NICE National Institute for Health and Care Excellence

Appendix B2: Stakeholder consultation

2019 surveillance of Type 2 diabetes in adults: management (2015)

Stakeholders were consulted on the surveillance proposal to update NICE guideline NG28 for 2 weeks. Consultation dates: 25 April 2019 to 8 May 2019

Themes from stakeholder comments

Overall, 39 stakeholders commented, and all agreed with the proposal to update the guideline. Several themes emerged from the comments received at consultation which are detailed below. Stakeholders highlighted concerns with the existing guideline relating to blood glucose lowering therapy, particularly in the need to consider clinical characteristics such as cardiovascular (CVD) and renal disease, and in dietary advice for the use of low carbohydrate and low calorie interventions. Additionally, stakeholders posited the need to update the section on managing complications to include periodontal disease management, specific recommendations for diabetic kidney disease, and to update the recommendations on eye disease.

Individualised care

Stakeholder feedback indicated the need for person-centred and personalised lifestyle management advice. Section 1.1 already covers individualised care and advice. The guideline will also be amended with the following standard text placed at the beginning of the recommendations section:

> 'People have the right to be involved in discussions and make informed decisions about their care, as described in your care. Making decisions using NICE guidelines explains how we use words to show the strength (or certainty) of our recommendations and has information about prescribing medicines (including off label use), professional guidelines, standards and laws (including on consent and mental capacity), and safeguarding.'

Comorbidities and frailty were highlighted as important issues in individualised care. Comorbidities, multimorbidity and the ability to benefit from long-term interventions because of reduced life expectancy are already covered in this section as part of an individualised approach. These factors will also be considered in the update of section 1.6 Blood glucose management.

Patient education

A review of the wording of the patient education recommendations was suggested to emphasise the importance of evidence-based online education. Although the new evidence identified for digital interventions is consistent with the evidenced-based principles set out in the existing guideline recommendations, this feedback on the wording will be considered in the update.

Motivational interviewing and mobile phone applications were also proposed for consideration. However, evidence submitted did not meet the surveillance inclusion criteria, and evidence identified in the surveillance review was inconclusive for these interventions.

Dietary advice

Many stakeholders proposed an update of the recommendations on dietary advice. The majority of comments concerned low carbohydrate, low calorie and very low calorie diet interventions. Total diet and meal replacement interventions were also suggested for inclusion. The proposed rationale was the need to move away from the perception of type 2 diabetes (T2D) as a progressive condition managed with either medicine or insulin, to one that is treatable and reversible through dietary intervention. Stakeholders highlighted the need for people living with T2D to receive more information on remission and dietary advice.

Evidence submitted was not eligible due to indirectness of population (relating to obesity without T2D, and to prevention not treatment), out of scope study designs, and studies published outside the surveillance search period. The joint American Diabetes Association (ADA) and European Association for the study of Diabetes (EASD) guideline Management of Hyperglycemia in Type 2 Diabetes (2018) was also cited as referring to low carbohydrate and low calorie diets. However, this guideline does not explicitly recommend these diets but states that 'advice should be given of the health benefits of weight loss and encouraged to engage in a programme of intensive lifestyle management, which may include food substitution'. NICE guideline NG28 already advises individualising recommendations for carbohydrate intake, and meal patterns, which could include low carbohydrate and low calorie diets.

Stakeholders also asserted that sufficient evidence was already available on the benefits of these diets to justify recommending them. However, the totality of evidence in this area is limited to short-term benefits of these interventions. It does not indicate that low carbohydrate diets are a superior approach to other strategies for weight loss and subsequent weight maintenance in the long-term. The surveillance impact statement is therefore retained; that the longer-term results of the DIRECT study (beyond 2 years), and other longer-term studies of low calorie and low carbohydrate diets are likely to be needed to establish any definite impact on the guideline. A joint working group of The Scientific Advisory Committee on Nutrition, NHS England and Diabetes UK, with input from the British Dental Association and Royal Colleges, is reviewing the evidence on low carbohydrate diets with publication expected in 2020. This will be tracked by the surveillance team and the results will be considered when available.

We will also pass the collective feedback in this area to the development team working on the update of the NICE guideline on obesity (CG189) as the main study identified in this area (DiRECT) fed into the decision to update NICE guideline CG189.

Blood glucose management

Self-monitoring of blood glucose

The inclusion of real time continuous glucose monitoring was proposed, based on the emergence of digital platforms and new clinical evidence. However, the studies submitted could not be included due to study designs being either out of scope or being published outside the surveillance search period. The new RCT evidence identified in the surveillance review supporting the use of continuous glucose monitoring for T2D is limited by the 6-month duration and no impact on the guideline is anticipated until the findings are substantiated by further longer-term studies.

Drug therapy

Glycaemic control and additional emerging CVD, renal outcomes

Many stakeholders agreed with the surveillance proposal to review the antidiabetic drug pathway with a focus on CVD, renal and other relevant clinical characteristics to ensure consideration of outcomes beyond glycaemia reduction alone. Some supporting studies were submitted and are now included in the evidence summary. Several additional studies were submitted which had already been considered in the 2018 NICE review of SGLT-2 inhibitors and GLP1 analogues. Other studies were outside the study design scope or search period of the surveillance review. The following specific points were raised, which will inform the proposed review of the antidiabetic drug pathway:

- The need to consider drug treatment to prevent renal complications, specifically
  - the CREDENCE study covering canagliflozin for renal protection. However, canagliflozin is covered by the technology appraisal TA390 Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes (May 2016). This information will be passed to the NICE TA team for consideration in reviewing this guidance.
  - DPP-4 inhibitors, particularly linagliptin, for patients with renal impairment. Linagliptin was highlighted with supporting evidence as the only DPP-4 inhibitor that does not require dose adjustment based on a patient's level of renal function. Renal outcomes are already proposed for consideration in the review of this section of the guideline, which will include the forthcoming results of the CAROLINA trial.
- Timing of treatment intensification. NICE guideline NG28 advises treatment escalation when HbA1c rises higher than 58 mmol/mol (>7.5%) until control is achieved. It was proposed that more information should be provided on the time a patient should spend at uncontrolled hyperglycaemia before treatment intensification, and this will be considered in the update.

- The risk-benefit profile of a medicine, rather than merely the safety and tolerability profile. The evidence base currently available may no longer support the recommendation of agents such as sulphonylureas, which can increase the risk of hypoglycaemia and weight gain and lack cardiovascular outcome trial data. This will be considered in the update.
- The distinction between individual and fixed combinations of GLP-1 analogues and basal insulin; stakeholders indicated that it is clinically important to distinguish these treatment options and provide guidance on each. This distinction will be considered in the update, including evidence identified in surveillance for fixed-ratio combinations of liraglutide and lixisenatide.
- For first and second intensification, semaglutide was highlighted as demonstrating cardiovascular benefit, superior glycaemia and weight reduction versus several comparators across the SUSTAIN clinical trial programme. This evidence has been added to the surveillance evidence summary and evidence for drugs in the GLP1 analogue class, including liraglutide and semaglutide, will be considered in update. The forthcoming results of the PIONEER 6 study will be considered following publication expected in late 2019.
- Class level comparisons between drug classes were highlighted as limited by differences within classes in terms of CVD outcomes, safety, tolerability and acquisition costs. This is already acknowledged in the surveillance review and will be highlighted for consideration in the update.
- The timing of withdrawal or switching between medications. Stakeholders highlighted the need for advice on when to withdraw or switch from ineffective medication, as well as when to initiate. However, no eligible evidence was submitted, and the research recommendation in this area remains valid.
- NICE guideline NG28 stipulates a body mass index (BMI) threshold of 35 kg/m^2 prior to being able to receive a GLP-1 analogue but stakeholder comments suggested that this is not evidence-based. The evidence submitted to support that GLP-1 analogues consistently reduce HbA1c and body weight regardless of baseline BMI was not within the scope or search period of the

surveillance review. However, since the feedback from stakeholders suggested the current recommendation may not be accurate this area will be considered in the update.

- The addition of a GLP-1 analogue to a basal insulin was proposed for inclusion as an option for people already on basal insulin who are not also on a GLP-1 analogue. However, the evidence submitted indicating safety and effectiveness was out of scope for the surveillance review. A further point was that, because most diabetes management takes place within primary care, the current recommendation to seek specialist advice when adding a GLP-1 analogue to basal insulin should be removed.
  In developing NICE guideline NG28, the committee agreed that to facilitate a flexible approach to enable access for individuals most likely to benefit, this combination should be available to people for whom obesity is a concern and only where other triple oral combinations are contraindicated or not effective. The guideline committee noted that there was a lack of evidence for combinations of GLP-1 mimetics and insulin, and therefore agreed that this option should only be offered in a specialist care setting. The surveillance review has not identified evidence to warrant a change to this position, but it will nevertheless be considered during the scoping of the update.
  Evidence supporting the use of GLP-1 analogues prior to initiating insulin therapy was submitted, demonstrating similar or greater reductions in HbA1c, greater weight loss and lower rates of hypoglycaemia compared to insulin. This was proposed as an option for patients who need greater glucose lowering benefit prior to insulin, in accordance with the ADA/EASD consensus statement. However, the evidence was not within the scope or search period of the surveillance review and no evidence was identified through the surveillance review to warrant an update in this area.
- The DUAL IX study was highlighted, which demonstrated safe use of IDegLira in combination with SGLT-2 inhibitors in insulin naïve patients. This study has been included in the surveillance review to inform the update decision.

- Stakeholders suggested that the guideline should clearly differentiate between available basal insulins, specifically taking into consideration those people at a higher risk of hypoglycaemia and prioritising a choice of insulin with a lower risk of hypoglycaemia in line with the ADA/EASD guideline. This is consistent with the surveillance review decision to review this area with consideration of key safety issues.

Managing complications

Diabetic kidney disease

It was also proposed that specific advice be provided for chronic kidney disease (CKD) as a complication of T2D as opposed to the existing cross reference to NICE's guideline on chronic kidney disease in adults. However, CKD and renal outcomes are already proposed for consideration in the review of the antidiabetic drug pathway. More specific advice for CKD in T2D will be considered for inclusion in NICE's guideline on chronic kidney disease in adults, which already includes advice for type 1 and 2 diabetes. A further comment proposed consideration of urinary albumin screening for cardiovascular risk, as opposed to impending end-stage renal disease. However, no evidence was submitted to support yearly screening for microalbuminuria in T2D.

Eye disease

Several points were raised about the surveillance proposal for managing eye disease in T2D:

- In updating the recommendations for diabetic retinopathy, specialist ophthalmic input was advised. This will be passed on to the developers for consideration in the update.

- Regarding the proposed withdrawal of recommendations on diabetic eye screening, it was suggested that the guideline still needs to emphasise the importance of regular screening. We will add in a cross referral to the NHS Diabetic Eye screening programme for ease of reference to this guidance.
- It was requested that data on the use of fibrates in addition to statins are reviewed in terms of the effects on diabetic retinopathy, based on evidence from Accord and FIELD studies, where fibrates were shown to reduce the rates of progression of retinopathy. However, these studies preceded the surveillance search period, but the NICE surveillance team is monitoring the ongoing Lowering Events in Nonproliferative Diabetic Retinopathy in Scotland study which also concerns fibrate use.
- It was highlighted that data is emerging about digital photographic and optical coherence tomography surveillance for certain patients who had already been referred to the diabetic eye clinics ('virtual clinics'). However, no evidence was submitted or identified in the surveillance review, and therefore this area will not be prioritised as part of the update.

Periodontal disease

Several stakeholders highlighted that periodontal disease has a bi-directional relationship with diabetes and that its effective management by the dental team has a role in prevention and treatment of diabetes.

Although the aetiology of diabetes is outside the scope of NICE guideline NG28, the NICE guideline on Dental recall will be considered for addition to the Type 2 diabetes pathway for information. This guideline highlights diabetes as a risk factor for developing dental disease. It also notes that 'People with diabetes (both type I and type II) are at increased risk of developing destructive periodontal disease. This may be due to an altered periodontal tissue response to plaque. Therefore, individuals with diabetes may need a more frequent dental recall. Inadequate plaque control and the presence of other risk factors will modify the recall interval further.'

This issue will be put forward for consideration for scoping discussions for NICE guidelines NG17 and NG28 as expert input is required to determine an appropriate way of highlighting oral health in people with diabetes.

Additional areas

Comments on several additional areas were submitted without supporting evidence by individual stakeholders and, in the absence of any evidence identified through surveillance, are not expected to impact on the guideline. These areas include:

- The effect of bariatric surgery on T2D with the resulting remission lasting up to 15 years. However, bariatric surgery is covered in NICE's guideline on Obesity which includes specific advice for T2D.
- In the section on antiplatelet therapy, the omission of drugs other than aspirin was considered to be too simplistic. For example, in a T2D patient with prior ischaemic stroke addition of dipyridamole retard to low dose aspirin or use of clopidogrel was proposed. However, recommendation 1.5.2 cross refers to NICE guidelines on cardiovascular disease and myocardial infarction for more detailed advice on antiplatelet therapy for primary and secondary prevention of CVD.
- The antihypertensive effect of SGLT-2 inhibitor therapy was highlighted as statistically significant and clinically relevant, warranting inclusion in the blood pressure management section. Although no evidence was identified, developers will be made aware of this point and the need to consider antihypertensive benefits of SGLT-2 inhibitors during the update.
- The inclusion of liver diseases as comorbidities of T2D, including Non-alcoholic steatohepatitis (NASH). However, liver disease is not a direct complication of T2D and is therefore not within the scope of the guideline. As there is a separate NICE guideline on Non-alcoholic fatty liver disease, which covers NASH, it will not be included in NG28. However, this related guideline will be added to the type 2 diabetes pathway for ease of reference.

Stakeholder consultation comments table

Consultation dates: 25 April 2019 to 8 May 2019

Do you agree with the proposal to update the guideline?			
Stakeholder	**Overall response**	**Comments**	**NICE response**
Surrey Downs CCG	Yes	No comments provided	Thank you for your response. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults.
NHS Leeds CCG	Yes	The algorithm for blood glucose lowering therapy should be updated so that the HbA1c targets for frail elderly reflect those in QOF. Also, evidence for individual drugs should reviewed to include recent cardiovascular outcome trials (CVOTs), with a view to providing separate guidance for patients with CVD.	Thank you for your comments. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults. The proposed review of the anti-diabetic drug pathway will consider age and frailty level, in addition to cardiovascular outcomes in the light of new evidence.
South Sefton Clinical Commissioning Group	Yes	No comments provided	Thank you.
British Dental Associaiton	Yes	No comments provided	Thank you.

Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees

Total Diet and Meal Replacements (TDMR) Europe	Yes	Total Diet and Meal Replacements (TDMR) Europe is the European trade body for manufacturers and distributors of formula diet products, including total diet replacement products (TDRs) and meal replacement products (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 aim to replace the whole of the daily diet. These formula foods are nutritionally balanced with key vitamins, minerals, high quality protein, essential fats, fibre and other nutrients, and are designed to replace conventional foods for a period to facilitate optimal weight loss. Meal replacements 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 guideline "*NG28 on Type 2 Diabetes in adults: management*", to keep it up to date with the latest available science and treatments for this condition. We are deeply concerned, however, by NICE's decision not to update section 1.3 of the guidelines regarding dietary advice. TDMR Europe believes that this would have been	Thank you for your comments. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults in several areas including blood glucose management, insulin therapy and management of complications. We retain our proposal not to update the guideline around very low calorie diets. Evidence submitted was not eligible due to indirectness of population (relating to obesity without T2D, and to prevention not treatment), out of scope study designs, and studies published outside the surveillance search period. The joint ADA and EASD guideline was also cited as referring to low carbohydrate and low calorie diets. However, this guideline does not explicitly recommend these diets but states that 'advice should be given of the health benefits of weight loss and encouraged to engage in a programme of intensive lifestyle management, which may include food substitution'. NICE guideline NG28 already advises individualising recommendations for carbohydrate intake, and meal patterns. This encompasses a range of interventions, which may include low carbohydrate and low calorie diets. The 2 year results of the DIRECT trial were included in the surveillance review. However, longer-term results of the DIRECT study (beyond 2 years), and other longer-term studies of low calorie and low carbohydrate diets are likely to be needed to establish any definite impact on the guideline. A joint working group of The Scientific Advisory Committee on Nutrition, NHS England and Diabetes UK, with input from the British Dental Association and Royal Colleges, is reviewing the evidence on low carbohydrate diets with publication expected in 2020. This will be tracked by the surveillance team and the results will be considered when available.

		an ideal opportunity to review the evidence for TDRs and consider their inclusion into the guidelines' dietary advice, in light of the new scientific evidence pointing to the usefulness of these products for the treatment of Type 2 Diabetes. In the Surveillance proposal consultation document, NICE acknowledges that *new evidence was identified concerning dietary advice and the effectiveness of low or very low-calorie diets on short-term remission of type 2 diabetes in adults*, however it proposes that *further evidence of long-term effectiveness of these diets is required before this is considered as an area for update*. NICE also includes the Diabetes Remission Clinical Trial (DiRECT) and its 2-year results in the consultation's evidence summary. As acknowledged by NICE, the preliminary results of the DiRECT trial revealed that almost half the participants (46%) receiving the programme (low-calorie, diet-based, weight management programme) were in type 2 diabetes remission after 12 months without taking medication for diabetes. The second year results of the trial showed that, of those in remission, 70% were still in remission by the end of year two. TDMR Europe welcomes NICE's acknowledgement of the evidence supporting TDRs as an effective treatment for type 2 diabetes, but we believe that the DiRECT trial' 2	We will also pass the collective feedback in this area to the development team working on the update of the NICE guideline on obesity (CG189) as the main study identified in this area (DiRECT) fed into the decision to update NICE guideline CG189. Please note that the studies submitted by Kent et al (2019) and Christensen (2018) were not included in the surveillance review due to indirectness of the population (covering prevention of T2D in people with obesity, as distinct from treatment of diagnosed T2D).

		years results should have been considered as enough evidence of the longer term benefits of this programme to tackle the condition. It is important to note that this type of intervention has recently been shown to be cost effective by Seamus Kent [Kent et al Is Doctor Referral to a Low-Energy Total Diet Replacement Program Cost-Effective for the Routine Treatment of Obesity? Obesity (2019) 27, 391-398. doi:10.1002/oby.22407] TDMR Europe would like to highlight that it was based on this study that the National Health Service (NHS) in England announced its decision to include TDRs in its Diabetes Prevention Programme (DPP), which shows that the effectiveness of TDRs in tackling this disease has been widely recognised by not only scientists and dieticians, but also professional health care providers. TDMR Europe would also like to draw NICE's attention to "The Prevention of diabetes through lifestyle Intervention and population studies in Europe and around the World" (PREVIEW) project, which aims to identify the most efficient lifestyle pattern to prevent type 2 diabetes in overweight or obese individuals that are pre-diabetic. Following 2500 individuals with pre-diabetes from eight sites in Europe, Australia and New-Zealand, it was found that, after following a low-energy diet, improvements in	

		insulin resistance were found in both men and women. The study showed that 35% of participants of both genders had reverted to a normal blood sugar level after an 8-week weight loss programme. These results show that the use of low-calorie diets lead to significant benefits when it comes to preventing type 2 diabetes in pre-diabetic individuals.[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] Further on 29th April 2019 Pia Christensen speaking at the European Congress on Obesity in Glasgow announced that at 3 years after the TDR weight loss, only 62 of 966 completers had developed diabetes, a lower rate than in the USDPP or the Finnish DPP. The low conversion rate to diabetes may be due to the greater initial weight loss facilitating greater recovery of pancreatic beta-cell function by the time the maintenance programme was commenced. In light of the points raised above, TDMR Europe urges NICE to reconsider its decision not to update section 1.3 of the guideline regarding dietary advice and then to consider the evidence for inclusion of TDRs in the dietary	

		recommendations for the treatment of type 2 diabetes in adults. Please note that EASD (European Association for the study of Diabetes) and ADA (American Diabetes Association) guidelines already refer to this type of intervention and there is a service evaluation of practice using the Counterweight-Plus programme in Scotland referring to the results of use of TDR followed by effective weight loss in 288 participants within NHS practice. [McCombie L et al Filling the intervention gap: service evaluation of an intensive nonsurgical weight management programme for severe and complex obesity. J Hum Nutr Diet 2018 https://doi.org/10.1111/jhn.12611 Nov 2018] If the current evidence for potential use of TDRs is not considered at this review point NICE guidance may well be significantly behind the guidance given by other organisations.	
Digital Diabetes Media Ltd	Yes	No comments provided	Thank you.
UK Clinical Pharmacy Association (UKCPA)	Yes	No comments provided	Thank you.

