hospital NHS Foundation Trust	Guideline	024	General	Visual Summary 3 - Insulin treatment which has significant impact on the patients' lives and also not that effective at improving HbA1c in overweight and obese Type 2 patients are put ahead of GLP-1 analogues which do target obesity. GLP-1 analogue needs to be higher up than insulin. Guidance needs to be provided when to use insulin and what to watch out for.	Thank you for your comment. The committee reviewed the stakeholder comments regarding the use of GLP-1 mimetics and examined the updated economic evidence relating to GLP-1 mimetic treatment for people with type 2 diabetes and high cardiovascular risk. In the NICE health economic analyses, when looking at GLP-1 mimetics as a class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of £20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the intervention as an effective use of NHS resources will specifically take account of the following factors." and • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending

					a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis." Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors. In addition, the committee noted that there were differences in the clinical effectiveness of the 2 forms of semaglutide. Although the acquisition costs for injectable and oral semaglutide are similar they showed marked differences in

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Wirral University Teaching Hospital NHS	Guideline	024	General	Visual Summary 3 - The new oral GLP-1 analogue is not mentioned in the pathway	Thank you for your comment. The committee reviewed the stakeholder comments regarding the use of GLP-1 mimetics and examined the updated economic evidence relating to

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
Foundation Trust					GLP-1 mimetic treatment for people with type 2 diabetes and high cardiovascular risk. In the NICE health economic analyses, when looking at GLP-1 mimetics as a class, the results from the probabilistic sensitivity analysis showed that GLP-1 mimetics had a very low probability of being cost-effective. Hence the committee were unable to recommend them as a class of drugs for people with established cardiovascular disease or those with a high risk of developing cardiovascular disease. The committee considered the results specifically for injectable semaglutide because this GLP-1 mimetic was the closest to being cost-effective of the drugs within this class. In the base-case analysis, for the majority of results looking at SGLT2 inhibitors, and for injectable semaglutide, the ICERs (across a range of scenarios) fell in the range of £20,000-£30,000/QALY. When considering results in this range, the NICE guideline manual says the following: • "Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the intervention as an effective use of NHS resources will specifically take account of the following factors." and • "As the ICER of an intervention increases in the £20,000 to £30,000 range, an advisory body's judgement about its acceptability as an effective use of NHS resources should make explicit reference to the relevant factors considered above." One of the factors referenced by these two statements is "The degree of certainty around the ICER. In particular, advisory bodies will be more cautious about recommending a technology when they are less certain about the ICERs presented in the cost-effectiveness analysis." Having considered the results, the committee agreed they were more certain about the results for SGLT2 inhibitors

					(considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of cardiovascular mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared to the conclusions for SGLT2 inhibitors. Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 mimetics there was considerable within class variation. Whilst the committee did not think a priori that GLP1 inhibitors should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again to the findings for SGLT2 inhibitors. In addition, the committee noted that there were differences in the clinical effectiveness of the 2 forms of semaglutide. Although the acquisition costs for injectable and oral semaglutide are similar they showed marked differences in cost-effectiveness in the economic analyses. This was caused by differences in the effect estimates for stroke, myocardial infarction and severe hypoglycaemia. From earlier discussions about the clinical evidence (see the discussion sections in the evidence review for more details)

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					the committee had agreed that it was uncertain whether the observed differences in effect on all-cause mortality compared to placebo between the 2 forms of semaglutide were real and they therefore decided not to place undue weight on them. They had also noted that this uncertainty and any other differences in effects between the drugs for other outcomes was probably due to wide 95% confidence intervals for many outcomes with these drugs, due to the smaller numbers of participants and events in the trials compared to other CVOTs. Due to the higher level of uncertainty surrounding the cost-effectiveness of the GLP-1 mimetics as a class compared to the SGLT2 inhibitors, the committee considered whether to recommend injectable semaglutide for people at high cardiovascular risk in whom an SGLT2 is contraindicated or not tolerated. However, taking into account the uncertainty in the cost-effectiveness and clinical effectiveness the committee decided against recommending injectable semaglutide for this population. In the absence of the GLP-1s being cost-effective treatments for people with high CV risk or established cardiovascular disease, the existing 2015 recommendations for when to use GLP-1s were retained.

Organisation name – Stakeholder or respondent	Disclosure on tobacco funding / links	Comments
Action on Smoking and Health (ASH)	ASH does not have any current or past, direct or indirect links to, or receive funding from, the tobacco industry, except for nominal shareholdings in Imperial Brands and BAT for research purposes.	For information - no further action required.

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