Diabetes and Endocrinology Group			
Merck Sharp & Dohme Limited	Yes	The proposal refers to the use of cardiovascular disease (CVD) evidence to support SGLT-2is. As such, the date of the review is critical. The CV Outcome study for ertugliflozin is not due to finish until December 2019 and results will not be published until Q2 2020. For the review to be comprehensive we feel it is critical that this study is included as this will mean that CV Outcome studies are available for all SGLT-2is. Therefore, we would ask that the review is delayed allowing this pivotal study to be included. There is considerable comment on CV Outcome studies for the GLP-1s and SGLT-2is in the scope, but all this data is in secondary prevention which is not reflective of the UK diabetes population. Patients with Diabetes and CVD make up about 10% of the UK diabetes population. This affects a very small percentage of T2DM patients and the guidelines should incorporate this ensuring adherence to the product labels for the products. Control of HbA_{1C} is critical to the overall population and this needs to remain a key focus of NG28. In addition, MSD believe that alignment with the recently published ADA/EASD guidelines is important as they have incorporated a clear pathway for patients with and without established CVD encouraging more individualised care for T2DM patients. MSD believes clinical practice is not moving away from the use of DPP-4is at first intensification. MSD believes this class of drugs is still used as the mainstay for the majority of patients and should be reflected. MSD agrees that	Thank you for your comments. Please note that ertugliflozin is covered by the NICE TA: TA572 Ertugliflozin as monotherapy or with metformin for treating type 2 diabetes for treating type 2 diabetes The VERTIS CV Study, covering CV outcomes for ertugluflozin, will be tracked by the surveillance team and will be considered in the context of the technology appraisal within the update of NICE NG28.

		metformin should remain the initial therapy choice for most patients.	
Diabetes Research Unit Cymru (Wales) (DRUC)	Yes	No comments provided	Thank you for your response.
Abbott Diabetes Care	Yes	No comments provided	Thank you for your response.
Royal College of Ophthalmologists	Yes	A lot of new evidence has emerged on ophthalmic complications and their management, the references would need updating. The document states: ''The evidence supports the use of anti-VEGF treatment and intravitreous injection of aflibercept for diabetic retinopathy and laser therapy for diabetic macular oedema. Currently the guideline has recommendations on screening and referral, but no recommendations on specific treatments. However, there are many treatments covered in NICE technology appraisal guidance, suggesting that there may be a gap in the recommendations of NICE guideline NG17. Given the growing evidence base and the related NICE technology appraisal guidance, we propose that this area is reviewed. '	Thank you for your comments. Recommendations on eye disease have been identified for inclusion in the update of both NICE guidelines NG17 and NG28. **Diabetic eye screening** Regarding the proposed withdrawal of recommendations on diabetic eye screening, it was suggested that the guideline still needs to emphasise the importance of regular screening. We will add in a cross referral to the NHS Diabetic Eye screening programme for ease of reference to this guidance. **Fibrates** It was requested that data on the use of fibrates in addition to statins are reviewed in terms of the effects on diabetic retinopathy, based on evidence from Accord and FIELD studies, where fibrates were shown to reduce the rates of progression of retinopathy. However, these studies preceded the surveillance search period, and in the absence of any other published evidence, this area will not be part of the update. The NICE surveillance team is monitoring

		In response to this, we fully agree that the treatment options for diabetic retinopathy need reviewing/updating and these have not previously been specified in the NICE guidelines. They have previously been detailed in RCOphth guidelines which are due for an update in terms of evidence for treatment of diabetic macular oedema and proliferative diabetic retinopathy. This will need specialist ophthalmic input, and there has been a considerable body of new evidence since the RCOphth last updated its guidelines. As per comments below, various highly relevant publications do not seem to be referenced int the document/table 7. It is also clear from that statement quoted above, as well as the statement on page 32 which says ' 'We identified new evidence on the treatment of proliferative diabetic retinopathy, supporting the use of anti-VEGF treatment and also intravitreous injection of aflibercept'' that there is some confusion about what aflibercept represents. In fact, intravitreal aflibercept IS an anti-VEGF treatment (and the anti-VEGF treatments are delivered by intravitreal injection), so the additional comment specifically about Aflibercept is not required in those paragraphs. The document also states: ''Topic experts also highlighted new evidence on the optimum frequency of diabetic eye screening. This area was not considered in the surveillance review because it falls under the remit of the NHS Diabetic Eye Screening Programme who cover screening and referral criteria for people with diabetes. However, to avoid an overlap in guidance we plan to withdraw the recommendations on screening and referral'' Whilst we agree that this work should not be repeated, it would seem	the ongoing Lowering Events in Nonproliferative Diabetic Retinopathy in Scotland study which also concerns fibrate use. The results will be considered when available. **Digital photographic and optical coherence tomography** It was highlighted that data is emerging about digital photographic and optical coherence tomography surveillance for certain patients who had already been referred to the diabetic eye clinics ('virtual clinics'). However, No new evidence was submitted or identified in the surveillance review, and therefore this area will not be part of the update.

		sensible to both reference the NHS Diabetic Eye screening programme here as well as including a short summary of the referral guidelines/recommendations, to emphasise the importance of regular screening etc. As with the paediatric guidelines, it would be good to also stress the benefits of discussing retinopathy screening results during the regular diabetes review appointments either by the GP/practice nurse or diabetologist. We would like request that data on the use of fibrates in addition to statin are reviewed in terms of the effects on diabetic retinopathy, based on evidence from Accord Eye study (and the FIELD study before that), where fibrates were shown to reduce the rates of progression of retinopathy. We are pleased to see that comment has been made about reviewing the results in due course from the Lowering Events in NPDR study (Scotland) which also concerns fibrate use. Data is also emerging about digital photographic and OCT surveillance for certain patients who had already been referred to the diabetic eye clinics ('virtual clinics') and that could be reviewed in the section about the treatment of diabetic retinopathy.	
UK Renal association	Yes	Please note the comments on chronic kidney disease below	Thank you for your comment, please see our response below.

Elcena Jeffers Foundation	Yes	No comments provided	Thank you for your response.
Novo Nordisk	Yes	**General Introductory statement and discussion points** 1) Thank you for the opportunity to submit comments via this public consultation. We welcome the new evidence considerations and the focus on a patient-centred approach as opposed to a glucose-centric one, specifically recognising the importance of assessing cardiovascular benefit, weight, risk of hypoglycaemia and multi-morbidity when considering therapeutic choices. This approach is in line with the recently published ADA-EASD Consensus Statement and more than 20 countries across Europe (including Scotland, France, Germany) and other major countries including the US, Canada, Australia, Brazil and Korea who have already updated their type 2 diabetes guidelines. 2) We note that the end search date was 12 February 2019 but that there is also a reference to consideration of future publications such as REWIND. We have therefore highlighted relevant imminent publications for consideration at this surveillance point of the guideline update. These include PIONEER 6 (due to be presented at ADA in June 2019) and CONCLUDE (due to be presented at EASD in September 2019) 3) We are keen to understand how the concurrent NICE Connect project will interplay with this guideline update. It is our understanding that one	Thank you for your comments. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults, including blood glucose management and managing complications as you have highlighted. Information obtained through the surveillance review, including feedback from stakeholders through this consultation, will be passed on to developers for consideration during the update of the guideline. This will include the eligible trials highlighted and a review of the health economic model. **First intensification** The evidence from SUSTAIN 6 and other eligible studies of semaglutide have been included in Appendix A. The cardiovascular and other benefits of semaglutide, alongside other GLP-1 analogues, will be considered in the update. Thank you for your suggestion to consider expert consensus opinion on cost effectiveness to agree appropriate placement of groups of glucose lowering medicines within the pathway. The NICE guidelines manual will be followed in the update process, which may include expert opinion if appropriate. **Second intensification** Evidence for drugs in the GLP1 analogue class including liraglutide and semaglutide, will be considered in update at both first and second intensification. The forthcoming results of the PIONEER 6 study will also be considered following publication.

		of the intentions for the Connect project is to enable responsive guideline updates and in doing so taking a pragmatic approach to published evidence which might at times include guidance based on expert consensus opinion. We also understand that NICE acknowledges the value of, at times, less rigorous search criteria and the value of including exploratory analysis such as post hoc studies and real world evidence trials and that this pragmatism is also an element of the NICE Connect project. We would therefore like NICE to consider published evidence which would currently fall outside of the selection criteria outlined on page 14 of the surveillance document. **Page 4 - First Intensification: Clinical Characteristics** As outlined above, we agree with the proposal to prioritise treatment management in the early stages based on important clinical characteristics such as CVD risk, weight, risk of hypoglycaemia and associated co-morbidities. We would like to point out that unlike usual efficacy trials, in the cardiovascular outcomes trials named on page 4, all trial participants were treated throughout the studies according to usual standard of care and therefore any cardiovascular benefits seen from these trials are over and above standard of care We would like to highlight at this point that SUSTAIN 6 (semaglutide) also demonstrated cardiovascular benefit: This was a 2-year, randomised, double-blind, placebo-controlled, parallel-group trial to evaluate CV and other long-term outcomes of semaglutide. A total of 3297 patients with type 2 diabetes and high risk of major adverse CV events were randomised and stratified	Please note that in July 2017, NICE reviewed the evidence on the effectiveness and impact of drugs used to manage diabetes in people with a high risk of CVD. The LIRA-SWITCH study you highlight study was included in this review and will inform the guideline update. **First and second intensification** **Stopping rules** In terms of stopping rules, the guideline committee acknowledged that there is a lack of evidence on the effects of stopping and/or switching drug treatments to control blood glucose levels. In the absence of any eligible new evidence, t**he research recommendation** in this area remains valid. The guideline committee noted the high costs of GLP-1 analogue combination treatment options and their associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. Therefore, the GDG chose to retain the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from the previous version of the guideline (NICE guideline CG87). The GDG noted the ABCD audit which indicated that individuals on GLP-1s may show benefit from improvement in HbA1c levels and inadequate weight loss or inadequate improvement in HbA1c levels and adequate weight loss. However, the GDG agreed that, given the lack of cost effectiveness of GLP-1s demonstrated in the health economic modelling, the starting and stopping rules from NICE guideline CG87 should be retained. The review of the health economic model will consider stopping rules in the light of any new cost effectiveness data identified. **Individual and fixed combinations**

		according to cardiovascular disease status (established cardiovascular or chronic kidney disease or cardiovascular risk factors only), insulin treatment (none, basal insulin only, or premixed insulin) and estimated glomerular filtration rate (≤30 ml or >30 ml per minute per 1.73 m2 of body-surface area) at screening to once-weekly semaglutide 0.5 mg (n=826), semaglutide 1.0 mg (n=822) or placebo (n=1649) in addition to standard of care treatments such as oral antidiabetic treatments, insulin, anti-hypertensives, diuretics and lipid-lowering therapies at investigator discretion. The primary endpoint was time from randomisation to first occurrence of a major adverse CV event (MACE) defined as CV death, non-fatal myocardial infarction or non-fatal stroke. Secondary endpoints included first occurrence from baseline to week 104 of the individual components of the composite outcomes; new or worsening of nephropathy and diabetic retinopathy complications; change from baseline to week 104 in body weight and HbA1c. Semaglutide (pooled) showed a 2.3% significant reduction in MACE (p<0.001) and a post hoc analysis showed that semaglutide was superior to placebo in MACE reduction (p=0.02). The driver being non-fatal stroke showing a 1.1% reduction in favour of semaglutide (p=0.04). Consistent cardiovascular (CV) risk reduction with semaglutide vs comparators was observed across type 2 diabetes populations at different levels of CV risk at baseline, i.e both with and without established CVD[1]. The ADA-EASD Consensus Statement specifically mentions that in patients where atherosclerotic CVD is a concern, consider a GLP-1RA with the strongest evidence. Being clear in the updated guideline could support clinicians (both	In terms of the distinction between individual and fixed combinations of GLP-1 analogues and basal insulin; we recognise that it is clinically important to distinguish these treatment options. This distinction will be included in the update, including evidence identified in surveillance for fixed-ratio combinations of liraglutide and lixisenatide. **GLP-1RA use prior to initiating insulin** The evidence you highlighted to support GLP-1RA use prior to initiating insulin was out of scope of the surveillance review but this area will be considered in the update of the antidiabetic drug pathway. The DUAL IX trial has been added to Appendix A to inform the update. **Evidence to support GLP-1RA use prior to insulin intensification (ie in addition to basal insulin)** In terms of the addition of a GLP-1 analogue to a basal insulin as an option for people already on basal insulin who are not also on a GLP-1 analogue, the evidence submitted indicating safety and effectiveness was out of scope for the surveillance review. However, this area will be considered as part of the update. We acknoweldge your point that, because the majority of diabetes management takes place within primary care, the current recommendation to seek specialist advice when adding a GLP-1 analogue to basal insulin may need to be reviewed. However, the evidence submitted was out of scope of the surveillance review. In developing NICE guideline NG28, the committee agreed that to facilitate a flexible approach to enable access for individuals most likely to benefit, this combination should be available to people for

		in primary and secondary care) in making an evidence-based choice. In addition to demonstrating cardiovascular benefit, semaglutide also showed superior glycaemia and weight reduction versus a number of comparators across the SUSTAIN clinical trial programme, these factors being an important clinical consideration in therapy choice. With reference to people with type 2 diabetes and chronic kidney disease treatment options are limited. Both in LEADER and SUSTAIN 6 trials liraglutide and semaglutide have shown a lower risk of new or worsening nephropathy. <u>References:</u> 1. Bain S etc al (2018) Semaglutide consistently reduces cardiovascular risk in patients with type 2 diabetes regardless of baseline cardiovascular risk level: post hoc analyses of the SUSTAIN trial programme. European Heart Journal 2018; 39:598 We would also like to point out that in addition to the SUSTAIN trials included within the reference section, there are some semaglutide references not included: 1. SUSTAIN 10: semaglutide 1.0mg versus liraglutide 1.2mg. Capehorn *et al.* Diabetes UK Professional Conference. 6–8 March 2019, Liverpool, UK (abstract and poster P439) 2. SUSTAIN 9 : Semaglutide 1.0mg added to SGLT2-inhibitors. Zinman B et al. *Lancet Diabetes*	whom obesity is a concern and only where other triple oral combinations are contraindicated or not effective. The guideline committee noted that there was a lack of evidence for combinations of GLP-1 mimetics and insulin, and therefore agreed that this option should only be offered in a specialist care setting. The surveillance review has not identified evidence to warrant a change to this position, but it will nevertheless be considered during the scoping of the update. **Insulin based treatments** The joint ADA and EASD guideline has been noted for contextual consideration in the proposed update. The studies by Heller et al. (2019), Pratley et al. (2019) and Evans M et al (2018) are included in Appendix A and will inform the update of the section on insulin based treatments. The other evidence you highlight in this area precedes the surveillance search period or does not meet the surveillance inclusion criteria. The following points you raise in the context of insulin based treatments will be considered as part of the proposed update: • prioritising choice of insulin with lower risk of hypoglycaemia • flexibility of dosing time with insulin degludec • The importance of age and frailty level in individualised care. **Search restrictions** Please also note that due to resource constraints and the large volume of studies retrieved, the following inclusion criteria were used in selecting evidence for the surveillance review across all sections of the guideline: • Studies with a sample size lower than 100 were excluded.

		Endocrinol 2019; DOI: https://doi.org/10.1016/S2213-8587(19)30066-X 3. Vilsbøll T et al. Semaglutide, reduction in glycated haemoglobin and the risk of diabetic retinopathy Diabetes Obes Metab 2018; 20:889–897 We agree therefore that the updated guidelines should have a focus on choosing medications with cardiovascular and other relevant clinical characteristics to ensure a more patient-centric approach and benefits beyond glycaemia reduction alone. **Page 4 - First Intensification: Cost effectiveness** The comprehensive NICE evidence review of SGLT2is and GLP-1RAs (published March 2018) recognises that the UKPDS outcomes model is not able to accurately assess the cost effectiveness of cardiovascular risk reduction and is poorly suited for modelling populations with high baseline CV risk. "The UKPDS equations may under-predict the magnitude of benefit of liraglutide, and potentially over-predict the benefit of lixisenatide". Additionally, it is unclear as to whether the NG28 model accurately predicts hypoglycaemia and weight variability. With a larger number of CVOTs now published for both SGLT-2is and GLP-1RAs demonstrating cardiovascular benefits it is vital that NICE is able to integrate these groups of medicines appropriately into the updated guideline. If the planned review of the current health	• Studies that included both type 1 and type 2 diabetes were excluded if they did not distinguish between the populations in the results. • Post-hoc, pilot and secondary analysis studies were excluded unless prespecified in study protocols • Single studies already included in a Cochrane review were excluded. • Non-Cochrane systematic reviews were only included for priority areas and if they had a publication date of 2018 or later. • Studies already included in the NICE 2017 evidence review of drugs used to manage diabetes in people with a high risk of CVD were excluded. Please note that the aim of surveillance is to check that published guidelines are current and decide whether updates are needed. To do this, all surveillance reviews rely on assessing 2 elements that influence the decision to update a published guideline as outlined in the guidelines manual: • Intelligence gathering on the perceived relevance of the guideline, which may include responses to questionnaires or external enquiries about the guideline recommendations • Abstracts of primary or secondary evidence that has been published since the end of the search period for the guideline It is the role of the guideline developers to consider the full text studies when they are conducting full systematic reviews for the guideline update – the guidelines manual is permissive of the use of

		economic model is unable to assess the benefits with accuracy, we suggest that an expert consensus opinion is sought to agree appropriate placement of these groups of medicines within the pathway. We would like to bring to your attention the following references relating to cost effectiveness which are not included within the current reference library: • Viljoen A et al (2019) Evaluation of the long-term cost-effectiveness of once-weekly semaglutide versus dulaglutide for treatment of type 2 diabetes mellitus in the UK.; Diabetes and Obesity Metabolism. 2019 Mar;21(3):611-621. doi: 10.1111/dom.13564. Epub 2018 Nov 28. • Pollock RF (2019) The value of once-weekly semaglutide in bringing people with type 2 diabetes to single and composite endpoints: A UK cost of control analysis versus dulaglutide, exenatide extended-release, sitagliptin and insulin glargine U100. Poster number: P434; Presenting author: RF Pollock. Presented at Diabetes UK Professionals Conference 2019 • Hoxer C et al (2019) Cost of introducing once-weekly semaglutide among other GLP-1 RAs for the treatment of type 2 diabetes: A UK budget impact analysis. Poster number: P431; Presenting author: CS Hoxer. Presented at Diabetes UK Professionals Conference 2019	broad types of data where appropriate in the development of guidelines. Due to these search restrictions, the following references you cited were not included: Abd El. Et al (2017), Bain S et al. (2018), Bailey T et al. (2016), Bo Ahrén et al. (2018), Buse JB et al. (2015), Capehorn et al. (2018), Eng C et al. (2014), Hoxer C et al. (2019), Ken Y et al. (2014), Levin PA et al. (2017), Maiorino MI et al. (2017), Montanya E et al. (2016), Pollock RF et al. (2019), Subodh V (2018), Vilsbøll T et al. (2018), Wysham CH et al (2017). **BMI threshold** NICE guideline NG28 stipulates a body mass index (BMI) threshold of 35 kg/m2 prior to being able to receive a GLP-1 analogue but stakeholder comments suggested that this is not evidence-based. The evidence submitted to support that GLP-1 analogues consistently reduce HbA1c and body weight regardless of baseline BMI was not within the scope or search period of the surveillance review. However, the feedback from stakeholders suggested the current recommendation may not be accurate therefore this area will be considered in the update. **NICE Connect** NICE has a dedicated webpage discussing the vision for NICE Connect and further developments will be communicated on this webpage.

		Page 6 - Second Intensification: We note that there are a number of inconsistencies between the studies included at first and second intensification. As the same groups of oral and non-insulin injectables need to be considered at both stages it is essential to ensure consistency of evidence review. Specifically, semaglutide is not currently included at the second intensification stage. Additionally, evidence at second intensification and not included in the references is the LIRA-SWITCH study which demonstrated in uncontrolled participants glycaemia benefits and weight reduction when switching from Sitagliptin to Liraglutide with no difference in hypoglycaemia[1] Reference: 1. Lira-SWITCH (Liraglutide vs Sitagliptin) Bailey T et al. *Diabetes Obes Metab* 2016;18:1191–1198 **General comments: First and Second intensification non-insulin treatments** **1) GLP-1RA stopping rules** There is no clinical evidence to support the use of GLP-1RA stopping rules. The ABCD audit[1] demonstrated that clinicians are not following the NICE GLP-1RA guideline criteria and that in practice less than a third of patients achieve NICE metabolic targets for continuation of a GLP-1RA. The stopping rules also do not consider the cardiovascular benefit that these medications have demonstrated and therefore may deny patients at high risk	

		of a cardiovascular event from a treatment they could benefit from. A recent post hoc analysis of LEADER and SUSTAIN 6 clinical trials presented at American Heart Association in November 2018 shows that cardiovascular and renal benefits of liraglutide and semaglutide vs placebo are observed across the spectrum of baseline BMI to a similar degree. These benefits were also consistent in individuals who achieved above and below the median weight loss.[2] The ambition of this review is to ensure a holistic approach to diabetes care – the current stopping rule based solely on glycaemic benefits seems counter to this ambition. We therefore recommend NICE to remove GLP-1RA related stopping criteria. <u>References:</u> 1. Ken Y. Thong et al (2014) GLP-1 receptor agonists in type 2 diabetes -NICE guidelines versus clinical practice. Br J Diabetes Vasc Dis 2014;14:52-59. 2. Bain S (2018) The glucagon-like peptide-1 receptor agonists liraglutide and semaglutide improve cardiovascular and renal outcomes across most body mass index categories in type 2 diabetes: results of the LEADER and SUSTAIN 6 Trials; Presented at the American Heart Association Scientific Sessions 2018. November 11, 2018, Chicago, IL, USA **2) <u>BMI restriction for GLP-1RAs</u>**	

Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees

		The general requirement to have a BMI> 35kg/m^2 is not based on clinical evidence. There is evidence to support that GLP-1RAs consistently reduce HbA1c and body weight regardless of baseline BMI[1-4]. Restricting GLP-1RA therapy to patients with BMI >35 kg/m2 to improve cost-effectiveness via greater weight loss may be counter-productive if glycaemic efficacy is not maintained. The restriction of having to have a minimum BMI prior to being able to receive a GLP-1RA potentially denies patients at risk of a cardiovascular event from receiving a therapy with proven clinical cardiovascular benefit. A recent post hoc analysis of LEADER and SUSTAIN 6 clinical trials presented at American Heart Association in November 2018 shows that cardiovascular and renal benefits of liraglutide and semaglutide vs placebo are observed across the spectrum of baseline BMI to a similar degree[5]. These benefits were also consistent in individuals who achieved above and below the median weight loss. 38% (n=3516) of participants included in LEADER and 36% (n=1180) of participants included in SUSTAIN 6 had a BMI < 30kg/m^2. These participants would have initially not been considered for a GLP-1RA or potentially had the treatment stopped due to not fulfilling stopping criteria according to the current NICE guidelines. We therefore recommend that any BMI restriction is removed. References: 1. E. Montanya,; Diabetes Obes Metab. 2016 Jul;18(7):707-10. doi: 10.1111/dom.12617; Improvement in glycated haemoglobin evaluated	

		by baseline body mass index: a meta-analysis of the liraglutide phase III clinical trial programme 2. S Colagiuri, Baseline BMI does not influence the HbA1c-lowering efficacy of liraglutide in patients with type 2 diabetes, Presented at the World Diabetes Congress, 2–6 December 2013, Melbourne, Australia. 3. Bo Ahrén et al, Semaglutide induces weight loss in subjects with type 2 diabetes regardless of baseline BMI or gastrointestinal adverse events in the SUSTAIN 1 to 5 trials, Diabetes Obes Metab. 2018;20:2210–2219.; DOI: 10.1111/dom.13353 4. Ken Y. Thong et al; Br J Diabetes Vasc Dis 2014; 14:52-59; GLP-1 receptor agonists in type 2 diabetes -NICE guidelines versus clinical practice. 5. Subodh Verma; The glucagon-like peptide-1 receptor agonists liraglutide and semaglutide improve cardiovascular and renal outcomes across most body mass index categories in type 2 diabetes: results of the LEADER and SUSTAIN 6 Trials; Nov 2018Circulation. 2018; 138:A14806 available at https://www.ahajournals.org/doi/10.1161/circ.138.suppl_1.14806#pane-pcw-details **3) <u>Evidence to support GLP-1RA use prior to insulin</u>** Evidence supports the use of GLP-1RAs prior to initiating insulin therapy with GLP-1RAs demonstrating similar or greater reductions in HbA1c (long-acting GLP-1RAs more so than short acting GLP-1RAs), greater weight loss and lower rates of hypoglycaemia compared to insulin[1-3] We therefore recommend that NICE considers GLP-1RAs in	

		patients who need greater glucose-lowering benefit prior to insulin in accordance with the ADA/EASD consensus statement[4]. We would like to highlight that on page 35 no distinction has been made between individual and fixed combinations of GLP-1RAs and basal insulin. It is clinically important to distinguish these treatment options and provide guidance on each. We would also like to bring to your attention the recently published DUAL IX trial. This study demonstrated safe use of IDegLira in combination with SGLT2 inhibitors in insulin naïve patients (N=420)[5]. References 1. Flag Buse JB, Peters A, Russell-Jones D et al (2015) Is insulin the most effective injectable antihyperglycaemic therapy? Diabetes Obes Metab 17:145–151. https://doi.org/10.1111/dom.12402 published 12Oct 2014 2. Levin PA, Nguyen H, Wittbrodt ET, Kim SC (2017) Glucagon-like peptide-1 receptor agonists: a systematic review of comparative effectiveness research. Diabetes Metab Syndr Obes Targets Ther 10:123 –139. https://doi.org/10.2147/DMSO.S130834 3. Abd El Aziz MS, Kahle M, Meier JJ, Nauck MA (2017) A metaanalysis comparing clinical effects of short- or long-acting GLP-1 receptor agonists versus insulin treatment from head-to-head	

		studies in type 2 diabetic patients. Diabetes Obes Metab 19:216–227. https://doi.org/10.1111/dom.12804 4. Davies et al (2018) 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 Sep; dci180033 5. Philis-Tsimikas A, Billings LK, Busch R, Portillo CM, Sahay R, Halladin N, Eggert S, Begtrup K, Harris S. Superior efficacy of insulin degludec/liraglutide versus insulin glargine U100 as add-on to sodium-glucose co-transporter-2 inhibitor therapy: A randomized clinical trial in people with uncontrolled type 2 diabetes. Diabetes Obes Metab. 2019 Feb 13. doi: 10.1111/dom.13666 **4) <u>Evidence to support GLP-1RA use prior to insulin intensification (ie in addition to basal insulin)</u>** Evidence shows that adding a GLP-1RA to a basal insulin is safe and effective[1-3]. We recommend therefore that this is clearly included as an option for people already on basal insulin who are not also on a GLP-1RA. For this reason and as the majority of diabetes management takes place within primary care the current recommendation to seek specialist advice when adding a GLP-1RA to basal insulin should be removed. <u>References:</u>	

Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees

		1. Eng C, Kramer CK, Zinman B, Retnakaran R (2014) Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. Lancet 384:2228–2234. https://doi.org/10. 1016/S0140-6736(14)61335-0 2. Wysham CH, Lin J, Kuritzky L (2017) Safety and efficacy of a glucagon-like peptide-1 receptor agonist added to basal insulin therapy versus basal insulin with or without a rapid-acting insulin in patients with type 2 diabetes: results of a meta-analysis. Diabetologia Postgrad Med 129:436–445. https://doi.org/10.1080/00325481.2017.1297669 3. Maiorino MI, Chiodini P, Bellastella G et al (2017) Insulin and glucagon-like peptide 1 receptor agonist combination therapy in type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. Diabetes Care 40:614–624. https://doi.org/10.2337/dc16-1957 **5) Pioneer (oral semaglutide)** Novo Nordisk submitted a Marketing Authorisation Application to the European Medicines Agency (EMA) for oral semaglutide on the 26th April 2019. The submission is based on the results from 10 PIONEER clinical trials, which included 9,543 adults with type 2 diabetes. Data from PIONEER 1[1] and PIONEER 2[2] has already been published and six oral semaglutide abstracts have been accepted for	

		poster/oral presentation at the 79th Scientific Sessions of the American Diabetes Association in June 2019. We are currently in dialogue with NICE regarding a potential appraisal for oral semaglutide. The topic is at Decision Point 3 and we are awaiting a draft scope. <u>References:</u> 1. Davies M, Pieber TR, Hartoft-Nielsen M, Hansen OKH, Jabbour S, Rosenstock J. Effect of Oral Semaglutide Compared With Placebo and Subcutaneous Semaglutide on Glycemic Control in Patients With Type 2 Diabetes: A Randomized Clinical Trial. JAMA. 2017;318(15):1460–1470. doi:10.1001/jama.2017.14752 2. Rosenstock J, Allison D, Birkenfeld AL, et al. 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. 2019;321(15):1466–1480. doi:10.1001/jama.2019.2942 **<u>Page 6 – Second Intensification: Insulin - based treatments</u>** Novo Nordisk welcomes the identification of the insulin degludec price reduction and agrees with the expert opinion to review the basal insulin section of this guideline. We also agree that it is important to differentiate between the available basal insulins, helping healthcare professionals to make the best choice for their patients. We would like to bring to your attention the ADA-EASD Consensus Statement which makes clear the choice that now exists for basal insulins and the compelling need to consider an insulin with a lower risk of hypoglycaemia, where insulin	

		degludec is named first as the basal insulin with the strongest evidence base[1] **1) <u>Hypoglycaemia</u>** As mentioned above the ADA-EASD Consensus Statement encourages clinicians to prioritise a choice of insulin with a lower risk of hypoglycaemia. Thank you for including the SWITCH 2 study and the DEVOTE study which together demonstrate the reduction in overall, nocturnal and severe hypoglycaemia versus insulin glargine U100. In addition, we would like to draw your attention to the wealth of phase 3 data: A two year randomised treat-to-target trial comparing insulin degludec with insulin glargine U100 in insulin-naive subjects with Type 2 diabetes found a significantly reduced risk of nocturnal hypoglycaemia[2] and a further trial also comparing insulin degludec versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes found that overall confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia were lower in the insulin degludec group[3]. In addition, we would like to highlight real world evidence that supports the randomised controlled trial data demonstrating a reduction in hypoglycaemia versus insulin glargine U100 [4,5]. Furthermore, real world evidence comparing insulin degludec and glargine U300 also demonstrated a hypoglycaemia advantage for insulin degludec[6] Novo Nordisk has recently completed double blind head-to-head randomised control trial investigating insulin glargine U300 versus insulin degludec involving more than 1400 people with type 2 diabetes and the top line results were made available through a press release on 3rd May.	

		The final results and publication are expected during the European Association for Study of Diabetes conference in September 2019. We request NICE to include this study in the list of ongoing studies to be considered during the development of the guidelines. We suggest that NICE provides clear guidance that differentiates between available basal insulins, specifically taking into consideration those people at a higher risk of hypoglycaemia. **2) <u>Flexibility</u>** We would like to highlight the flexibility in dosing time with insulin degludec, having a minimum dosing time of 8 hours between doses, which can be advantageous to certain adult populations [7]. This could particularly be of benefit where third party administration is necessary. With respect to the definition of 'ultra long', for the purpose of clarity, Novo Nordisk suggests adding the insulin duration of action to those insulins categorised as 'ultra long' within the guideline **3) <u>Frail / Elderly</u>** The reduction in hypoglycaemia shown with insulin degludec versus glargine U100 has been demonstrated in the frail and elderly who are a vulnerable patient population worthy of special consideration in the guideline since they are particularly prone to hypoglycaemia. Post hoc analyses of both the SWITCH 2 study and DEVOTE study in the elderly show that the reduction in	

		hypoglycaemia versus insulin glargine is also shown in this group[8,9]. Additionally, a meta-analysis of phase 3a trials found that elderly people with diabetes experienced a lower rate of nocturnal hypoglycaemia with insulin degludec than with insulin glargine[10]. The recognition of the need to individualise targets for people in this group is also demonstrated through the recent changes in the QOF indicators for frailty. Given the evidence showing lower rates of hypoglycaemia in this vulnerable patient group, insulin degludec should be recommended as a therapy choice. **4) <u>Safety and cost effectiveness</u>** Not currently included in the references is the Liu et al meta-analysis demonstrating the eefficacy and safety of Insulin degludec versus Insulin Glargine[11]. This is a systematic review and meta-analysis of 15 clinical trials and we would ask please that it is included to inform the next stage of guideline development. Also not currently included in the references, an economic analysis estimated that insulin degludec would be cost effective relative to insulin glargine U100 in both type 1 and type 2 diabetes in the UK[12]. <u>References</u> 1. Davies et al (2018) 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 Sep; dci180033 2. Garber A et al (2012) Insulin degludec, an ultra-long acting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial 3. Rodbard et al on behalf of the BEGIN Once Long Trial Investigators (2013) Comparison of insulin degludec with insulin glargine in insulin-naive subjects with Type 2 diabetes: a 2-year randomized, treat-to-target trial. Diabetic Medicine DOI: 10.1111/dme.12303 4. Siegmund T et al (2017) A European, multicentre, retrospective, non-interventional study (EU-TREAT) of the effectiveness of insulin degludec after switching basal insulin in a population with type 1 or type 2 diabetes. Diabetes, Obesity and Metabolism. 2017;1-9. 5. Fadini G (2019) Reduced rates of overall hypoglycaemia in patients with Type 2 diabetes after switching to insulin degludec: A European, multinational, multicentre, prospective, observational study (ReFLeCT) Diabetic Medicine, 36 (Suppl. 1), 34–174 and presented at Diabetes UK Professionals Conference 2019 6. Tibaldi J (2018) A comparative effectiveness study of degludec and insulin glargine 300 U/mL in insulin-naïve patients with type 2 diabetes. Diabetes and Obesity Metabolism 2019;1–9. 7. SmPC Tresiba November 2018 8. Heller S et al (2019) Lower rates of hypoglycaemia in older individuals with type 2 diabetes using insulin degludec versus insulin glargine U100:	

		Results from SWITCH 2. Diabetes and Obesity Metabolism 2019 Mar 20. doi: 10.1111/dom.13708 9. Pratley et al (2019) Cardiovascular safety and lower severe hypoglycaemia of insulin degludec versus insulin glargine U100 in patients with type 2 diabetes aged 65 years or older: Results from DEVOTE. Diabetes and Obesity Metabolism 2019;1–9. 10. Sorli C et al (2013) Elderly Patients with Diabetes Experience a Lower Rate of Nocturnal Hypoglycaemia with Insulin Degludec than with Insulin Glargine: A Meta-Analysis of Phase IIIa Trials. Drugs Aging (2013) 30:1009–1018 11. Liu W et al (2018) Efficacy and Safety of Insulin Degludec versus Insulin Glargine: A Systematic Review and Meta-Analysis of Fifteen Clinical Trials. International Journal of Endocrinology. 2018 Mar 12;2018:8726046. doi: 10.1155/2018/8726046 12. Evans M, Mehta R, Gundgaard J, Chubb B (2018) Cost-Effectiveness of Insulin Degludec vs. Insulin Glargine U100 in Type 1 and Type 2 Diabetes Mellitus in a UK Setting. Diabetes Therapy 9(5):1919–30	
British Society of Periodontology	Yes	**There is sufficient new evidence to justify this**	Thank you for your response.
X-PERT Health	No	X-PERT support the continued inclusion of guidance to individualise carbs and meal patterns, but feel that more specific information is required in relation to what approaches are supported by this as many health care professionals do not feel comfortable and confident in promoting approaches not explicitly covered	Thank you for your comments. **Evidence on dietary advice** Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults in several areas

		The existing guidelines for dietary advice are very limited in scope. As many non-dietitians are informed by NICE guidance, more specific advice is essential to help GPs, nurses etc. feel more competent and confident with recommending individualised approaches. Many healthcare professionals do not have any specific training in nutrition, and so more complete and flexible guidance would be of great benefit. This guidance should include recommendations for patients to be referred to suitably qualified professionals where necessary and for sufficient support to be provided and monitoring of health to be carried out to minimise any risks associated with these approaches The majority of the dietary guidance has not been updated since 2009, which is inconsistent with progress in research and practice during this time. Reflecting this, other relevant bodies have updated their position and guidance, sometimes significantly. Notably: • Diabetes UK guidance from 2011 and 2018 concluded there is insufficient evidence to promote a specific dietary approach, that adherence to a diet is the best predictor of long-term success, that individualisation of approaches is important, and support carbohydrate restriction as a suitable option. A 2017 Diabetes UK position statement also supports carbohydrate restriction as a suitable option	including blood glucose management, insulin therapy and management of complications. We retain our proposal not to update the guideline around very low calorie diets. Evidence submitted was not eligible due to indirectness of population (relating to obesity without T2D, and to prevention not treatment), out of scope study designs, and studies published outside the surveillance search period. The joint ADA and EASD guideline was also cited as referring to low carbohydrate and low calorie diets. However, this guideline does not explicitly recommend these diets but states that 'advice should be given of the health benefits of weight loss and encouraged to engage in a programme of intensive lifestyle management, which may include food substitution'. The other guidelines cited, including Diabetes UK, are consistent with NICE guideline NG28 which advises individualising recommendations for carbohydrate intake, and meal patterns. This encompasses a range of interventions, which may include low carbohydrate and low calorie diets. **Long-term benefits of dietary interventions** The totality of evidence for dietary interventions is currently limited to short-term benefits. It does not indicate conclusively that low carbohydrate and low calorie diets are a superior approach to other strategies for weight loss and subsequent weight maintenance in the long-term. The review you cite by McArdle et al (2018) concluded that there was no overall pooled effect on HbA1c in favour of restricting carbohydrate; however, restriction of carbohydrate to 50-130 g per day had beneficial effects on HbA1c in trials up to 6 months. It further recommended trials of over 12 months in duration. As you point out, this is consistent with other systematic review evidence and indicates that the short term findings require longer term substantiation. The surveillance impact statement is

		• The British Dietetic Association released a position statement in 2018 supporting carbohydrate restriction as a viable option • A 2018 joint position statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) (Davies, M. J., et al. [2018]. "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) reached conclusions similar to Diabetes UK, promoting individualised approaches for all patients • A 2019 report from the Legislative Assembly of Western Australia's Education and Health Standing Committee (Education and Health Standing Committee [2019]. The Food Fix: The role of diet in type 2 diabetes prevention and managements. Western Australia Parliament Legislative Assembly Committees. Perth.) also reached conclusions supportive of VLCD and low carbohydrate approaches for the management of Type 2 diabetes • A 2019 consensus report from the American Diabetes Association (Evert, A. B., et al. [2019]. "Nutrition Therapy for Adults with Diabetes or Prediabetes: A Consensus Report." Diabetes Care **42**(5): 731-754) concluded that "a variety of eating patterns are acceptable for the management of diabetes" supporting the need to individualise approaches. In relation to carb restriction specifically, this report acknowledges:	therefore retained; that the longer-term results of the DIRECT study (beyond 2 years), and other longer-term studies of low calorie and low carbohydrate diets are likely to be needed to establish any definite impact on the guideline. The collective evidence and intelligence in this area will also be considered in the update of the NICE guideline on obesity (CG189) as the main study identified in this area (DiRECT) fed into the decision to update NICE guideline CG189. **Joint SACN, NHS England and Diabetes UK review** The joint review highlighted has been noted and will be tracked by the surveillance team. The report is expected to publish in 2020 and any potential impact will be considered when the results are available. **Specific dietary advice, including low fat diets** Thank you for your feedback on the assertion that individuals with T2D should be given the same dietary recommendations as the general population. Section 1.3 actually recommends individualising nutritional advice (1.3.1) and advice for carbohydrate and alcohol intake, and meal patterns (1.3.6). It does not explicitly recommend either a low fat diet or low carbohydrate diet. In the absence of compelling evidence in this area, there is not a strong signal to change this advice. **Search restrictions** Please note that NICE took a decision not to consider evidence prior to 2014 on the premise that the guideline committee considered the evidence in this area to be up to date at the time of developing NICE guideline NG28 in 2014, and that a search from 2009 was not considered necessary at that time.

		○ Glucose requirements can be met by the body's metabolic processes, thus there is no lower limit of necessary carbohydrate intake ○ "Reducing overall carbohydrate intake for individuals with diabetes has demonstrated the most evidence for improving glycaemia and may be applied in a variety of eating patterns that meet individual needs and preferences" ○ "For select adults with type 2 diabetes not meeting glycaemic targets or where anti-glycemic medications is a priority, reducing overall carbohydrate intake with low- or very low-carbohydrate eating plans is a viable approach" ○ Low carbohydrate or very low carbohydrate eating plans are the most studied eating patterns for type 2 diabetes (and thus have more evidence than any other approach) ○ "…from the current evidence, this eating pattern does not appear to increase overall cardiovascular risk…" (note: this includes in relation to increased saturated fat intake in many of the studies)	Please also note that due to resource constraints and the large volume of studies retrieved, the following inclusion criteria were used in selecting evidence for the surveillance review across all sections of the guideline: • Studies with a sample size lower than 100 were excluded. • Studies that included both type 1 and type 2 diabetes were excluded if they did not distinguish between the populations in the results. • Post-hoc, pilot and secondary analysis studies were excluded unless prespecified in study protocols • Single studies already included in a Cochrane review were excluded. • Non-Cochrane systematic reviews were only included for priority areas and if they had a publication date of 2018 or later with a recent search date. • Studies already included in the NICE 2017 evidence review of drugs used to manage diabetes in people with a high risk of CVD were excluded. **Balance of recommendations between dietary and pharmaceutical interventions** Please note that the guideline recommendations on dietary advice in section 1.3 precede those on drug therapy in blood glucose management in 1.6 and are given sufficient prominence. In its first bullet point, the algorithm for blood glucose lowering therapy also recommends reinforcement of advice on diet and lifestyle, in addition to adherence to drug therapy. Drug therapy is not prioritised as such, but nevertheless needs to reflect the body of available evidence in the area.

		We feel that the NICE guidelines should be more consistent with the positions of the most relevant professional bodies (particularly in this case Diabetes UK and the British Dietetic Association), with the members of the organisations who update their position and guidelines having more specialist skills and knowledge in relation to diet than those involved in updating the NICE guidelines. We feel that NICE's position is inconsistent with those stated above, and is out of line with the available body of evidence Although important for patient safety and optimum blood glucose control, the continued increase in the volume and specificity of advice on pharmaceutical interventions is in distinct contrast to the inertia of the lifestyle guidance. This increases the perception that drug based therapies are prioritised, despite the fact lifestyle changes are supposed to be the first line intervention for the management of Type 2 diabetes. Without clarity on the first line intervention the chances of pharmaceutical therapy being needed is increased dramatically As the purpose of these guidelines is to inform practice, relevant practical evidence should be considered in addition to the evidence provided by controlled trials and systematic reviews. Although the level of evidence may be considered inferior on some levels it also has its strengths (e.g. ecological validity), and the limitations can be	**Nutrition expertise** It was considered that the necessary expertise in nutrition and all other areas of the guideline was available from the experts consulted. None of these experts indicated that the dietary advice section of the guideline required updating. Similarly, in developing NG28, none of the committee members indicated that an update of this section was needed. The British Dietetic Association was also a registered stakeholder and provided nutrition expertise in the development of NG28. **Terminology and presentation** Thank you for your comments on specific sections, which have been amended, including: The distinction between evidence on low calorie and low carbohydrate diets has been made clearer. Evidence regarding intermittent energy restriction and structured aerobic exercise training has been retained in this section, since lifestyle advice is also covered in this section. The impact statement is retained, since it does reflect the evidence of short term benefits of low carbohydrate and low calorie diets whilst stating that longer term studies of effectiveness are likely to be needed to establish any definite impact on the guideline. Medication changes were not reported in the included studies and therefore could not inform the impact statement. NICE guideline NG28 does not make specific recommendations for bariatric surgery, but cross refers to NICE's guideline on obesity. We have not identified any strong indications to indicate that bariatric surgery should be listed separately from dietary advice.

		considered accordingly. Relevant evidence of this nature, pertaining to carbohydrate restriction, includes: o The growing popularity and evidence of success of Diabetes.co.uk's online programme demonstrates a change in opinion and culture related to the use of carbohydrate restriction for the management of Type 2 diabetes. Outcomes from this programme have been published (Saslow, L. R., et al. [2018]. "Outcomes of a Digitally Delivered Low-Carbohydrate Type 2 Diabetes Self-Management Program: 1-Year Results of a Single-Arm Longitudinal Study." JMIR Diabetes.). This programme is also included in the NHS App library and is part of an NHS innovation accelerator, supporting it's acceptability, safety and efficacy o The success demonstrated by Virta Health's 12 month outcomes (Hallberg SJ, McKenzie AL, Williams PT, Bhanpuri NH, Peters AL, Campbell WW, et al. [2018]. "Effectiveness and Safety of a Novel Care Model for the Management of Type 2 Diabetes at 1 Year: An Open-Label, Non-Randomized, Controlled Study". Diabetes Therapy) support the efficacy of a low carbohydrate approach for the management, and possible remission, of Type 2 diabetes. These outcomes also demonstrate that motivated individuals are able to adhere to this approach, and there was no evidence that this approach was unsafe The safety of this approach is further supported by Virta's results in relation to cardiovascular disease risk, published in a separate paper (Bhanpuri, N. H., et al. (2018). "Cardiovascular disease risk factor responses to a type 2 diabetes care model including nutritional ketosis induced by sustained carbohydrate	The use of the health economic word "dominated" you refer to in relation to inter-group comparison has been amended to 'more cost-effective'.

		restriction at 1 year: an open label, non-randomized, controlled study." Cardiovasc Diabetol **17**(1): 56) Virta's 24 month results are also available in pre-print form (Athinarayanan, S. J., et al. [2018]. "Long-Term Effects of a Novel Continuous Remote Care Intervention Including Nutritional Ketosis for the Management of Type 2 Diabetes: A 2-year Non-randomized Clinical Trial." bioRxiv preprint first posted online Nov. 28, 2018; doi: http://dx.doi.org/10.1101/476275) supporting the longer-term safety and efficacy of this approach o Evidence that low carbohydrate approaches can be successful in the management of Type 2 diabetes is also available from within a primary care setting in the UK, for example in David Unwin's GP practice (e.g. Unwin D and Unwin J [2014]. Low carbohydrate diet to achieve weight loss and improve HbA1c in type 2 diabetes and pre-diabetes: experience from one general practice. Practical Diabetes **31**(2):76-9.). Dr Unwin has also produced infographics which have been approved by NICE and developed an online learning module that is provided through the Royal College of General Practitioners, further supporting the acceptance of such approaches as safe and effective The decision to appraise the evidence looking at carbohydrate restriction for the management of Type 2 diabetes whilst a review is being carried out jointly by the Scientific Advisory Committee on Nutrition (SACN), NHS England and Diabetes UK is surprising. The NICE review appears to be limited in scope and detail compared to this review. Will the findings of the SACN review be used to	

		inform an additional update to the relevant NICE guidelines if carb restriction is concluded to be safe and effective, and if so what would the likely timeframe of this be? NICE guideline NG17 (management of Type 1 diabetes) states that “Carbohydrate is the macronutrient that has the greatest impact on glycaemic control”. We believe that this same assertion should be included and considered when setting guidance for individuals with T2DM, as it is no less valid for this population Specific comments: • Page 7, areas not proposed for update, paragraph 2: ○ We disagree with the assertion that further evidence of long-term effectiveness is required before this is considered an area for update. There is an abundance of evidence demonstrating low carb diets perform as well as, or better than, existing approaches. There is also an absence of high quality research of a longer duration to support the existing approach, and what evidence does exist fails to support the superiority of a low fat diet; for example in the Women’s Health Initiative glycaemic control was worse in the low fat arm (e.g. Shikany, J. M., et al. (2011). "Effects of a low-fat dietary intervention on glucose, insulin, and insulin resistance in the Women's Health Initiative (WHI) Dietary Modification trial." Am J Clin Nutr **94**(1): 75-85) and in the LookAHEAD trial there	

		was no reduction in cardiovascular disease risk (The Look AHEAD Research Group (2013). "Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes." N Eng J Med **369**: 145-154.) ○ Although we agree that advising on low-calorie diets would not be at odds with the current recommendations we do not believe that this is sufficient. The relevant guidance should be updated to explicitly acknowledge that this approach is supported by the current guidelines to avoid any ambiguity or confusion. Many of the health care professionals we work with do not feel comfortable recommending something that is not explicitly supported • Appendix A2: ○ Page 14, search and selection strategy: it is stated that studies published between 1 June 2014 and 12 Feb 2019 were searched for, but literature searches relevant to dietary advice were not performed for the 2015 NICE guidance update. As the majority of the dietary guidelines are dated 2009, and are based on literature searches carried out in 2008, any evidence published between 2008 and the beginning of this most recent literature search would therefore not be considered unless included in systematic reviews or meta-analyses. This risks important research being omitted, and important facets of studies included in these reviews not being acknowledged as their findings are limited to their influence on pooled effects.	

		There are at least 8 RCTs that would have met the inclusion criteria of previous NICE evidence appraisals (i.e. 50 participants or more) demonstrating that low carbohydrate diets can be effective for managing Type 2 diabetes. In many cases the outcomes are comparable or superior for the low carb arm in relation to the low fat arm, whilst also reducing medication requirements. These studies are listed below: 1. Stern et al 2004 (Stern L, Iqbal N, Seshadri P, Chicano KL, Daily DA, McGrory J, et al. The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. Ann Intern Med. 2004;140(10):778-85.): Conclusion "Participants on a low-carbohydrate diet had more favourable outcomes overall at 1 year than did those on a conventional diet. Weight loss was similar between groups, but effects on atherogenic dyslipidaemia and glycaemic control were still more favourable with a low-carbohydrate diet after adjustment for differences in weight loss" 2. Daly et al 2005 (Daly ME, Paisey R, Paisey R, Millward BA, Eccles C, Williams K, et al. Short-term effects of severe dietary carbohydrate-restriction advice in Type 2 diabetes- a randomized controlled trial. Diabet Med. 2005;23(1):15-20.): Conclusion "Carbohydrate restriction was an effective method of achieving short-term weight loss compared with standard advice, but this was at the expense of an increase in relative saturated fat intake" (N.B. An increase in	

		relative saturated fat intake in the absence of any detrimental effect on health should not be treated as a negative outcome) 3. Westman et al 2008 (Westman EC, Yancy WS, Jr., Mavropoulos JC, Marquart M, McDuffie JR. The effect of a low-carbohydrate, ketogenic diet versus a low-glycemic index diet on glycemic control in type 2 diabetes mellitus. Nutr Metab (Lond). 2008;5:36.): Conclusion "Dietary modification led to improvements in glycemic control and medication reduction/elimination in motivated volunteers with type 2 diabetes. The diet lower in carbohydrate led to greater improvements in glycemic control, and more frequent medication reduction/elimination than the low glycemic index diet. Lifestyle modification using low carbohydrate interventions is effective for improving and reversing type 2 diabetes." 4. Davis et al 2009 (Davis NJ, Tomuta N, Schechter C, Isasi CR, Segal-Isaacson CJ, Stein D, et al. Comparative study of the effects of a 1-year dietary intervention of a low-carbohydrate diet versus a low-fat diet on weight and glycemic control in type 2 diabetes. Diabetes Care. 2009;32(7):1147-52.): Conclusion "Among patients with type 2 diabetes, after 1 year a low-carbohydrate diet had effects on weight and A1c similar to those seen with a low-fat diet. There was no significant effect on blood pressure, but the low-carbohydrate diet produced a greater increase in HDL cholesterol."	

		5. Guldbrand et al 2012 (Guldbrand H, Dizdar B, Bunjaku B, Lindström T, Bachrach-Lindström M, Fredrikson M, et al. In type 2 diabetes, randomisation to advice to follow a low-carbohydrate diet transiently improves glycaemic control compared with advice to follow a low-fat diet producing a similar weight loss. Diabetologia. 2012;55(8):2118-27.): Conclusion "Weight changes did not differ between the diet groups, while insulin doses were reduced significantly more with the LCD at 6 months, when compliance was good. Thus, aiming for 20% of energy intake from carbohydrates is safe with respect to cardiovascular risk compared with the traditional LFD and this approach could constitute a treatment alternative." 6. Jonasson et al 2014 (Jonasson L, Guldbrand H, Lundberg AK, Nystrom FH. Advice to follow a low-carbohydrate diet has a favourable impact on low-grade inflammation in type 2 diabetes compared with advice to follow a low-fat diet. Annals of medicine. 2014;46(3):182-7.): Conclusion "To conclude, advice to follow LCD or LFD had similar effects on weight reduction while effects on inflammation differed. Only LCD was found significantly to improve the subclinical inflammatory state in type 2 diabetes." 7. Sato et al 2017 (Sato J, Kanazawa A, Makita S, Hatae C, Komiya K, Shimizu T, et al. A randomized controlled trial of 130 g/day	

		low-carbohydrate diet in type 2 diabetes with poor glycemic control. Clin Nutr. 2017;36(4):992-1000.): Conclusion "Our study demonstrated that 6-month 130 g/day LCD reduced HbA1c and BMI in poorly controlled Japanese patients with T2DM. LCD is a potentially useful nutrition therapy for Japanese patients who cannot adhere to CRD." 8. Tay et al 2017 (Tay J, Thompson CH, Luscombe-Marsh ND, Wycherley TP, Noakes M, Buckley JD, et al. Effects of an energy-restricted low-carbohydrate, high unsaturated fat/low saturated fat diet versus a high carbohydrate, low fat diet in type 2 diabetes: a 2 year randomized clinical trial. Diabetes, obesity & metabolism. 2017.): Conclusion "Both diets achieved comparable weight loss and HbA1c reductions. The LC sustained greater reductions in diabetes medication requirements, and improvements in diurnal blood glucose stability and blood lipid profile, with no adverse renal effects, suggesting greater T2D management optimisation." Previous publications from the same trial were published 2014 and 2015 (details below), the latter of which is included in the evidence review for the current NICE surveillance (though it would perhaps be more suitable to include the 2017 publication). • 2014 (Tay J, Natalie D L-M, Thompson CH, Noakes M, Buckley JD, Wittert GA, et al. A Very Low Carbohydrate,	

		Low Saturated Fat Diet for Type 2 Diabetes Management: A Randomized Trial. Diabetes Care. 2014;37:2909–18.) Conclusion "Both diets achieved substantial improvements for several clinical glycemic control and CVD risk markers. These improvements and reductions in GV and antiglycemic medication requirements were greatest with the LC compared with HC. This suggests an LC diet with low saturated fat may be an effective dietary approach for T2DM management if effects are sustained beyond 24 weeks." • 2015 (Tay J, Luscombe-Marsh ND, Thompson CH, Noakes M, Buckley JD, Wittert GA, et al. Comparison of low- and high-carbohydrate diets for type 2 diabetes management: a randomized trial. The American journal of clinical nutrition. 2015;102:780–90.) Conclusion "Both diets achieved substantial weight loss and reduced HbA1c and fasting glucose. The LC diet, which was high in unsaturated fat and low in saturated fat, achieved greater improvements in the lipid profile, blood glucose stability, and reductions in diabetes medication requirements, suggesting an effective strategy for the optimization of T2D management." o Page 14, selecting relevant studies: we do not feel that the decision to only select studies with 100	

		participants or more is justified, and disagree with the assertion these criteria are appropriate for ensuring only relevant studies were selected. A study with less than 100 participants is not irrelevant if it is of sufficient quality, and increasing the limit of what is considered admissible as evidence simply serves to protect the existing guidelines as the volume of evidence permitted for consideration will be reduced considerably. As this decision was not made prior to the onset of the evidence search it also introduces an unacceptable level of bias. The decision that there were too many studies to appraise is a position that is hard to defend when the end goal is to inform national guidelines. All relevant evidence of sufficient quality should be included based on criteria agreed before the onset of the evidence appraisal phase ○ Page 16, views of topic experts: based on the assertion that all 7 responding experts felt that the guidelines are in need of updating, alongside the fact the dietary guidelines section was not felt to need updating, it can be inferred that no topic experts in the area of nutrition were consulted (or at least none replied). Although expert opinion is inferior to many forms of evidence in the research hierarchy the absence of involvement of additional subject experts is remarkable in relation to the development of guidance relevant to the management of what is a largely a nutritional condition ○ Page 17, Other sources of information: irrelevant of the decision reached after an appraisal of the evidence it is astounding that “none of the	

		stakeholders or guideline committee members involved in developing NG28 raised the issue of high fat, low carbohydrate diets." This would show a complete lack of awareness of recent guideline updates of other relevant organisations, of the existing literature, and of one of the key areas of debate and discussion within the field (though it is noted that an appraisal of the relevant evidence was subsequently carried out despite the apparent initial omission) o Page 18, 1.2. Patient education, 2019 surveillance summary: the use of the word "dominated" in relation to inter-group comparison is inappropriate o Page 19, 1.2. Patient education, 2019 surveillance: triglycerides is spelt incorrectly. We also believe that the term "blood glucose" should be used throughout rather than "blood sugar", to avoid reinforcing the archaic perspective that sugar is uniquely damaging in relation to health and diabetes control o Page 20, section title: we believe that dietary advice and bariatric surgery should be independent sections o Page 20/21, 2019 surveillance summary: ▪ the evidence identified is inconsistent with that identified by the ongoing SACN-NHS England-DUK review of this subject, which identified and included six systematic reviews	

		and 36 publications from 31 studies (though it is acknowledged that they did not apply the same 100 participant minimum, which we reiterate we feel is not justified). 18 of the studies identified by SACN-NHS England-DUK were greater than 12 months in duration ▪ within this section it states that three further RCTs were identified on low carbohydrate diets for Type 2 diabetes in adults, but two of the three included papers are not appropriate. In Liu et al 2018 (reference 15) the target carbohydrate intake was 42% of total energy, significantly higher than what would generally be considered to be a low carbohydrate diet, and Carter et al 2018 (reference 17) is a study of intermittent fasting. The third paper included, Tay et al 2015 (reference 16), should also arguably not be included as a more recent paper from the same study (Tay et al 2017, detailed above) has been published and thus supersedes (or should at least be considered in addition to) these findings ▪ Page 21, evidence regarding intermittent energy restriction and structured aerobic exercise training should not be within the low carb diet section, though are important areas relevant to this and deserve additional coverage o Page 22, impact statement: ▪ We disagree with the assertion individuals with Type 2 diabetes should be given the	

		same dietary recommendations as the general population, and do not feel that the available evidence or consensus within the scientific or dietetic communities support this position. There is abundant evidence that alternative dietary approaches can be as good as, or superior to, existing guidelines and this should be reflected in the update in a manner similar to how it is reflected by many other relevant organisations ▪ The recommendation of a low fat diet is outdated and inconsistent with the position of many other organisations; e.g. US dietary guidelines no longer recommend an upper limit for fat intake, reflecting the current research on the impact of dietary fat on weight management and health (Dietary Guidelines For Americans. 2015-2020. Eighth Edition. USDA). It fails to consider the differential health impacts of different types of fat and different foods containing fat; and is out of step with a move towards food based, and eating pattern based, guidelines of others ▪ The saturated fatty acids founds in dairy products have been associated with positive health outcomes (e.g. Alexander DD, Bylsma LC, Vargas AJ, Cohen SS, Doucette A, Mohamed M, et al. Dairy consumption and CVD: a systematic review and meta-analysis. Br J Nutr. 2016;115(4):737-50.), and as such the promotion of low-fat milk and yoghurts is also not consistent with much of the currently available evidence. The demonisation of all	

		saturated fat is invalid as different chain lengths, and whether the chains have an odd or even number of carbons, are differentially associated with cardiovascular disease risk (e.g. Forouhi NG, Koulman A, Sharp SJ, Imamura F, Kröger J, Schulze MB, et al. Differences in the prospective association between individual plasma phospholipid saturated fatty acids and incident type 2 diabetes: the EPIC-InterAct case-cohort study. The Lancet Diabetes & Endocrinology. 2014;Oct;2(10):810-8. doi: 10.1016/S2213-8587(14)70146-9. Epub 2014 Aug 5.) o Page 23, impact statement: the statement regarding systematic reviews of low carb diets is far too strong in relation to the available evidence. At most the statement should reflect that **based on the existing evidence** the benefits **may** only be short-term. As stated before, the claim that longer-term evidence is needed before guidelines are updated places a higher burden of evidence on alternative dietary approaches than have been used for the existing guidelines. Importantly, even if the appraisal of evidence is limited to that identified for the review carried out for the current surveillance, none of the reported outcomes were inferior for the low carb dietary approach (as summarised in Table 3, page 54). If there is no evidence that the existing guidelines are superior to an alternative then the alternative should be included as a viable option. The appraisal of evidence here also fails to consider medication changes, which often favours the low carb arm of studies and results in any possible benefits being understated	

		• A systematic review and meta-analysis by Mcardle et al (McArdle, P. D., et al. (2018). "Carbohydrate restriction for glycaemic control in Type 2 diabetes: a systematic review and meta-analysis." Diabetic Medicine **36**(3): 335-348) should have been included (it was first published on November 13th 2018, before the 12th February 2019 cut point). The stated conclusions of this review are consistent with those of the other reviews included	
AstraZeneca Ltd. (UK)	Yes	Comment 1. We welcome the recognition of the need to update the NG28 guideline and we agree with the proposed scope (focus on blood glucose management and complications) for this guideline update. AstraZeneca feels this is an important opportunity for NICE to bring the current guideline in line with the emerging outcome data (for example SGLT2 and GLP1 class of medicines) in patients with Type 2 diabetes. This will also further align the guideline with other publications such as the recently published NHS long term plan which has highlighted diabetes as a key priority focus, particularly with regards to diabetes prevention, the management of long-term conditions, co-morbidities and preventing complications e.g. cardiovascular risk. NHS health checks are being used to identify patients at increased risk of cardiovascular and renal disease and recently the diabetes QOF indicators have been updated to better understand and manage this population with regards to cardiovascular disease. Individualising patient care has been a focal point in care planning for number of years and remains a key factor in managing those living with type 2 diabetes. The recently	Thank you for your comments. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults. Information obtained through the surveillance review, including feedback from stakeholders through this consultation, will be considered during the update of the guideline. This will include the points you raise: • evidence for preventing primary cardiovascular and renal events seen in recent clinical trials with SGLT2 inhibition, including the DECLARE-TIMI trial • the request to clarify the health economic modelling element of the update. Details of this have yet to be determined but it is proposed that an update to the economic model be conducted for NG28 in conjunction with NICE technology appraisals. Further details will be available on the update web page.

		published ADA/EASD (The American Diabetes Association / European Association for the Study of Diabetes) position statement gives guidance on the management of glycaemia in adults with type 2 diabetes, with the goal of reducing complications and maintaining quality of life in the context of comprehensive cardiovascular risk management and patient-centred care. These recommendations have recognised the recent evidence base from clinical trials with both SGLT2 inhibitors and GLP-1 receptor agonists. Comment 2. AstraZeneca welcomes the recognition, that both SGLT2 inhibitors and GLP-1 receptor agonist CVOT trials have evidence providing CV and renal benefits in patients with atherosclerotic cardiovascular disease. We would like to highlight also that there is growing evidence for preventing primary CV and renal events seen in recent clinical trials with SGLT2 inhibition. The American College of Cardiology/The American Heart Association (ACC/AHA) has recently published their guideline on the primary prevention of cardiovascular disease which recognises the preventative risk reduction evidence of the SGLT2 and GLP1 class medicines in adults with T2DM and reserves a place for these medicines for primary prevention of CVD (Arnett et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease DOI:10.1161/CIR. 0000000000000678). Given the focus within the NHS on prevention AstraZeneca believes it is important for this to be considered as part of the review and necessary update of the diabetes guidelines and we will provide relevant data from DECLARE trial (that demonstrated significant	

		reduction of CV death or hospitalisation for heart failure in T2DM patients with and without established CVD, compared to placebo) to support this position. Comment 3. We would welcome further clarity on the proposal of health economic modelling e.g. cost effectiveness of SGLT2/GLP1 class medicines both in terms of the proposed process and any related need for subsequent updates of single (STA) and/or multiple technology appraisals(MTA) for SGLT2 inhibitors. We understand that a cost-effectiveness analyses of the evidence base can be considered and included as part of the guideline update rather that a need to update associated STAs/MATs. It would be appreciated if this clarification could be built into the publication of this phase of consultation results in June 2019.	
Eli Lilly and Company Ltd	Yes	A thorough review has been performed and we agree with the proposal to update the guideline. Brief comments are provided below: 1. For clarity, the REWIND data will be presented at the American Diabetes Association (ADA) conference on 9 June 2019, with full publication expected soon thereafter. 2. Second intensification (pg. 6/88): The proposal has recommended a review of evidence supporting the use of liraglutide for T2D in combination with insulin, particularly for	Thank you for your comments. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults, including the blood glucose management section. Information obtained through the surveillance review, including feedback from stakeholders through this consultation, will be considered during the update of the guideline. This will include the evidence you highlight on GLP-1 analogues other than liraglutide, such as the REWIND and AWARD series of trials for dulaglutide in both first and second intensification

		improving glucose control, cardiovascular outcomes and weight loss. A review should consider not only evidence supporting the use of liraglutide for T2D in combination with insulin, but also other GLP-1 mimetics for T2D in combination with insulin including dulaglutide. The relevant studies for consideration for dulaglutide are: Combination with insulin (dulaglutide/comparator): • Once-weekly dulaglutide versus bedtime insulin glargine, both in combination with prandial insulin lispro, in patients with type 2 diabetes (AWARD-4): a randomised, open-label, phase 3, non-inferiority study (1) • Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial (2) • Placebo-controlled, randomized trial of the addition of once-weekly glucagon-like peptide-1 receptor agonist dulaglutide to titrated daily insulin glargine in patients with type 2 diabetes (AWARD-9) (3) 3. Dulaglutide (pg 32/88): The proposal has identified 4 RCTs and a cost effectiveness study covering dulaglutide intensification treatment for T2D. Whilst this may be highlighting only those studies published after the date of the previous version of guideline NG28, if it is meant to include all relevant studies, they include:	of treatment. The evidence has been included in Appendix A accordingly.

		First Intensification (metformin + dulaglutide/comparator): • Efficacy and Safety of Dulaglutide Versus Sitagliptin After 52 Weeks in Type 2 Diabetes in a Randomized Controlled Trial (AWARD-5) (4) • Safety and efficacy of once-weekly dulaglutide versus sitagliptin after 2 years in metformin-treated patients with type 2 diabetes (AWARD-5): a randomized, phase III study (5) • Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial (6) **Second Intensification (metformin + AN other + dulaglutide/comparator):** • Efficacy and Safety of Dulaglutide Added on to Pioglitazone and Metformin Versus Exenatide in Type 2 Diabetes in a Randomized Controlled Trial (AWARD-1) (7) • Efficacy and Safety of Once-Weekly Dulaglutide Versus Insulin Glargine in Patients With Type 2 Diabetes on Metformin and Glimepiride (AWARD-2) (8) • Dulaglutide as add-on therapy to SGLT2 inhibitors in patients with inadequately controlled type 2 diabetes (AWARD-10): a 24-week, randomised, double-blind, placebo-controlled trial (9) **Combination with insulin (dulaglutide/comparator):** • AWARD 4, 7 and 9 (references provided above)	

UCL Eastman Dental Institute	Yes	A bulk of evidence suggests that oral health is closely linked to diabetes in a bidirectional manner.	Thank you for your comment. The aetiology of diabetes is not within scope for NICE guideline NG17, NG18 or NG28 however NICE guideline NG18 cross-refers to NICE guideline CG19 on dental recall. This highlights diabetes as a risk factor for developing dental disease and notes that 'People with diabetes (both type I and type II) are at increased risk of developing destructive periodontal disease … individuals with diabetes may need a more frequent recall. Inadequate plaque control and the presence of other risk factors will modify the recall interval further.' This issue will be put forward for consideration for scoping discussions for NICE guidelines NG17 and NG28 as expert input is required to determine an appropriate way of highlighting oral health in people with diabetes.
Gilead Sciences	Yes	No comments provided	Thank you.
MedTech Europe	Yes	**Assess observational data/Real World Evidence (RWE):** HTA bodies should not only focus on RCTs but draw on broader sources of evidence, especially observational data / RWE. This is to support early adoption and help managing uncertainty risks.	Thank you for your comment. Please note that for the purposes of this surveillance review only Cochrane reviews and RCTs are included. Therefore, studies submitted within other study designs were not included and are stated as out of scope. This included real world data. NICE is considering how real world data may be further used to inform guideline development and a public consultation on this will be taking place in the Summer 2019.

Bayer plc	Yes	No comments provided	Thank you.
Association for Clinical Biochemistry and Laboratory Medicine	Yes	Very much needed given newer agents	Thank you for your comment.
Takeda UK Ltd	Yes	No comments provided	Thank you.
Boehringer Ingelheim Ltd.	Yes	**Comments Summary:** Boehringer Ingelheim agrees with the National Institute for Health and Care Excellence's proposal to undertake a full review and update of the antidiabetic drug pathway within National Guideline 28, for the management of adults with type 2 diabetes. Boehringer Ingelheim also welcomes the opportunity to review the guideline, alongside the surveillance proposal consultation document, and provide comments. In summary, Boehringer Ingelheim proposes the following key points to consider when undertaking the guideline update, with further details provided thereafter: - Based on the current evidence base, treatment should be selected to target specific complications and inherent risks, and move away from purely HbA1c considerations in the management of patients with type 2 diabetes. This should include evidence surrounding cardiovascular and renal outcomes trials to aim to reduce micro- and macro-vascular complications.	Thank you for your comments. Please note that for the purposes of this surveillance review only Cochrane reviews and RCTs are included. Therefore, studies submitted within other study designs were not included and are stated as out of scope. This included real world data. NICE is considering how real world data may be further used to inform guideline development and a public consultation on this will be taking place in the Summer 2019. Please also note that studies already covered by the comprehensive NICE 2017 evidence review of drugs used to manage diabetes in people with a high risk of CVD, such as the EMPA-REG OUTCOME trial publications, were not included in the surveillance review. **Feedback on specific aspects of drug treatment for blood glucose lowering** The proposed update will include the feedback on the following points:

		- A risk stratification model that incorporates cardiovascular disease management as an integral part of the management of type 2 diabetes, is likely to promote a patient-centred approach to drug therapy. This, along with recommending newer medicines with published cardiovascular outcome data earlier in the treatment pathway, could remove the barrier to appropriate treatment escalation and bring NG28 in line with the NHS Long Term Plan to reduce treatment inertia and variation and prevent premature death and hospitalisations. - Boehringer Ingelheim recommends, based on the evidence available, that antidiabetic agents with proven cardiovascular benefit, particularly reduction in cardiovascular death and hospitalisation for heart failure, are recommended in preference to medicines with cardiovascular safety. Medicines with no cardiovascular data, such as sulphonylurea and pioglitazone, should only be recommended in rare cases, such as contraindications or patients not tolerating medicines that are otherwise recommended. - There is considerable clinical and cost-effectiveness data to support the use of SGLT2 inhibitors, particularly empagliflozin, earlier in the treatment escalation pathway, alongside metformin. - There is an important place in the antidiabetic treatment pathway for DPP4 inhibitors, specifically linagliptin for patients with renal impairment, as a first or second intensification option. - In addition, Boehringer Ingelheim asks that antidiabetic medications are not grouped together and referred to on a class level, as there are a number of differences between compounds	• The need to consider drug treatment to prevent renal complications, specifically – the CREDENCE study covering canagliflozin for renal protection. However, canagliflozin is covered by the technology appraisal TA390 Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes (May 2016). This information will be passed to the NICE TA team for consideration in reviewing this guidance. – DPP-4 inhibitors, particularly linagliptin, for patients with renal impairment. Linagliptin was highlighted with supporting evidence as the only DPP-4 inhibitor that does not require dose adjustment based on a patient's level of renal function. Renal outcomes are already proposed for consideration in the review of this section of the guideline, which will include the forthcoming results of the CAROLINA trial. • Timing of treatment intensification. NICE guideline NG28 advises treatment escalation when HbA1c rises higher than 58mmol/mol (>7.5%) until control is achieved. The proposal to provide more information on the time a patient should spend at uncontrolled hyperglycaemia before treatment intensification will be considered during the scoping of the update of the guideline. • The risk-benefit profile of a medicine, rather than merely the safety and tolerability profile. The evidence base currently available may no longer support the recommendation of agents such as sulphonylureas, which can increase the risk of hypoglycaemia and weight gain and lack cardiovascular outcome trial data. This will be considered in the update.

		within the same classes that need to be considered. Further details are provided below. **<u>Inclusion of CVOTs in NG28</u>** In particular, Boehringer Ingelheim asks that NICE adopt a similar approach to the methodology outlined in the joint American Diabetes Association (ADA) and European Association for the study of Diabetes (EASD) guideline for the Management of Hyperglycaemia in Type 2 Diabetes published in October 2018. The ADA/EASD guideline specifically advocates the appropriate management of both glycaemic and cardiovascular risk factors as well as the careful consideration of patient factors to promote a patient-centred approach to treatment escalation. In both instances, SGLT2 inhibitors (specifically empagliflozin and canagliflozin) and some GLP1 agonists are highlighted as medicines which have proven cardiovascular benefit and are recommended as part of glycaemic management. In NHS England, prescribing trends show an increase in the use of these two classes of antidiabetic agents. Therefore, an update to NG28 should aim include evidence published since the last update, including the following key cardiovascular outcomes trial (CVOT) not mentioned in the surveillance proposal consultation document: - EMPA-REG OUTCOME®: the first dedicated CVOT to demonstrate a 14% relative risk reduction (RRR) in major adverse cardiac events (MACE), 38% RRR in cardiovascular mortality, and a 35% RRR hospitalisation for heart failure with a	• The distinction between individual and fixed combinations of GLP-1 analogues and basal insulin; stakeholders indicated that it is clinically important to distinguish these treatment options and provide guidance on each. This proposed distinction will be considered during the scoping of the update of the guideline, including evidence identified in surveillance for fixed-ratio combinations of liraglutide and lixisenatide. • Class level comparisons between drug classes were highlighted as limited by differences within classes in terms of CVD outcomes, safety, tolerability and acquisition costs. This is already acknowledged in the surveillance review and will be highlighted for consideration in the update.

		glucose lowering agent, the sodium glucose co-transporter 2 (SGLT2) inhibitor empagliflozin, given on top of standard-of-care therapy for patients with type 2 diabetes with established cardiovascular disease (defined as coronary artery disease, peripheral arterial disease, pervious MI, and previous stroke). Key publications for the EMPA-REG OUTCOME® trial include: o Zinman et al (2015). Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. NEJM; https://www.nejm.org/doi/full/10.1056/NEJMoa1504720 o Fitchett et al (2016). Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial. European Heart Journal; https://www.ncbi.nlm.nih.gov/pubmed/26819227 o Wanner et al (2016). Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. NEJM; DOI: https://www.nejm.org/doi/full/10.1056/NEJMoa1515920 - CARMELINA: dedicated randomised CVOT investigating the effect of linagliptin compared to placebo on the risk of major cardiovascular events in type 2 diabetes patients with high cardiovascular risk. This study met its primary endpoint, with linagliptin showing a similar cardiovascular safety profile compared with placebo when added to standard of care (Rosenstock et al: https://jamanetwork.com/journals/jama/fullarticle/2714646).	

		- CAROLINA: the first DPP-4 inhibitor CVOT to compare versus an active comparator, glimepiride. The study met its primary endpoint, showing that there are no safety signals observed with linagliptin added to standard of care. Full results publication is expected in June 2019. (https://clinicaltrials.gov/ct2/show/NCT01243424). **Real world data support results from CVOTs for Empagliflozin** In addition, initial effectiveness results from the real-world EMPagliflozin compaRative effectIveness and SafEty (EMPRISE) study showed empagliflozin was associated with a 44 percent relative risk reduction in hospitalisation for heart failure (HHF) compared with dipeptidyl peptidase-4 (DPP-4) inhibitors in routine clinical practice in the U.S. The EMPRISE analysis of data from approximately 35,000 people with type 2 diabetes between August 2014 and September 2016 will be presented at the American Heart Association® (AHA). Further information can be found in the following publication adbstract: - Patorno et al (2018). Abstract 14741: Empagliflozin and the Risk of Heart Failure Hospitalization in Routine Clinical Care: A First Analysis From the Empagliflozin Comparative Effectiveness and Safety (EMPRISE) Study. *Circulation;* vol 138, Issue Suppl. 1. A similar study is currently being conducted within the UK clinical practice setting comparing against DPP4 inhibitors	

		and all other oral antidiabetic medications. This study (EMPRISE-UK) is due to complete December 2019. **<u>Both improvement of glycaemic control and reduction of cardiovascular morbidity and mortality are an integral part of the treatment of type 2 diabetes</u>** Boehringer Ingelheim also agrees with the statement in the surveillance proposal consultation document stating that other comorbidities, such as heart failure and chronic kidney disease need to inform the choice of first intensification medication. Boehringer Ingelheim proposes that this statement also needs to be incorporated into the "managing complications" section 1.7 of the guideline, by adding a specific section with further guidance on the management of cardiovascular complications and chronic kidney disease. Ideally, when updating NG 28, the guideline should move away from purely HbA1c lowering as a treatment goal, and incorporate a more holistic view of the management of type 2 diabetes and its complications, of which cardiovascular complications are the most common. Patient factors beyond HbA1c to assess when choosing an add-on therapy include coronary artery disease, lipid levels, blood pressure and weight, which all contribute to the risk of cardiovascular and renal events. Therefore, Boehringer Ingelheim recommends incorporating the management of cardiovascular and renal outcomes as an integral part of type 2 diabetes management throughout NG28, including the treatment algorithm.	

		Empaglifloin is a cost effective treatment option In terms of cost-effectiveness analyses, the surveillance proposal consultation documents highlights the lack of cost-effectiveness analyses based directly on cardiovascular outcomes reported in randomised trials. Boehringer Ingelheim and NICE were in conversation during 2017 and 2018 regarding the appraisal of empagliflozin for reducing the risk of cardiovascular events in type 2 diabetes (ID1037). That appraisal has since been suspended; however, the results continue to show a favourable incremental cost-effectiveness ratio (ICER) for empagliflozin versus standard of care. Specifically, cost-effectiveness analyses show an ICER of £4,365 per quality adjusted life year (QALY) gained for empagliflozin versus standard of care (https://www.valueinhealthjournal.com/article/S1098-3015(16)33242-9/abstract). Boehringer Ingelheim would welcome the opportunity to provide further information regarding the cost-effectiveness of empagliflozin. **Class effect cannot be assumed for SGLT2 inhibitors** Throughout NG 28, recommendations regarding SGLT2 inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors are referred to as a group of drugs at a class level. Boehringer Ingelheim agrees with the statement in the surveillance proposal consultation document that highlights that referring to medicines at as class level may no longer give sufficient clarify on the appropriate use of medicines given that a class effect cannot always be assumed. The	

		difference between medicines within the same class is well documented in respective key clinical studies; for example, of the three SGLT2 inhibitor CVOTs, EMPA-REG OUTCOME® for empagliflozin, DECLARE-TIMI 58 for dapagliflozin, and the CANVAS programme for canagliflozin, only the empagliflozin and canagliflozin CVOTs showed primary superiority for the reduction of MACE endpoints. In addition, the empagliflozin study was the only CVOT to show superiority in the reduction of cardiovascular death and death from any cause. Due to a lack of CVOT evidence for ertugliflozin, another SGLT2 inhibitor, one cannot assume a cardiovascular benefit for this compound based on the results of other medicines. Similarly, the safety and tolerability results from individual SGLT2 inhibitors are not uniform across the class. For example, the CANVAS programme showed an increased risk of lower limb amputations and fractions, whereas EMPA-REG OUTCOME® and DECLARE-TIMI 58 did not show this safety signal. This illustrates that within a class, each compound will have a different clinical and cost-effectiveness profile. **Linagliptin is the only DPP4 inhibitor that does not require dose adjustment** When considering DPP-4 inhibitors, there are clinical considerations that need to be taken into account, including the requirement for dose-adjustment. Linagliptin is the only DPP-4 inhibitor that does not require dose adjustment based on a patient's level of renal function (https://www.medicines.org.uk/emc/product/4762/smpc).	

		This is particularly pertinent in clinical practice as results from a cross-sectional study using UK general practice data shows that of patients prescribed a DPP-4 requiring dose adjustment (alogliptin, sitagliptin, saxagliptin and vildagliptin) 32% of patients were initiated on a higher dose than recommended in the Summary of Product Characteristics (SmPC) of each product (https://www.clinicaltherapeutics.com/article/S0149-2918(17)31073-1/pdf) . In addition, 10% of patients were initiated on a lower dose than recommended in the SmPCs (https://www.clinicaltherapeutics.com/article/S0149-2918(18)30253-4/abstract). Therefore, it is not appropriate to imply or assume a class effect for any class of medicines, and factors beyond drug acquisition cost should direct clinicians toward prescribing the most appropriate treatment for each individual patient whilst taking account of numerous co-morbidities. **Updating NG28 to include specific guidance on timelines around treatment intensification could improve current treatment inertia** The current NICE guidelines advise treatment escalation when HbA1c rises to >58mmol/mol (>7.5%) until control is achieved. Little information is offered regarding the time a patient should spend at hyperglycaemia before treatment intensification. This propagates a reactive approach wherein clinicians wait for the worsening of hyperglycaemia or complications to arise before intensifying treatment, and patients will likely reach glycaemic targets for only short periods. A study carried	

		out on 81,573 patients found that the time to treatment intensification for a patient with an HbA1c >7% (>53 mmol/mol) while on monotherapy was 1.6 years and >6.9 years for patients on two oral antidiabetic medications. Therefore, there is insufficient focus in the current NG28 on how long a patient should remain uncontrolled before intensification of treatment and an update to the guideline provides an opportunity to improve appropriate treatment escalation. **Data support treatment recommendations based on the risk-benefit profile of an antidiabetic medicine** Additional clinical characteristics listed in the surveillance document include taking account of the risk of adverse events, particularly hypoglycaemia and weight gain. As such, the evidence base currently available may no longer support the recommendation of agents such as sulphonylureas, which can increase the risk of hypoglycaemia and weight gain and lack cardiovascular outcome trial data. Overall, there is data to support making treatment decisions based on the risk-benefit profile of a medicine, rather than merely the safety and tolerability profile. In summary, Boehringer Ingelheim supports the proposition that a full review of the antidiabetic drug pathway be undertaken. During this process, Boehringer Ingelheim encourages NICE to follow methodology similar to that outlined in the ADA/EASD consensus statement, including	

		the need to adopt risk stratification and appropriate treatment escalation to manage patient co-morbidities.	
Perspectum Diagnostics	Yes	No comments provided	Thank you.
South Asian Health Foundation	Yes	No comments provided	Thank you for your response.
Roche Diabetes Care, Ltd	Yes	Agree with the proposal to update the guideline and would ask NICE to consider the following general points: • More consideration should be given to real world evidence generated to support adoption of innovative technologies. The recently published evidence framework for digital health technologies should be consulted and referenced to allow evidence beyond traditional RCTs to be considered, particularly when reviewing smartphone applications and telemedicine. • Where provision of support (e.g. structured education) has traditionally been via face-to-face methods, the wording of the guidelines should be reviewed to include clarity where digital alternatives may be appropriate. • Where generated, patient reported outcomes should be given more consideration in addition to clinical outcomes - Bradley et al 2018 Predictors of Quality of Life and Other Patient-Reported Outcomes in the PANORAMA Multinational Study of People With Type 2 Diabetes. Diabetes Care Feb, 41 (2) 267-276	Thank you for your comments. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults. Please note that for the purposes of this surveillance review only Cochrane reviews and RCTs are included. Therefore, studies submitted within other study designs were not included and are stated as out of scope in the summaries below. This included real world data. NICE is considering how real world data may be further used to inform guideline development and a public consultation on this will be taking place in the Summer 2019. Thank you for your feedback suggesting a review of the wording of the patient education recommendations to emphasise the importance of digital alternatives. The new evidence identified for digital interventions is consistent with the evidenced-based principles set out in the existing guideline recommendations. However, your feedback on the wording will be considered in the update.

			Thank you for your feedback on patient reported outcomes. In line with the NICE guidelines manual, input on the main outcomes to be considered will be obtained through the scoping process and protocol development for the update. We will pass your comment regarding patient reported outcomes to the developers working on the update so this information can be considered during the scoping and protocol development phases.
Medtronic Ltd	Yes	No comments provided	Thank you.
Primary Care Diabetes Society	Yes	No comments provided	Thank you.
Royal College of Nursing	Yes	Needs to be in line with EASD and ADA for cardiovascular outcomes Full section on SGLT2 use, when to use and when to stop	Thank you for your comments. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults. Information obtained through the surveillance review, including feedback from stakeholders through this consultation, will be passed on to developers for consideration during the update of the guideline. The joint ADA and EASD guideline has been noted for contextual consideration in the proposed update.
Napp Pharmaceuticals Ltd.	Yes	Napp Pharmaceuticals Ltd are strongly in favour of the proposal to update NG28. Since the last issuance of this guideline, several significant and highly relevant clinical trials have been published concerning a number of	Thank you for your comments. Following consideration of stakeholder comments, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults, including drug treatment for blood glucose management.

		different T2DM pharmacological interventions. These trials are large, robust, and have provided high-grade evidence indicating a number of major additional benefits on T2D morbidity and mortality for some therapies, in addition to the known glycaemic control effects of these drugs. NG28 therefore at present does not represent an optimal approach to management of T2D based on all evidence now available. Several national and international guidelines have already been updated to include these new data, including the ADA/EASD guidance on management of T2D, and the corresponding SIGN guidance. Because NG28 has not yet been updated with these new data, the guideline is now significantly out of step with the guidelines that have been more recently updated, leading to conflicting messages and confusion amongst healthcare professionals involved in the management of T2D. Napp would be happy to furnish a list of all the newly available data for all agents on request.	As you suggest, the update will include a comprehensive search for all eligible trials that have been published subsequently to the guideline.
Dexcom Operating Ltd	Yes	No comments provided	Thank you.
Newcastle University	Yes	No comments provided	Thank you.

The British Dietetic Association	Yes	We agree with updating the guideline but disagree to the decision not to update the dietary advice on the grounds of: • Not having 'long-term' evidence of the effectiveness of these diets; and • The advice conflicting current recommendations to ensure individualised care (see below box for justification).	Thank you for your comments. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults in several areas including blood glucose management, insulin therapy and management of complications. We retain our proposal not to update the guideline around dietary advice. Long-term benefits of dietary interventions The totality of evidence for dietary interventions is currently limited to short-term benefits. It does not indicate conclusively that low carbohydrate and low calorie diets are a superior approach to other strategies for weight loss and subsequent weight maintenance in the long-term. The surveillance impact statement is therefore retained; that the longer-term results of the DIRECT study (beyond 2 years), and other longer-term studies of low calorie and low carbohydrate diets are likely to be needed to establish any definite impact on the guideline. A joint working group of The Scientific Advisory Committee on Nutrition, NHS England and Diabetes UK, with input from the British Dental Association and Royal Colleges, is reviewing the evidence on low carbohydrate diets with publication expected in 2020. This will be tracked by the surveillance team and the results will be considered when available. We will also pass the collective feedback in this area to the development team working on the update of the NICE guideline on obesity (CG189) as the main study identified in this area (DiRECT) fed into the decision to update NICE guideline CG189. Individualised care Please note that Section 1.1 already covers individualised care and advice. The guideline will also be updated with the following

			standard text placed at the beginning of the recommendations section: 'People have the right to be involved in discussions and make informed decisions about their care, as described in your care. Making decisions using NICE guidelines explains how we use words to show the strength (or certainty) of our recommendations, and has information about prescribing medicines (including off label use), professional guidelines, standards and laws (including on consent and mental capacity), and safeguarding.' Section 1.3 also recommends individualising nutritional advice (1.3.1) and advice for carbohydrate and alcohol intake, and meal patterns (1.3.6). The surveillance review and stakeholder consultation have not identified any conflict in these recommendations to warrant changing them.
Association of British Clinical Diabetologists	Yes	*We wish to say that the 2019 surveillance of 4 diabetes guidelines is welcomed and that there has obviously been a lot of thought and work put in to identifying areas ripe for updating. We are supportive of all areas annotated in the document.*	Thank you for your comment. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults. Information obtained through the surveillance review, including feedback from stakeholders through this consultation, will be passed on to developers for consideration during the update of the guideline.
NHS England	Yes	A National Project Board established by the Office of Chief Dental Officer, England had developed a Commissioning Standard – Dental Care for Patients with Diabetes (type 1 and type 2), which is now at the final stages of the	Thank you for your comment. The aetiology of diabetes is not within scope for NICE guideline NG17, NG18 or NG28 however NICE guideline NG18 cross-refers to NICE guideline CG19 on dental recall. This highlights diabetes as a risk factor for developing dental

		Gateway process and will be published on NHS England and NHS Improvement website. Production of this standard involved key dental (British Society of Periodontology, European Federation of Periodontology) and medical stakeholders (National Clinical Directors for Diabetes and Obesity, Programme Director NHS Diabetes Programme). As stated in the commissioning standard and evidenced below, the effective management of periodontal disease by the dental team has a role in prevention and treatment of diabetes. (SJH)	disease and notes that 'People with diabetes (both type I and type II) are at increased risk of developing destructive periodontal disease … individuals with diabetes may need a more frequent recall. Inadequate plaque control and the presence of other risk factors will modify the recall interval further.' This issue will be put forward for consideration for scoping discussions for NICE guidelines NG17 and NG28 as expert input is required to determine an appropriate way of highlighting oral health in people with diabetes.
Royal College of Physicians		We would like to endorse the responses submitted by the Diabetes Technology Network (DTN) and the Association of British Clinical Diabetologists (ABCD).	Thank you for your comment. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults. Information obtained through the surveillance review, including feedback from stakeholders through this consultation, will be passed on to developers for consideration during the update of the guideline.
Diabetes UK	Yes	Diabetes UK agrees with the proposal to update NG28, and supports the specific areas for review that have been identified (including the use of SGLT2s for blood glucose management and recommendations for diabetic eye disease). However, we would strongly suggest that additional topics also need reviewing and updating.	Thank you for your comment. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults. Information obtained through the surveillance review, including feedback from stakeholders through this consultation, will be passed on to developers for consideration during the update of the guideline.

Do you have any comments on areas excluded from the scope of the guideline?			
Stakeholder	**Overall response**	**Comments**	**NICE response**
Surrey Downs CCG	Yes	Second intensification - Evidence supporting the use of all GLP-1s for T2D in combination with insulin (not just liraglutide) should be considered, to reflect clinical practice. At all levels of treatment for T2D, advice is needed on when to withdraw or switch from ineffective medication as well as when to initiate. Otherwise patients remain on treatments that have not benefitted them and may put them at risk from side effects.	Thank you for your comment. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults. Information obtained through the surveillance review, including feedback from stakeholders through this consultation, will be passed on to developers for consideration during the update of the guideline. This will include evidence on GLP-1 mimetics other than liraglutide, such as semaglutide and dulaglutide.
NHS Leeds CCG	No	No comments provided.	Thank you.
South Sefton Clinical Commissioning Group	No	No comments provided.	Thank you.
British Dental Associaiton	Yes	The BDA believes that this guideline needs to be updated to include discussion of oral health maintenance and complications, and to recommend the inclusion of dentists in the multi-disciplinary teams providing care to diabetes patients. In particular, periodontal disease has a bi-directional relationship with diabetes.	Thank you for your comment. The aetiology of diabetes is not within scope for NICE guideline NG17, NG18 or NG28 however NICE guideline NG18 cross-refers to NICE guideline CG19 on dental

		https://www.nature.com/articles/sj.bdj.2017.544 https://www.nature.com/articles/sj.bdj.2014.907	recall. This highlights diabetes as a risk factor for developing dental disease and notes that 'People with diabetes (both type I and type II) are at increased risk of developing destructive periodontal disease … individuals with diabetes may need a more frequent recall. Inadequate plaque control and the presence of other risk factors will modify the recall interval further.' This issue will be put forward for consideration for scoping discussions for NICE guidelines NG17 and NG28 as expert input is required to determine an appropriate way of highlighting oral health in people with diabetes.
Total Diet and Meal Replacements (TDMR) Europe	No	No comments provided.	Thank you.
Digital Diabetes Media Ltd	Yes	With the increased awareness of type 2 diabetes remission there has been a significant shift in the approach to type 2 diabetes in clinical practice. A greater emphasis is now being placed on person-centred and personalised lifestyle management. Physiology, published evidence, and clinical practice support the role of very low calorie diets, and low carbohydrate approaches. Although the current NICE guideline is not unsupportive of these approaches, it does not adequately reflect the significance of these approaches, and thus there is risk that clinicians may provide inadequate lifestyle management options and support to patients. Improving the balance in the guideline to reflect the published evidence base and clinical practice would now be appropriate. There are numerous academic publications in recent years discussing this topic. Two recent publications that give a reasonable overview of the evidence to date are:	Thank you for your comments. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults. Information obtained through the surveillance review, including feedback from stakeholders through this consultation, will be passed on to developers for consideration during the update of the guideline. Please note that Section 1.1 already covers individualised care and advice. The guideline will also be updated with the following standard text placed at the beginning of the recommendations section: 'People have the right to be involved in discussions and make informed decisions about their care, as described in your care. Making decisions using NICE guidelines explains how we use words to show the strength (or certainty) of our recommendations, and has information about prescribing medicines (including off label use),

		The recent publication in Diabetes Care from Evert et al. *Nutrition Therapy for Adults With Diabetes or Prediabetes: A Consensus Report* *Diabetes Care 2019 May; 42(5): 731-754.* *http://care.diabetesjournals.org/content/42/5/731* A narrative review for the variety of methods to achieve type 2 diabetes remission was published in April 2019 by Hallberg et al. *Reversing Type 2 Diabetes: A Narrative Review of the Evidence* *Nutrients 2019, 11(4), 766* *https://www.mdpi.com/2072-6643/11/4/766/htm* Balancing the NICE guideline to adequately reflect the above would be helpful in supporting best practice and the delivery of person-centred personalised medicine.	professional guidelines, standards and laws (including on consent and mental capacity), and safeguarding.' Please note that for the purposes of this surveillance review only Cochrane reviews, recent systematic reviews in priority areas, and RCTs are included, due to resource constraints and the volume of evidence. Therefore, studies submitted within other study designs were not included.
UK Clinical Pharmacy Association (UKCPA) Diabetes and Endocrinology Group	Yes	Evidence was identified on individualised care, patient education and antiplatelet therapy which directly supports or is consistent with existing recommendations and therefore has no impact on NICE guideline NG28. Targets for frail and multi-morbid older people have not been specified in previous guidelines however since the last guideline was updated there has been significant evidence reviewed and published with regards to HbA1c targets for this population. Please consider review with regards to adding targets such as these given the relationship between HbA1c and mortality in this patient group. All the topics proposed to be reviewed are appropriate, but no mention of updating recommendations on blood glucose control in respect to frailty level, which is just as important aspect as the consideration of placing therapy based on cardiovascular outcomes.	Thank you for your comments. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults. Information obtained through the surveillance review, including feedback from stakeholders through this consultation, will be passed on to developers for consideration during the update of the guideline. This will include age and frailty level, GLP-1 analogue drugs in addition to liraglutide, and evaluation of individual drugs within classes at first and second intensification as well as class level comparisons. Long-term data on dietary interventions The totality of evidence for dietary interventions is currently limited to short-term benefits. It does not indicate conclusively that low carbohydrate and low calorie diets are a superior approach to other strategies for weight loss and subsequent weight maintenance in the long-term. The surveillance impact statement is therefore retained;

		Under 'Second intensification', the first bullet point 'The evidence indicating that GLP1 mimetics as a class may be cost effective, with additional drug costs offset by diabetes-related complications decreases, leading to slightly lower direct medical costs.' This statement would also apply to the SGLT2s. Although SGLT2s are already listed as an option for first and second intensification, the point to emphasise is both of these classes may lead to reduced costs due to complications. This is also linked to the 'Cost effectiveness' section where the committee stated it would not be appropriate to make specific recommendations about the place of SGLT2s and GLP1s in the diabetes management pathway. This points needs clarification. Under 'second intensification' again, second bullet point 'Evidence supporting the sue of liraglutide for T2D in combination with insulin, particularly for improving glucose control, CV outcomes and weight loss.' This seems to be a very specific recommendation just considering liraglutide, and not other GLP1s that have also demonstrated these 3 benefits. If considering cost comparison, dulaglutide is slightly cheaper than liraglutide, with the added benefit of once weekly administration. In clinical practice once weekly administration has been favoured by patients. Evidence on the effectiveness of very low-calorie diets on short-term remission has been proposed not to be updated, the committee thinks best to await for further long term effectiveness data. Given after this guideline update, it	that the longer-term results of the DIRECT study (beyond 2 years), and other longer-term studies of low calorie and low carbohydrate diets are likely to be needed to establish any definite impact on the guideline. A joint working group of The Scientific Advisory Committee on Nutrition, NHS England and Diabetes UK, with input from the British Dental Association and Royal Colleges, is reviewing the evidence on low carbohydrate diets with publication expected in 2020. This will be tracked by the surveillance team and the results will be considered when available.

		might be a long time until the next update, is it still worthwhile to consider the short-term remission data?	
Merck Sharp & Dohme Limited	Yes	MSD is of the opinion the key to effective management of diabetes patients is individualised care. Therefore, issues such as co-morbidities and frailty should be given due prominence in making evidence-based treatment decisions.	Thank you for your comments. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults. Information obtained through the surveillance review, including feedback from stakeholders through this consultation, will be passed on to developers for consideration during the update of the guideline. This will include factors such as co-morbities and frailty level to inform individualised care.
Diabetes Research Unit Cymru (Wales) (DRUC)	Yes	First intensification (P4, Surveillance proposal consultation document): DRUC strongly supports the proposal that co-morbidities including atherosclerotic cardiovascular disease, chronic kidney disease and congestive cardiac failure should influence the first (and subsequent) intensification of glucose-lowering therapies. It would be positive if a guideline consistent with the EASD/ADA consensus statement could be produced in a short timeline. First intensification (P4, Surveillance proposal cons ultation document): DRUC also supports the proposal that the risk of specific adverse medicine effects, particularly hypoglycaemia and weight gain, should influence therapy choices. Second intensification (P5, Surveillance proposal consultation document): See comments in response to ID 5 & 6	Thank you for your comments. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults. Information obtained through the surveillance review, including feedback from stakeholders through this consultation, will be passed on to developers for consideration during the update of the guideline. This will include therapies at initial, first and second intensification stages as highlighted. **BMI threshold** NICE guideline NG28 stipulates a body mass index (BMI) threshold of 35 kg/m2 prior to being able to receive a GLP-1 analogue but stakeholder comments suggested that this is not evidence-based. The evidence submitted to support that GLP-1 analogues consistently reduce HbA1c and body weight regardless of baseline BMI was not within the scope or search period of the surveillance

		Treatment intensification in people not receiving metformin: NG28 does not support the use of GLP-1RA therapies in people not receiving metformin – this should be reassessed. Treatment intensification with GLP-1Ras: NG28 only supports the prescription of GLP1-RAs after failure of triple oral therapy and only in combination with metformin and sulfonylureas – this should be reassessed. BMI limitation for GLP-1RA prescriptions: NG28 requires that people should have a BMI of 35 Kg/m2 or more before being considered for GLP-1RAs - this should be reassessed. Eye disease (P7, Surveillance proposal consultation document): In view of the continuing delay in implementing the recommended UK National Screening Committee Diabetic Retinopathy recommendations for screening intervals, NICE should retain their support for these recommendations and not withdraw as suggested in the document. Managing complications (P7, Surveillance proposal consultation document): At present, there appears to be no plan to revise guidance concerning diabetic nephropathy. The recent publication of the CREDENCE study, which examined primary renal end-points in people with type 2 diabetes, supports the use of canagliflozin for renal protection. The results are also entirely consistent with benefits in the secondary renal end-points reported from the EMPA-REG, CANVAS and DECLARE-TIMI 58 cardiovascular outcome trials, supporting a class effect for the SGLT-2 inhibitors. These	review. However, the feedback from stakeholders suggested the current recommendation may not be accurate therefore this area will be considered in the update. **Chronic kidney disease and T2D** CKD and renal outcomes are already proposed for consideration in the review of the antidiabetic drug pathway. More specific advice for CKD in T2D will be considered for inclusion in NICE's guideline on chronic kidney disease in adults, which already includes advice for type 1 and 2 diabetes. **Urinary albumin screening** A further comment proposed consideration of urinary albumin screening for cardiovascular risk, as opposed to impending end-stage renal disease. However, no evidence was submitted to support yearly screening for microalbuminuria in T2D, and in the absence of any evidence identified in the surveillance review, this area will not be included in the update. **Antiplatelet therapy** Please note that recommendation 1.5.2 cross refers to NICE guidelines on cardiovascular disease and myocardial infarction for more detailed advice on antiplatelet therapy for primary and secondary prevention of CVD. **Self-monitoring of blood glucose** NG28 recommends (1.6.5) that patients are involved in discussions around their individual HbA1c target, considering adverse effects such as hypoglycaemia. Self-monitoring of blood sugar is only recommended in specific circumstances and not routinely (1.6.13). It also recommends (1.6.32) continuing telephone support when

		data should lead to an update of the guidance for this complication. Managing complications (P7, Surveillance proposal consultation document): NG28 makes no mention of microalbuminuria screening, referring readers to CG182 'Chronic kidney disease in adults:assessment and management'. Given that the majority of urinary albumin screening is for cardiovascular risk rather than impending end-stage renal disease, the clinical and financial justification for yearly screening for microalbuminuria in type 2 diabetes needs to be reassessed. Areas not proposed for update: antiplatelet therapy (P24, Surveillance proposal consultation document): The document speaks to 'antiplatelet therapy' but only mentions aspirin. The area is more complex than this, for example in a type 2 diabetes patient with prior ischaemic stroke addition of dipyridamole retard to low dose aspirin or use of clopidogrel should be recommended. Areas not proposed for update: Self-monitoring of blood glucose (P25, Surveillance proposal consultation document): It is suggested that newest evidence is unlikely to change guideline recommendations, based on the assertion that for people with type 2 diabetes (T2D) who are not using insulin, any benefit from self-monitoring is relatively small (< 6 mmol/mol, 0.5%) and is unlikely to last beyond 6 months. However, one of the new RCTs [Ref 31, Surveillance proposal consultation document] clearly demonstrates that structured SMBG reduced HbA1c by 12mmol/mol (1%) at 12 months (a statistically and clinically significant reduction) compared to a control group receiving usual care not involving SMBG. This reduction in HbA1c is greater than that required to demonstrate	starting insulin therapy but does not mention other forms of telemedicine. The collective new evidence indicates that for people with T2D who are not using insulin, any benefit from self-monitoring is small and is unlikely to last beyond 6 months. This supports NG28 recommendation 1.6.13 that self-monitoring is not used routinely for people with type 2 diabetes unless there is a specific reason to do so. Doctors may consider offering self-monitoring of blood glucose in the short term for people starting treatment with steroids or to confirm suspected hypoglycaemia (recommendation 1.6.14).

		efficacy of a glucose-lowering agent. Importantly, structured SMBG was also 3 times more likely to achieve a HbA1c target of ≤53 mmol/mol (≤7%) than standard care. Other studies that have utilised structured SMBG have also shown benefit in glycaemic control, quality of life, and a reduction in depression and distress. DRUC strongly believes that structured Self-Monitoring of Blood Glucose (SMBG), i.e. using paired BG readings (pre- and postprandial) to generate BG profiles that identify patterns of glycaemic abnormalities, followed by the taking of appropriate action, is needed as part of the self-management process for people with sub-optimally controlled T2 D, either chronic or short-term. People living with T2D not on insulin therapy should not be denied the option of structured SMBG. Introduction of SMBG should include the necessary sampling and monitoring equipment alongside training to help them accurately determine and record their BG results correctly. With the knowledge to interpret the results they should be able to take appropriate action, such as making lifestyle changes and/or seek further advice. The frequency of monitoring can be determined according to need but should involve "paired testing". Those not able to engage fully with the procedure and/or respond appropriately to the BG profiles should be offered additional support or structured SMBG be discontinued.	
Abbott Diabetes Care	Yes	There is a recently published RCT: Yaron et al: Effect of Flash Glucose Monitoring Technology on Glycaemic Control and Treatment Satisfaction in Patients with Type 2 Diabetes, Diabetes Care, https://doi.org/10.2337/dc18-0166	Thank you for your comments. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults. Information obtained through the surveillance review, including feedback from

		101 patients randomised to either intervention Flash Glucose Monitoring or standard care (SMBG). The changes in HbA1c were −0.82% (9 mmol/mol) vs. −0.33% (3.6 mmol/mol) in the intervention and control group, respectively (P = 0.005); in Non prespecified post hoc analysis, 68.6% of the patients in the intervention group had their HbA1c reduced by ‡0.5% (5.5 mmol/mol) compared with 30.2% in the control group (P < 0.001), and 39.2% had their HbA1c reduced by ‡1.0% (10.9 mmol/mol) vs. 18.6% in the control group (P = 0.0023) without an increased frequency of hypoglycaemia. Conclusions: Flash Glucose Monitoring tends to improve treatment satisfaction and may lead to amelioration of glycaemic control in patients with type 2 diabetes on MDI without increasing the frequency of hypoglycaemia. Prospective real-world studies are important data to show the generalisation of RCTs results in real world settings and should therefore be considered. Some of the challenge to conducting medical device HTA may be overcome by applying pragmatic approaches to adjust assessment processes and drawing on broader sources of evidence; especially observational/real world evidence to support early adoption and help to manage the risks associated with uncertain evidence. Additionally, with the digitalisation of Health, observational data and real-world evidence is becoming increasingly significant. According to a recent analysis done by the EY (Healthcare data summit, Paris) a 44-fold increase in the volume of data created each year is expected worldwide by 2020, with 80 billion connected devices by 2020. To not consider real world	stakeholders through this consultation, will be passed on to developers for consideration during the update of the guideline. **Flash glucose monitoring** The RCT on flash glucose monitoring has been added to the surveillance review. The NICE medtech innovation briefing on Freestyle Libre for glucose monitoring (MIB110) emphasises that all evidence to date is limited to people with well-controlled diabetes and that the resource impact is unclear due to uncertainty around staff training and support requirements that may be needed. Long-term impact on patient outcomes is also uncertain, with the longest follow-up being 6 months. We are monitoring the progress of 2 ongoing trials in this area (ISRCTN87654534 and ISRCTN12543702) which may clarify the long-term effectiveness of FreeStyle Libre in patients with T2D. We will review these results and assess impact on the guideline as soon as they are published. **Study selection criteria** Please note that for the purposes of this surveillance review only Cochrane reviews, recent systematic reviews in priority areas, and RCTs are included, due to resource constraints and the volume of evidence. Therefore, studies submitted within other study designs were not included. This included real world data. NICE is considering how real world data may be used to inform guideline development and a public consultation on this will be taking place in the Summer 2019.

		evidence/observational studies would exclude an invaluable source of data that should be of value as it reflects how devices are used in real world settings. Below are the key additional data pieces, both clinical and cost effectiveness, Abbott would like to highlight for consideration. Seibold et al. poster, published at ADA June 2018 A meta-analysis on the impact of flash glucose monitoring on glycaemic control as measured by HbA1c https://ada.apprisor.org/index.cfm?k=b313xetsc2 A series of 17 studies were identified as reporting longitudinal HbA1c data in a total 1338 participants with type 1 (n=1112) or type 2 diabetes (n=226) using the FreeStyle Libre flash glucose monitoring system. Data included observations on children, adolescents and adults. Overall mean change in HbA1c was -0.56, 95% CI (-0.76, -0.36), with substantial heterogeneity between trials (I2=92.6%), mainly due to the different HbA1c levels at baseline. No significant differences were detected based on length of study, type of diabetes (T1DM v T2DM) or children versus adults. There has recently been an extended meta-analysis data set analysed and submitted for publication. Dunn et al publication: Real-world flash glucose monitoring patterns and associations between self- monitoring frequency and glycaemic measures: A European analysis of	

		over 60 million glucose tests: diabetes research and clinical practice 137 (2018) 37-46 This worldwide multinational database of over 50 000 users, 64.3 million glucose scan and 86.4 million hours of automatic glucose monitoring provides an unprecedented view into the usage of a new glucose monitoring technology. The data demonstrate high frequency of scanning, emphasising the ease by which glucose levels are checked. Moreover, this shows a strong correlation between the number of glucose scans and improvement in glycaemic markers including reduction in time spent in hypo and hyperglycaemia and increased time in euglycemia. This indicates that the FreeStyle Libre system, in real world settings, represents a powerful glucose monitoring strategy to improve glycaemia in patients with diabetes. This data set has since been updated and was presented at ATTD Berlin 2019 with nearly 500,000 patients data. Poster 0299: "Expanded real-world use confirms strong association between frequency of flash glucose monitoring and glucose control" The conclusion is the same: there is an association between increased glucose testing and lower mean glucose, less time spent in hypoglycaemia and hyperglycaemia, and greater time in range. Although the sample is not described in these data the patient numbers are extremely high and so there is	

		advantage to considering these results when assessing FreeStyle Libre flash glucose monitoring. Hellmund et al: "Cost Calculation for a Flash Glucose Monitoring System for Adults with Type 2 Diabetes Mellitus using Intensive Insulin – a UK Perspective". European Endocrinology http://www.touchendocrinology.com/articles/cost-calculation-flash-glucose-monitoring-system-adults-type-2-diabetes-mellitus-using	
Royal College of Ophthalmologists	Yes	As per comment above: The document also states: ''Topic experts also highlighted new evidence on the optimum frequency of diabetic eye screening. This area was not considered in the surveillance review because it falls under the remit of the NHS Diabetic Eye Screening Programme who cover screening and referral criteria for people with diabetes. However, to avoid an overlap in guidance we plan to withdraw the recommendations on screening and referral'' Whilst we agree that this work should not be repeated, it would seem sensible to both reference the NHS Diabetic Eye screening programme here as well as including a short summary of the referral guidelines/recommendations, to emphasise the importance of regular screening etc. As with the paediatric guidelines, it would be good to also stress the benefits of discussing retinopathy screening results during the regular diabetes	Thank you for your comments. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults, including the recommendations on eye disease. Information obtained through the surveillance review, including feedback from stakeholders through this consultation, will be passed on to developers for consideration during the update of the guideline. **Diabetic eye screening** Regarding the proposed withdrawal of recommendations on diabetic eye screening, it was suggested that the guideline still needs to emphasise the importance of regular screening. We will add in a cross referral to the NHS Diabetic Eye screening programme for ease of reference to this guidance. **Digital photographic and optical coherence tomography**

		review appointments either by the GP/practice nurse or diabetologist. On page 30 the document states '' We identified 2 Cochrane reviews and 3 RCTs on interventions to manage eye disease in type 1 diabetes (table 7). Two Cochrane reviews (55,56) and 5 RCTs (57–61) focussed on the use of anti-vascular endothelial growth factor (anti-VEGF) for diabetic macular oedema which relate to the NICE technology appraisal guidance on Ranibizumab for treating diabetic macular oedema (TA274). Therefore, these studies will not be considered in this surveillance review''. Table 7 is missing various key publications, such as a number of DRCR-net studies on the management of diabetic retinopathy (such as Protocol T and Protocol I). We think it would be desirable to include the evidence for the various treatments in one place, so it would seem unusual to exclude data assessed in TA 274, especially as the Aflibercept, Ozurdex and Iluvien data all needs to be considered as well as the data for Ranibizumab, to be taken in context. The studies generally to NOT only include patients with either Type 1 vs Type 2 diabetes, so the same data would be reviewed and would be relevant to both the guidelines. With respect to proliferative diabetic retinopathy, reference is made to the Clarity study but data from the DRCR-net Protocol S study should also be included and discussed. Key sight threatening complications of diabetes – proliferative diabetic retinopathy and diabetic macular oedema has seen revolutionary treatments with advent of	It was highlighted that data is emerging about digital photographic and optical coherence tomography surveillance for certain patients who had already been referred to the diabetic eye clinics ('virtual clinics'). However, No evidence was submitted or identified in the surveillance review, and therefore this area will not be part of the update. **Treatment for diabetic retinopathy** The surveillance team did not consider the evidence relating to NICE technology appraisals; as such, the DRCR-net Protocol study was not included in the Appendix A. However, the information has been passed on to the appraisals team for consideration. Management of overlaps and linkages between the diabetes clinical guidelines and technology appraisal guidance on diabetic retinopathy will be considered as part of the update to NG28.

		AntiVEGF, this would need to be included in the revised guidelines. Furthermore, technological advances – OCT and some exciting developments in use of AI in diabetic screening/ grading will be of use	
UK Renal association	Yes	**Comments from UK Renal Association for the NICE guideline on NG28; Type 2 diabetes in adults: management: diagnosis and management** The proposal does not address the following issues 1. Mention of chronic kidney disease (CKD) associated with diabetes as a population with high risk for cardiovascular disease and CKD progression. 2. Mention of impact of Sodium Glucose cotransporter 2 (SGLT2) inhibitors in diabetes patients with CKD. **Patients with diabetes and chronic kidney disease** A significant percentage of patients with diabetes develop chronic kidney disease (CKD), and diabetes is also a leading cause of end-stage kidney disease (ESKD). More than a quarter of patients who are on dialysis in the UK have diabetes. Diabetic kidney disease is associated with high morbidity and mortality, which are predominantly related to cardiovascular complications and the progression of kidney disease that requires renal replacement therapy. The patients with different stages of CKD suffer from slightly different outcomes (example progression ESKD versus CV death) and evidence for interventions are different. For example the evidence for lower BP control (<130/80 mmHg) are different between CKD stage 3 and CKD stages 4/5 which should be acknowledged (ABCD-RA guidelines on Hypertension management and renin-angiotensin-aldosterone system blockade in patients with	Thank you for your comments. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults. Information obtained through the surveillance review, including feedback from stakeholders through this consultation, will be passed on to developers for consideration during the update of the guideline. **Patients with diabetes and chronic kidney disease** CKD and renal outcomes are already proposed for consideration in the review of the antidiabetic drug pathway. More specific advice for CKD in T2D will be considered for inclusion in NICE's guideline on chronic kidney disease in adults, which already includes advice for type 1 and 2 diabetes. **Sodium Glucose cotransporter 2 inhibitors in patients with diabetes and CKD** As stated above, CKD and renal outcomes are already proposed for consideration in the review of the antidiabetic drug pathway. This will include the trials highlighted. The ongoing EMPA-KIDNEY and DAPA-CKD trials will be monitored for publication.

		diabetes, nephropathy and/or chronic kidney disease 2017; https://doi.org/10.15277/bjd.2017.152) **Sodium Glucose cotransporter 2 inhibitors in patients with diabetes and CKD** Sodium Glucose cotransporter 2 (SGLT2) inhibitors are a new group of oral hypoglycaemic agents with proven benefit in prevention of progression of CKD and End Stage Kidney Failure in addition to their benefits on cardiovascular outcomes which needs to be included based on evidence as follows: A prespecified analysis of the EMPA-REG OUTCOME trial demonstrated that use of 10 mg of empagliflozin was associated with 40% reduction renal endpoints including doubling of serum creatinine, end-stage kidney disease and renal death. Patients had eGFR>30 ml/min/1.73m2 and 7% of patients were with eGFR between 30 and 45. In the DECLARE "Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes" study there was a 24% reduction in secondary renal outcomes (≥40% decrease in estimated glomerular filtration rate to <60 ml per minute per 1.73 m2 of body-surface area, new end-stage renal disease, or death from renal or cardiovascular causes). In the CANVAS "Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes" study there was a 40% reduction in the composite outcome of a sustained 40% reduction in the estimated glomerular filtration rate, the need for renal-replacement therapy, or death from renal causes using canagliflozin 300 or 100 mg/day versus placebo. The recently published Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy (CREDENCE) trial	

		demonstrated a 30% reduction in primary outcomes including ESKD (dialysis, transplantation or persistent eGFR<15ml/min/1.73m^2), doubling of serum creatinine or renal death. 30% of patients had eGFR between 30 and 45 ml/min/1.73m^2. Based on the trial data, treatment of 1000 patients over 2.5 years reduced primary outcome in 47 fewer patients and ESKD in 26 fewer patients (NNT 28, 95%CI 19-54). The study was stopped early by the data safety monitoring committee due to observed benefits of canagliflozin 100 mg/day over placebo. There was no increased risk of lower limb amputation, fracture but increased risk of diabetic ketoacidosis with canagliflozin. There are two large on-going trials of SGLT2 inhibitors in CKD patients. The EMPA-KIDNEY "The Study of Heart and Kidney Protection With Empagliflozin" is recruiting patients with eGFR 20-90 including non-diabetes patients. The DAPA-CKD "A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease" is recruiting non-diabetes patients with eGFR between 25-75 ml/min/1.73m2.	
Elcena Jeffers Foundation	Yes	This can be picked up next time	Thank you for your comment. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults. Information obtained through the surveillance review, including feedback from stakeholders through this consultation, will be passed on to developers for consideration during the update of the guideline.

Novo Nordisk	Yes	See above	Thank you for your previous comments. Please see our response to your comments above.
British Society of Periodontology	Yes	1. **Periodontal and dental diseases should be included within the assessment of diabetes-related complications and other comorbidities that affect people with diabetes.** • (Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Medical Care in Diabetes d2019 Diabetes Care 2019;42(Suppl. 1):S34–S45). (Oral health: local authorities and partners Public health guideline Published: 22 October 2014 nice.org.uk/guidance/ph55) 2. **Evidence suggests that periodontitis is more severe and more prevalent in patients with type 2 diabetes.** • (Scientific evidence on the links between periodontal diseases and diabetes: Consensus report and guidelines of the joint workshop on periodontal diseases and diabetes by the International diabetes Federation and the European Federation of Periodontology. Sanz M, Ceriello A, Buysschaert M, Chapple I, Demmer RT, Graziani F, Herrera D, Jepsen S, Lione L, Madianos P, Mathur M, Montanya E, Shapira L, Tonetti M, Vegh D. Diabetes Res Clin Pract. 2018 Mar;137:231-241). • (Oral health: local authorities and partners Public health guideline Published: 22 October 2014 nice.org.uk/guidance/ph55) 3. **When diagnosed in patients with diabetes, periodontitis is associated with increased risk of cardio-renal complications.**	Thank you for your comments. The aetiology of diabetes is not within scope for NICE guideline NG17, NG18 or NG28 however NICE guideline NG18 cross-refers to NICE guideline CG19 on dental recall. This highlights diabetes as a risk factor for developing dental disease and notes that 'People with diabetes (both type I and type II) are at increased risk of developing destructive periodontal disease … individuals with diabetes may need a more frequent recall. Inadequate plaque control and the presence of other risk factors will modify the recall interval further.' This issue will be put forward for consideration for scoping discussions for NICE guidelines NG17 and NG28 as expert input is required to determine an appropriate way of highlighting oral health in people with diabetes. Thank you highlighting the evidence in this area. With the exception of Simpson et al (2015) and D'Aiuto et al (2018), the highlighted studies will not be added to Appendix A for the following reasons: - Diabetes Care 2019, Scottish Dental Clinical Effectiveness Programme, Canada Clinical Practice Guidelines (2018), Swedish National Guidelines for Diabetes Care, International Diabetes Federation and the European Federation of Periodontology: The surveillance team at

		• (Evidence summary: The relationship between oral diseases and diabetes. D'Aiuto F, Gable D, Syed Z, Allen Y, Wanyonyi KL, White S, Gallagher JE. Br Dent J. 2017 Jun 23;222(12):944-948). • (IDF Clinical Guidelines Task Force. IDF Guideline on oral health for people with diabetes. Brussels, Belgium: International Diabetes Federation (IDF); 2009. Available from: https://www.idf.org/e-library/guidelines/83-oral-health-for -people-with-diabetes). 4. **Treatment of periodontitis is associated with a mild but consistent improvement in glucose management over 3-4 months, with no other complications.** • (Treatment of periodontal disease for glycaemic control in people with diabetes mellitus. Simpson TC, Weldon JC, Worthington HV, Needleman I, Wild SH, Moles DR, Stevenson B, Furness S, Iheozor-Ejiofor Z. Cochrane Database Syst Rev. 2015 Nov 6;(11):CD004714). 5. **Recent evidence suggests that management of periodontitis is linked to improved metabolic outcomes, better vascular and kidney functions after 12 months.** • (Systemic effects of periodontitis treatment in patients with type 2 diabetes: a 12 month, single-centre, investigator-masked, randomised trial. D'Aiuto F, Gkranias N, Bhowruth D, Khan T, Orlandi M, Suvan J, Masi S, Tsakos G, Hurel S, Hingorani AD, Donos N, Deanfield JE; TASTE Group. Lancet Diabetes Endocrinol. 2018 Dec;6(12):954-965). 6. **Patients with diabetes should be referred to a dentist for comprehensive dental and periodontal examination as a routine element of care pathways,**	NICE do not consider guidelines from other organisations as an evidence type. - D'Aiuto et al (2017), Jeffcoat et al (2014), Solowiej-Wedderburn (2017), Nasseh et al (2017): Do not meet study type inclusion criteria. Due to the large volume of evidence available for this topic, this surveillance review focussed specifically on RCTs and Cochrane reviews.

Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees

		and treatment should be supported with no extra cost to patients. • (Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Medical Care in Diabetes d2019 Diabetes Care 2019;42(Suppl. 1):S34–S45). • (Scottish Dental Clinical Effectiveness Programme, 2014) • (Clinical Knowledge Summaries, Gingivitis and Periodontitis, https://cks.nice.org.uk/gingivitis-and-periodontitis#!scenario) • (Oral health: local authorities and partners Public health guideline Published: 22 October 2014 nice.org.uk/guidance/ph55) • (2018 Clinical Practice Guidelines Introduction Diabetes Canada Clinical Practice Guidelines Expert Committee, Can J Diabetes 42 (2018) S1–S5) • (Swedish National Guidelines for Diabetes Care from the National Board of Health and Welfare – Support for governance and management. https://www.socialstyrelsen.se/publikationer2015/2015-4-12) 7. **Oral health education should be provided to all patients with diabetes as part of their overall educational programme.** • (Scientific evidence on the links between periodontal diseases and diabetes: Consensus report and guidelines of the joint workshop on periodontal diseases and diabetes by the International diabetes Federation and the European Federation of Periodontology. Sanz M, Ceriello A, Buysschaert M, Chapple I, Demmer RT, Graziani F, Herrera D, Jepsen S, Lione L, Madianos P, Mathur M, Montanya E,	

		Shapira L, Tonetti M, Vegh D. Diabetes Res Clin Pract. 2018 Mar;137:231-241). • (Oral health: local authorities and partners Public health guideline Published: 22 October 2014 nice.org.uk/guidance/ph55) • (IDF Clinical Guidelines Task Force. IDF Guideline on oral health for people with diabetes. Brussels, Belgium: International Diabetes Federation (IDF); 2009. Available from: https://www.idf.org/e-library/guidelines/83-oral-health-for -people-with-diabetes). 8. **Evidence from cost-effective analyses showed that promotion of oral health measures will lead to reduced medical costs in patients with diabetes.** • (Swedish National Guidelines for Diabetes Care from the National Board of Health and Welfare – Support for governance and management. https://www.socialstyrelsen.se/publikationer2015/2015-4-12) • (The Relationship between Periodontal Interventions and Healthcare Costs and Utilization. Evidence from an Integrated Dental, Medical, and Pharmacy Commercial Claims Database. Nasseh K, Vujicic M, Glick M. Health Econ. 2017 Apr;26(4):519-527). • (Cost-effectiveness of non-surgical periodontal therapy for patients with type 2 diabetes in the UK. Solowiej-Wedderburn J, Ide M, Pennington M. J Clin Periodontol. 2017 Jul;44(7):700-707). • (Impact of periodontal therapy on general health: evidence from insurance data for five systemic conditions. Jeffcoat MK, Jeffcoat RL, Gladowski PA, Bramson JB, Blum JJ. Am J Prev Med. 2014 Aug;47(2):166-74).	

X-PERT Health	No	No comments provided.	Thank you.
AstraZeneca Ltd. (UK)	No	No comments provided.	Thank you.
Eli Lilly and Company Ltd	No	No comments provided	Thank you.
UCL Eastman Dental Institute	Yes	**1. Periodontal and dental diseases should be included within the assessment of diabetes-related complications and other comorbidities that affect people with diabetes.** • (Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Medical Care in Diabetes d2019 Diabetes Care 2019;42(Suppl. 1):S34–S45). • (Oral health: local authorities and partners Public health guideline Published: 22 October 2014 nice.org.uk/guidance/ph55) **2. Evidence suggests that periodontitis is more severe and more prevalent in patients with type 2 diabetes.** • (Scientific evidence on the links between periodontal diseases and diabetes: Consensus report and guidelines of the joint workshop on periodontal diseases and diabetes by the International diabetes Federation and the European Federation of Periodontology. Sanz M, Ceriello A, Buysschaert M, Chapple I, Demmer RT, Graziani F, Herrera D, Jepsen S, Lione L, Madianos P, Mathur M, Montanya E, Shapira L, Tonetti M, Vegh D. Diabetes Res Clin Pract. 2018 Mar;137:231-241).	Thank you for your comments. The aetiology of diabetes is not within scope for NICE guideline NG17, NG18 or NG28 however NICE guideline NG18 cross-refers to NICE guideline CG19 on dental recall. This highlights diabetes as a risk factor for developing dental disease and notes that 'People with diabetes (both type I and type II) are at increased risk of developing destructive periodontal disease … individuals with diabetes may need a more frequent recall. Inadequate plaque control and the presence of other risk factors will modify the recall interval further.' This issue will be put forward for consideration for scoping discussions for NICE guidelines NG17 and NG28 as expert input is required to determine an appropriate way of highlighting oral health in people with diabetes. Thank you highlighting the evidence in this area. With the exception of Simpson et al (2015) and D'Aiuto et al (2018), the highlighted studies will not be added to Appendix A for the following reasons: - Diabetes Care 2019, Scottish Dental Clinical Effectiveness Programme, Canada Clinical Practice Guidelines (2018), Swedish National Guidelines for Diabetes Care, International Diabetes Federation and the European Federation of Periodontology: The surveillance team at

		• (Oral health: local authorities and partners Public health guideline Published: 22 October 2014 nice.org.uk/guidance/ph55) **3.When diagnosed in patients with diabetes, periodontitis is associated with increased risk of cardio-renal complications.** • (Evidence summary: The relationship between oral diseases and diabetes. D'Aiuto F, Gable D, Syed Z, Allen Y, Wanyonyi KL, White S, Gallagher JE. Br Dent J. 2017 Jun 23;222(12):944-948). • (IDF Clinical Guidelines Task Force. IDF Guideline on oral health for people with diabetes. Brussels, Belgium: International Diabetes Federation (IDF); 2009. Available from: https://www.idf.org/e-library/guidelines/83-oral-health-for -people-with-diabetes). **4. Treatment of periodontitis is associated with a mild but consistent improvement in glucose management over 3-4 months.** • (Treatment of periodontal disease for glycaemic control in people with diabetes mellitus. Simpson TC, Weldon JC, Worthington HV, Needleman I, Wild SH, Moles DR, Stevenson B, Furness S, Iheozor-Ejiofor Z. Cochrane Database Syst Rev. 2015 Nov 6;(11):CD004714). **4. Recent evidence suggests that management of periodontitis is linked to improved metabolic outcomes, better vascular and kidney functions after 12 months.** • (Systemic effects of periodontitis treatment in patients with type 2 diabetes: a 12 month, single-centre, investigator-masked, randomised trial. D'Aiuto F, Gkranias N, Bhowruth D, Khan T, Orlandi M, Suvan J, Masi S, Tsakos G, Hurel S, Hingorani AD, Donos N, Deanfield JE; TASTE	NICE do not consider guidelines from other organisations as an evidence type. - D'Aiuto et al (2017), Jeffcoat et al (2014), Solowiej-Wedderburn (2017), Nasseh et al (2017): Do not meet study type inclusion criteria. Due to the large volume of evidence available for this topic, this surveillance review focussed specifically on RCTs and Cochrane reviews.

		Group. Lancet Diabetes Endocrinol. 2018 Dec;6(12):954-965). 5. **Patients with diabetes should be referred to a dentist for comprehensive dental and periodontal examination.** • (Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Medical Care in Diabetes d2019 Diabetes Care 2019;42(Suppl. 1):S34–S45). • (Scottish Dental Clinical Effectiveness Programme, 2014) • (Clinical Knowledge Summaries, Gingivitis and Periodontitis, https://cks.nice.org.uk/gingivitis-and-periodontitis#!scenario) • (Oral health: local authorities and partners Public health guideline Published: 22 October 2014 nice.org.uk/guidance/ph55) • (2018 Clinical Practice Guidelines Introduction Diabetes Canada Clinical Practice Guidelines Expert Committee, Can J Diabetes 42 (2018) S1–S5) • (Swedish National Guidelines for Diabetes Care from the National Board of Health and Welfare – Support for governance and management. https://www.socialstyrelsen.se/publikationer2015/2015-4-12) 6. **Oral health education should be provided to all patients with diabetes as part of their overall educational programme.** • (Scientific evidence on the links between periodontal diseases and diabetes: Consensus report and guidelines of the joint workshop on periodontal diseases and diabetes by the International diabetes Federation and the European Federation of Periodontology. Sanz M, Ceriello A, Buysschaert M, Chapple I,	

		Demmer RT, Graziani F, Herrera D, Jepsen S, Lione L, Madianos P, Mathur M, Montanya E, Shapira L, Tonetti M, Vegh D. Diabetes Res Clin Pract. 2018 Mar;137:231-241). • (Oral health: local authorities and partners Public health guideline Published: 22 October 2014 nice.org.uk/guidance/ph55) • (IDF Clinical Guidelines Task Force. IDF Guideline on oral health for people with diabetes. Brussels, Belgium: International Diabetes Federation (IDF); 2009. Available from: https://www.idf.org/e-library/guidelines/83-oral-health-for -people-with-diabetes). **7. Evidence from cost-effective analyses showed that promotion of oral health measure will lead to reduced medical costs in patients with diabetes.** • (Swedish National Guidelines for Diabetes Care from the National Board of Health and Welfare – Support for governance and management. https://www.socialstyrelsen.se/publikationer2015/2015-4-12) • (The Relationship between Periodontal Interventions and Healthcare Costs and Utilization. Evidence from an Integrated Dental, Medical, and Pharmacy Commercial Claims Database. Nasseh K, Vujicic M, Glick M. Health Econ. 2017 Apr;26(4):519-527). • (Cost-effectiveness of non-surgical periodontal therapy for patients with type 2 diabetes in the UK. Solowiej-Wedderburn J, Ide M, Pennington M. J Clin Periodontol. 2017 Jul;44(7):700-707). • (Impact of periodontal therapy on general health: evidence from insurance data for five systemic conditions. Jeffcoat MK, Jeffcoat RL, Gladowski	

		PA, Bramson JB, Blum JJ. Am J Prev Med. 2014 Aug;47(2):166-74).	
Gilead Sciences	Yes	The guideline excludes liver diseases as a comorbidity of diabetes (e.g. Non-alcoholic steatohepatitis) we think this is a big miss considering the extremely high prevalence of NASH in diabetic patients. Many primary care physicians are not monitoring the liver of their patients, when they could do by readily available tests like AST, ALT & platelets. Some GPs collect these test but do not use them to understand the state of the liver with simple calculations such as the fib-4 score. If these simple, cheap and readily available calculators where used to rule out liver fibrosis or identify patients that require further investigation by the hepatologist were used, the long term impact of developing NASH due to diabetes could be avoided/delayed/prevented. NG28 Gilead Sciences PDF.pdf	Thank you for your comment. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults. Information obtained through the surveillance review, including feedback from stakeholders through this consultation, will be passed on to developers for consideration during the update of the guideline. Please note that liver disease is not a direct complication of T2D and is therefore not within the scope of the guideline. As there is a separate NICE guideline on Non-alcoholic fatty liver disease, which covers NASH, it will not be included in NG28. However, the NICE guideline on Non-alcoholic fatty liver disease will be added to the type 2 diabetes pathway for ease of reference.
MedTech Europe	Yes	**Expand to surrogate endpoints**: With new technology, more data becomes available. We would suggest collecting and looking at data around surrogate endpoints (i.e. not only focusing on HbA1c but take into consideration Time In Range and other therapy relevant clinical endpoints).	Thank you for your comment. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults, which will include reviewing outcomes other than HbA1c, such as time in range,as part of the update.
Bayer plc	Not answered	No comments provided	Thank you.

Association for Clinical Biochemistry and Laboratory Medicine	Yes	Appreciate lack of evidence on low carbohydrate dietary interventions, however such a key topic for people with diabetes. A section reviewing existing studies, even though questionable quality is important – even if it just highlights the need for further research.	Thank you for your comment. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults in several areas including blood glucose management, insulin therapy and management of complications. We retain our proposal not to update the guideline around very low calorie diets. Evidence submitted was not eligible due to indirectness of population (relating to obesity without T2D, and to prevention not treatment), out of scope study designs, and studies published outside the surveillance search period. The joint ADA and EASD guideline was also cited as referring to low carbohydrate and low calorie diets. However, this guideline does not explicitly recommend these diets but states that 'advice should be given of the health benefits of weight loss and encouraged to engage in a programme of intensive lifestyle management, which may include food substitution'. NICE guideline NG28 already advises individualising recommendations for carbohydrate intake, and meal patterns. This encompasses a range of interventions, which may include low carbohydrate and low calorie diets. Note that information obtained through the surveillance review, including feedback from stakeholders through this consultation, will be passed on to developers for consideration during the update of the guideline.
Takeda UK Ltd	No	No comments provided	Thank you.

Boehringer Ingelheim Ltd.	No	No comments provided	Thank you.
Perspectum Diagnostics	Yes	In the NICE guideline on type 2 diabetes in adults: management (NG28) published in December 2015, section 1.7 Managing Complications lists seven complications associated with type 2 diabetes in adults. It is proposed that **non-alcoholic fatty liver disease (NAFLD)** is added to the list of complications within this section. 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: type 2 diabetes or metabolic syndrome (T2DM). In support, we recommend that the type 2 diabetes in adults: management guideline is appropriately aligned and linked to the NICE guidance on non-alcoholic fatty liver disease (NAFLD): assessment and management (NG49) to ensure the cross referral is current. In addition, recommendation 1.2 Patient education of the type 2 diabetes in adults: management NICE guideline does not state that adults with type 2 diabetes are offered a continuing programme of education that includes the complications of type 2 diabetes. We would also like to recommend that this recommendation includes reference to a continuing programme of education of the complications of type 2 diabetes, in continuity with recommendation 1.3.1 of the diabetes (type 1 and type 2) in children and young people NICE guideline. In line with the NICE guideline on non-alcoholic fatty liver disease (NAFLD): assessment and management we are recommending that investigations for the assessment of NAFLD should be considered in adults with type-2 diabetes and indication of abnormal liver blood tests or	Thank you for your comment. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults. Information obtained through the surveillance review, including feedback from stakeholders through this consultation, will be passed on to developers for consideration during the update of the guideline. Please note that liver disease is not a direct complication of T2D and is therefore not within the scope of the guideline. As there is a separate NICE guideline on Non-alcoholic fatty liver disease, which covers NASH, it will not be included in NG28. However, the NICE guideline on Non-alcoholic fatty liver disease will be added to the type 2 diabetes pathway for ease of reference.

		ultrasound examination results. NAFLD is prevalent in 59.67% of T2DM patients and increases the burden of secondary complications and adverse outcomes including mortality[2]. An increase in microvascular defects such as retinopathy and chronic kidney disease and a 1.87-fold increase in cardiovascular adverse events associated with NAFLD in the scope of pre-existing type-2 diabetes has been reported[1,3]. Furthermore, a 1.5-fold increase in coronary microvascular dysfunction has been reported in NAFLD patients that strongly predicted future major cardiac adverse events[7]. Ectopic accumulation of hepatic lipids is strongly associated to the development of type-2 diabetes, hepatic insulin resistance and eventual progressive hepatic fibrosis resulting in higher rates of mortality due to cirrhosis[2]. Adult and paediatric symptomatic NAFLD may include complaints of abdominal pain (45%), vomiting (13.8%) and general fatigue[4] although >80% of patients may still present with normal liver blood tests (https://www.nice.org.uk/guidance/NG49)[8]. There is a requirement to screen adults at high risk of NAFLD via non-invasive methods and allocate interventional strategies accordingly. Treatments that target metabolic defects in T2DM, such as weight loss and improved glycaemic control, are also advantageous in NAFLD management and therefore transferable[4,5]. Furthermore, the American Diabetes Association (ADA) 2019 guidelines already recommend that 'Patients with type 2 diabetes or prediabetes and elevated liver enzymes (alanine aminotransferase) or fatty liver on ultrasound should be evaluated for presence of non-alcoholic steatohepatitis and liver fibrosis'[6]. References	

Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees

		1. Dharmalingam, M. and Yamasandhi, P.G., 2018. Nonalcoholic fatty liver disease and Type 2 diabetes mellitus. *Indian journal of endocrinology and metabolism*, *22*(3), p.421. 2. Anstee, Q.M., McPherson, S. and Day, C.P., 2011. How big a problem is non-alcoholic fatty liver disease?. *Bmj*, *343*, p.d3897. 3. Targher, G., Lonardo, A. and Byrne, C.D., 2018. Nonalcoholic fatty liver disease and chronic vascular complications of diabetes mellitus. *Nature Reviews Endocrinology*, *14*(2), p.99. 4. American Gastroenterological Association. American Gastroenterological Association medical position statement: nonalcoholic fatty liver disease. Gastroenterology 2002; 123:1702 – 1704. 5. Cusi K, Orsak B, Bril F, et al. Long-term pioglitazone treatment for patients with non-alcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus: a randomized trial. Ann Intern Med 2016; 165:305–315. 6. Care, D., 2019. Standards of Medical Care in Diabetes 2019. *Diabetes Care*, *42*, p.S81. 7. Vita, T., Murphy, D.J., Osborne, M.T., Bajaj, N.S., Keraliya, A., Jacob, S., Diaz Martinez, A.J., Nodoushani, A., Bravo, P., Hainer, J. and Bibbo, C.F., 2019. Association between nonalcoholic fatty liver disease at CT and coronary microvascular dysfunction at myocardial perfusion PET/CT. *Radiology*, p.181793. 8. https://www.nice.org.uk/guidance/NG49, published July 2016	

Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees

South Asian Health Foundation	Yes	The evidence form DIRECT trial highlights the importance of VLCD and early promotion of lifestyle programme/management can have significant benefit in putting type 2 diabetes into remission. New guidelines need to highlight and reflect this at the forefront. The guidance needs to now move towards evidence based recommendation for people with established CVD. We need to follow the other international guidelines that have changed in view of the new evidence. All these trials have shown the benefits seem higher in south Asians than white populations. With recent changes in QOF as well as more evidence suggesting the importance of frailty in management choices, new guidelines should specifically have a section on frailty and older adults with diabetes to reflect this area as one that differs from the younger adult and the importance of avoiding harm and hypoglycaemia. International guidelines such as IDF and ADA already acknowledge this in separate sections and previous NICE guidelines are inadequate and vague on this issue. As recognised, cardiovascular outcome trials have provided key impetus to change current guidelines however further data from these trials as well as recent primary outcome studies have also highlighted the importance of considering renal benefits of medications and renal outcomes when considering medication initiation and should be considered for new guideline update.	Thank you for your comments. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults, including drug therapy for blood glucose lowering for people with established CVD. Age and frailty level will also be considered. Information obtained through the surveillance review, including feedback from stakeholders through this consultation, will be passed on to developers for consideration during the update of the guideline. **Dietary advice** The totality of evidence for dietary interventions is currently limited to short-term benefits. It does not indicate conclusively that low-calorie or low-calorie diets are a superior approach to other strategies for weight loss and subsequent weight maintenance in the long-term. The surveillance impact statement is therefore retained; that the longer-term results of the DIRECT study (beyond 2 years), and other longer-term studies of low calorie and low carbohydrate diets are likely to be needed to establish any definite impact on the guideline. A joint working group of The Scientific Advisory Committee on Nutrition, NHS England and Diabetes UK, with input from the British Dental Association and Royal Colleges, is reviewing the evidence on low carbohydrate diets with publication expected in 2020. This will be tracked by the surveillance team and the results will be considered when available. We will pass the collective feedback in this area to the development team working on the update of the NICE guideline on obesity (CG189) as the main study identified in this area (DiRECT) fed into the decision to update NICE guideline CG189.

Roche Diabetes Care, Ltd	Yes	**1.1 Individualised care:** We believe that more explicit inclusion of the diabetes feedback loop as described in the ADA/EASD consensus report will support a better understanding and implementation of this section and as such, the section should be reviewed. - Davies et al 2018 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 Dec; 41(12):2669-2701. Epub Oct 4. **1.2 Patient education**: We understand that new evidence generated for digital education is consistent with the evidenced-based principles of the guidelines. However, we believe there is value in reviewing the wording of this section to make it clear that evidence-based online education can be a valuable alternative to face to face. **1.6 Blood glucose management** As noted in the review, structured SMBG has a positive impact on glycaemic outcomes. This form of regular monitoring for people with Type 2 diabetes has benefits beyond the specific situations noted in the current guidelines, including as part of the feedback loop required for adaptations to therapy. This section should be reviewed and updated to include guidelines for structured testing in the context of therapy changes. - Li et al 2016 Comparison of Different Models of Structured Self-Monitoring of Blood Glucose in Type 2 Diabetes. Diabetes Technol Ther;18(3):171-7 - Kulzer B et al 2018 Integrated personalized diabetes management improves glycemic control in patients with insulin-treated type 2 diabetes:	Thank you for your response. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults. Information obtained through the surveillance review, including feedback from stakeholders through this consultation, will be passed on to developers for consideration during the update of the guideline. **Individualised care** The ADA/EASD consensus report will be considered for contextual information in the update process. However, the feedback loop is not explicitly described and this area will require expert input. The guideline will also be amended with the following standard text placed at the beginning of the recommendations section: 'People have the right to be involved in discussions and make informed decisions about their care, as described in your care. Making decisions using NICE guidelines explains how we use words to show the strength (or certainty) of our recommendations and has information about prescribing medicines (including off label use), professional guidelines, standards and laws (including on consent and mental capacity), and safeguarding.' **Patient education** The new evidence for digital interventions is consistent with the evidenced-based principles set out in the existing guideline recommendations. The collective feedback from topic experts and stakeholders does not indicate a need to prioritise a review of the wording of this section. Self monitoring of Blood glucose

		Results of the PDM-ProValue study program. Diabetes Research and Clinical Practice Oct; 144: 200-212 Rather than attempt to define an optimal frequency of SMBG for people with Type 2 diabetes, we believe that the focus should be on obtaining meaningful data with a structured approach and appropriate support. **Diabetes management solutions:** We believe that people with Type 2 diabetes can also benefit from diabetes management support through mobile phone applications and this section should be reviewed: - Hou et al 2016 Do Mobile Phone Applications Improve Glycemic Control (HbA1c) in the Self-management of Diabetes? A Systematic Review, Meta-analysis, and GRADE of 14 Randomized Trials. Diabetes Care. 2016 Nov;39(11):2089-2095 **Coaching, education and training**: We also feel more consideration could be made towards how self-management of diabetes can be supported with education, training and coaching. With improvements in glycaemic control previously demonstrated: - Captieux M, Pearce G, Parke HL, et al. Supported self-management for people with type 2 diabetes: a meta-review of quantitative systematic reviews. BMJ Open 2018;8:e024262. - Chrvala CA, Sherr D, Lipman RD. Diabetes self-management education for adults with type 2 diabetes mellitus: a systematic review of the effect on glycemic control. Patient Educ Couns 2016;99:926–943 - Sherifali 2017 Diabetes coaching for individuals with type 2 diabetes: A state-of-the-science review and rationale for a coaching model Journal of diabetes 9 (6) 547-554	The collective new evidence and intelligence indicates that for people with T2D who are not using insulin, any benefit from self-monitoring is small and is unlikely to last beyond 6 months. This supports NG28 recommendation 1.6.13 that self-monitoring is not used routinely for people with type 2 diabetes unless there is a specific reason to do so. Doctors may consider offering self-monitoring of blood glucose in the short term for people starting treatment with steroids or to confirm suspected hypoglycaemia (recommendation 1.6.14). Please also note that due to resource constraints and the large volume of studies retrieved, studies with a sample size lower than 100 were excluded. This included the study you have highlighted by Li et al (2016). The other study Kulzer et al (2018) is already included in Appendix A. **Study design criteria** Please note that for the purposes of this surveillance review only Cochrane reviews, recent systematic reviews in priority areas, and RCTs are included, due to resource constraints and the volume of evidence. Therefore, studies submitted within other study designs were not included. This includes the evidence submitted on diabetes management solutions, coaching, education and training, and motivational interviewing.

		Motivational interviewing: More recent studies have been published to demonstrate the effectiveness of motivational interviewing as a successful technique to support people with diabetes therefore we believe this section should be reviewed: - Salimi et al 2016 A review on the effectiveness of motivational interviewing in the management of diabetes mellitus. Journal of Psychology and Clinical Psychiatry 5(4):294 - 299	
Medtronic Ltd	No	No comments provided.	Thank you.
Primary Care Diabetes Society	Yes	• We feel that CKD should be included in the new guidance (rather than linking to another guideline document)	Thank you for your comment. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults. Information obtained through the surveillance review, including feedback from stakeholders through this consultation, will be passed on to developers for consideration during the update of the guideline. **Chronic kidney disease and T2D** CKD and renal outcomes are already proposed for consideration in the review of the antidiabetic drug pathway. More specific advice for CKD in T2D will be considered for inclusion in NICE's guideline on chronic kidney disease in adults, which already includes advice for type 1 and 2 diabetes.
Royal College of Nursing	Yes	The inclusion of Flash glucose monitoring not being recommended in Type 2 DVLA recommendations update on flash glucose monitoring	Thank you for your comment. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults. Information obtained

			through the surveillance review, including feedback from stakeholders through this consultation, will be passed on to developers for consideration during the update of the guideline. **Flash glucose monitoring** The NICE medtech innovation briefing on Freestyle Libre for glucose monitoring (MIB110) emphasises that all evidence to date is limited to people with well-controlled diabetes and that the resource impact is unclear due to uncertainty around staff training and support requirements that may be needed. Long-term impact on patient outcomes is also uncertain, with the longest follow-up being 6 months. We are monitoring the progress of 2 ongoing trials in this area (ISRCTN87654534 and ISRCTN12543702) which may clarify the long-term effectiveness of FreeStyle Libre in patients with T2D. We will review these results and assess impact on the guideline as soon as they are published.
Napp Pharmaceuticals Ltd.	Yes	**Intelligence gathering – Drug treatment – SGLT2 inhibitors** This section correctly identifies the three SGLT2i cardiovascular outcome trials (CVOTs) that have been published since the most recent update of NG28. However, the section fails to include the first dedicated SGLT2i renal outcome trial, CREDENCE, which was published in April 2019. This trial demonstrated very significant reductions in risk of progression of CKD in T2DM patients, providing the first evidence for disease modifying therapy for CKD in T2D since the RAAS inhibitor renal outcome trials were published ~18 years ago. The effect size identified in this trial also exceeds any previously observed in reduction of CKD progression. Failure to consider this data in a review	Thank you for your comments. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults, which will include drug treatment with SGLT-2 inhibitors and additional outcomes such as change in blood pressure, cardiovascular safety, renoprotection, effects on bodyweight, and risk of hypoglycaemia. Information obtained through the surveillance review, including feedback from stakeholders through this consultation, will be passed on to developers for consideration during the update of the guideline. **Chronic kidney disease and T2D** CKD and renal outcomes are already proposed for consideration in the review of the antidiabetic drug pathway. More specific advice

		of NG28 would represent a major missed opportunity for NICE to provide further relevant evidence based guidance. **Section 1.4 Blood pressure management** The proposed editorial amendments to this section do not include mention of the statistically significant and clinically relevant antihypertensive effects of SGLT2i therapy. This effect should be considered in any assessment of appropriate antihypertensive treatment in patients with T2DM. **Section 1.6 Blood glucose management** The diabetology community now recommends across a number of guidelines, academic publications and other published articles that magnitude of glycaemic effects should not be the primary deciding factor in selecting the optimal pharmacotherapy for blood glucose management in T2DM patients. In terms of glycaemic control, there is somewhat limited difference in efficacy amongst many of the currently available pharmacotherapies. However, recent trial data has made it increasingly clear that very significant differences exist between different agents and classes in terms of cardiovascular safety, renoprotection, effects on bodyweight, and risk of hypoglycaemia. A focus solely on HbA1c would therefore no longer represent an evidence based approach to blood glucose management, as it has now been conclusively demonstrated that this surrogate endpoint does not always directly correlate with morbidity and mortality reductions. It is therefore crucial that any update of NG28 examines these intra- and inter-class differences in agents, and consequently provides specific guidance on selection of the most appropriate glucose control agent based on individual patient characteristics. **Section 1.7 Managing complications**	for CKD in T2D will be considered for inclusion in NICE's guideline on chronic kidney disease in adults, which already includes advice for type 1 and 2 diabetes.

		Napp strongly recommend that specific guidance should be offered within this section on the management of CKD as a complication of T2D. CKD as a result of T2DM represents an enormous morbidity and mortality burden on T2D patients, as well as a very large and rapidly growing financial burden on the NHS. Evidence regarding the specific disease modifying effects of RAAS inhibitors should be included in this section, as well as the most recent evidence from the CREDENCE trial of canagliflozin in T2DM patients with CKD. CKD in T2DM is a distinct disease process from CKD of other aetiologes, and should therefore be included in this section of NG28, as different recommendations will be applicable in this context to those of general CKD management principles as described in CG182.	
Dexcom Operating Ltd	Yes	Rt-CGM should be included in the scope of NG28. This is due to recent clinical evidence that should result in the recommendation that rt-CGM should be offered to all Type 2 diabetics with suboptimal glycaemic control. The evidence gaps identified which should lead to the inclusion of rt-CGM in the scope are presented in order of importance: 1. HbA1c – suboptimal glycemic control 2. Rt-CGM digital platforms <u>HbA1c – suboptimal glycemic control</u> Since the publication of the last update in 2017, the Advanced Technologies & Treatments for Diabetes (ATTD)	Thank you for your comments. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults. Information obtained through the surveillance review, including feedback from stakeholders through this consultation, will be passed on to developers for consideration during the update of the guideline. The new RCT evidence supporting the use of continuous glucose monitoring for T2D is limited by the 6-month duration and no impact on the guideline is anticipated until the findings are substantiated by further longer-term studies. Please note that for the purposes of this surveillance review only Cochrane reviews, recent systematic reviews in priority areas, and RCTs are included, due to resource constraints and the volume of

		consensus statement[1] has been produced on rt-CGM & additional studies have been completed evaluating rtCGM in patients with T2 Diabetes. This growing body of evidence regarding the benefit of rt-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. <u>Clinical Evidence</u> B Billings et al (2018)[2] conducted a post hoc analysis to investigate whether the DIAMOND study participants at progressively higher baseline HbA1c levels benefit from using rt-CGM. This included 158 people with T2D with a mean baseline 69 mmol/mol (8.5% [range 58 to 85 mmol/mol [7.5% to 9.9%]). The study observed that in all study groups, the change in HbA1c was significantly greater among participants in the rt-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. This is a significant finding as it demonstrates that through the use of rt-CGM, significant reductions in HbA1c can be achieved. <u>Rt-CGM digital platforms</u> The NHS England long term plan communicates that the health care service will strive to offer a digital first option	evidence. Therefore, studies submitted within other study designs were not included. These include Danne et al (2017), Billings et al (2019), Pazos-Couselo et al (2015) and Ishikawa et al (2018). Studies were not included if they preceded the surveillance search period, including Ehrhardt et al (2011).

		for most people. This document recognises that the potential benefits of the wider utilisation of technology will empower patients to better manage their condition. To support the objectives set out in the long term plan NICE should include rt-CGM in the scope of NG28. *"When ill, people will be increasingly cared for in their own home, with the option for their physiology to be effortlessly monitored by wearable devices. People will be helped to stay well, to recognise important symptoms early, and to manage their own health, guided by digital tools."* (NHS England 2019, p92)[6] Ehrhardt et al (2011)[3] conducted a prospective, 52-week, two-arm, randomized trial comparing rt-CGM versus self-monitoring of blood glucose (SMBG) in 50 people with T2D. 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 rt-CGM group and 0.5% in the SMBG group. The participants who used the rt-CGM for ≥48 days reduced their HbA1c by 1.2% versus 0.6% in those who used it <48 days. The author suggests that the real time feedback provided by rt-CGM enables people with T2D to see the glycaemic effects of meals and exercise, and may teach lifestyle skills. Pazos-Couselo et at (2015)[4] 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. 33% of 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. This data highlights 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 issue was further highlighted by Ishikawa et al (2018)[5]. 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 ATTD Consensus on Use of Continuous Glucose Monitoring[1], 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, p1632, 2017) References	

		1) Danne, T., Nimri, R., Battelino, T., Bergenstal, R. M., Close, K. L., DeVries, J. H., … Phillip, M. (2017). *International Consensus on Use of Continuous Glucose Monitoring. Diabetes Care*, *40(12), 1631–1640*.doi:10.2337/dc17-1600 2) Billings, L.K., C.G. Parkin, and D. Price, 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 3) Ehrhardt, N. M., Chellappa, M., Walker, M. S., Fonda, S. J., & Vigersky, R. A. (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 4) Pazos-Couselo, M., García-López, J. M., González-Rodríguez, M., Gude, F., Mayán-Santos, J. M., Rodríguez-Segade, S., … Casanueva, F. (2015). *High Incidence of Hypoglycemia in Stable Insulin-Treated Type 2 Diabetes Mellitus: Continuous 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	

Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees

		5) Ishikawa, T., Koshizaka, M., Maezawa, Y., Takemoto, M., Tokuyama, Y., Saito, T., & Yokote, K. (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 6) The Long Term Plan, NHS England, 2019 (accessed on 02.05.2019 https://www.longtermplan.nhs.uk/wp-content/uploads/2019/01/nhs-long-term-plan.pdf)	
Newcastle University	Yes	1. The initial Surveillance Proposal document on Type 2 Diabetes in Adults appears to take no cognizance of the profound change in understanding of Type 2 Diabetes achieved in the last few years. Instead of being an inevitably progressive condition requiring steadily increasing pharmacotherapy it is now established as a potentially reversible condition if adequate weight loss is achieved. Evidence of this international change in attitudes to Type 2 Diabetes is reflected by policy statements from National diabetes organisations. The American Diabetes Association changed its longstanding guidance, and in June 2018 recognised remission of type 2 diabetes (ie HbA1c <48mmol/mol off all anti-diabetic drugs) as being an aim of management (Davies MJ et al. Management of hyperglycemia in type 2 diabetes,	Thank you for your comments. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults. We retain our proposal not to update the guideline around very low calorie diets. Evidence submitted was not eligible due to indirectness of population (relating to obesity without T2D, and to prevention not treatment), out of scope study designs, and studies published outside the surveillance search period. The joint ADA and EASD guideline was also cited as referring to low carbohydrate and low calorie diets. However, this guideline does not explicitly recommend these diets but states that 'advice should be given of the health benefits of weight loss and encouraged to engage in a programme of intensive lifestyle management, which may include

		2018. A consensus report by the ADA and the European association for the Study of Diabetes. Diabetes Care 2018. 41: 2669-7010). The new understanding was first described in full in 2013 (Taylor R. Type 2 Diabetes: Etiology and Reversibility. *Diabetes Care*, April 2013; 36(4):1047-105; doi: 10.2337/dc12-1805), and the Major shift in policy was expedited by demonstration of the durability of weight loss induced remission of type 2 diabetes (Steven S, et al. Very low-calorie diet and 6 months of weight stability in type 2 diabetes: Pathophysiologic changes in responders and nonresponders. *Diabetes Care* 2016 May 39(5):808-15. doi: 10.2337/dc15-1942), but especially by demonstration that a simple, robust approach to weight loss could successfully be taught to Primary Care nurses or dietitians in an 8 hour structured programme. The latter study was a rigorous RCT based in UK Primary Care (Lean MEJ, et al. Primary care weight-management for type 2 diabetes: the cluster-randomised Diabetes Remission Clinical Trial (DiRECT). *Lancet* 2017; 391:541-51 doi.org/10.1016/S0140-6736(17)33102-1). 2. The Surveillance Proposal document disregards the informed view of people with diabetes. This was reflected in the findings of the James Lind Alliance survey (Finer S et al. Top ten research priorities for type 2 diabetes: results from the Diabetes UK- James Lind Alliance Prioirity Setting	food substitution'. NICE guideline NG28 already advises individualising recommendations for carbohydrate intake, and meal patterns. This encompasses a range of interventions, which may include low carbohydrate and low calorie diets. The 2 year results of the DIRECT trial were included in the surveillance review. However, longer-term results of the DIRECT study (beyond 2 years), and other longer-term studies of low calorie and low carbohydrate diets are likely to be needed to establish any definite impact on the guideline. A joint working group of The Scientific Advisory Committee on Nutrition, NHS England and Diabetes UK, with input from the British Dental Association and Royal Colleges, is reviewing the evidence on low carbohydrate diets with publication expected in 2020. This will be tracked by the surveillance team and the results will be considered when available. We will pass the collective feedback in this area to the development team working on the update of the NICE guideline on obesity (CG189) as the main study identified in this area (DiRECT) fed into the decision to update NICE guideline CG189.

		Partnership. Lancet Daibetes and Endorinol 2017; 5: 935-36. http://dx.doi.org/10.1016/ S2213-8587(17)30324-8). 3. Data on effectiveness of achieving remission of type 2 diabetes was presented in 2017 for up to one year, but this was extended in 2019 to include up to 2 years in the formal RCT setting (Lean et al. Two-year results of the randomised Diabetes Remission Clinical Trial (DiRECT). *Lancet* 2019; doi:10.1016/s2213-8587(19)30068-3.). Published description of much longer remissions are available. It is incorrect to state (page 7 of the Surveillance document) that further evidence of long-term effectiveness is required before considering. It must be noted that the work does not concern 'a diet' but rather effective weight loss and maintenance. It does not focus upon the fuzzy concept of 'lifestyle'. It has to be considered that the specific weight loss approach was associated with lower serious adverse event, (largely vascular) in the second year of DiRECT and in this respect differs from previous attempts to modify adverse consequences of type 2 diabetes. 4. The statement in the Surveillance document (page 7, 7) that the use of this approach 'would not be at odds with the current recommendations' is quite extraordinary. The approach is entirely different, and hence was controversial when first used in 2008. Not only does it differ fundamentally from current guidance, but the latter concerning dietary change has repeatedly shown to be ineffective. 5. The reason for excluding the two year DiRECT study in section 1.4 is not explained.	

		6. NHS England is rolling out pilot studies of the new approach to managing type 2 diabetes, and this has been done after careful review of evidence.	
The British Dietetic Association	Yes	We do not agree with the decision not to update the dietary section of NG28. This section has not been reviewed since 2009, and as suggested by NICE, in this time there has been a significant amount of new evidence with respects to dietary management of type 2 diabetes. Both in respect of the types of diets shown to be effective and perhaps most significantly the new clinical outcome in the form of remission from type 2 diabetes which has the potential to have significant benefits with respect to healthcare economics and quality of life. Since the last review of the NICE Type 2 diabetes guidelines, there has been considerable amount of evidence with respect to dietary advice and bariatric surgery which should inform patient care, especially with respect to the emergence of de-prescribing of medication and remission of type 2 diabetes. This has the potential to significantly change the treatment paradigm, from lifestyle including dietary management being seen as an adjunct to pharmaceutical management to become a primary therapeutic strategy. This is a key philosophical shift which has been incorporated in the most recent Diabetes UK Nutritional Management Guidelines published in 2018 (1). The potential of remission from type 2 diabetes emerged from Look AHEAD (2) in 2012 which reported that sustained remission from type 2 diabetes could be achieved via weight loss at rates of 11.5% at 1 year and 7% at 4 years from a cohort of 1852 participants. The potential to achieve remission was also reported in a cohort following a Mediterranean diet intervention where 15% of a cohort of 105 participants achieved remission at 1 year with 5% still	Thank you for your comment. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults. We retain our proposal not to update the guideline around dietary advice. Evidence submitted was not eligible due to indirectness of population (relating to obesity without T2D, and to prevention not treatment), out of scope study designs, and studies published outside the surveillance search period. The joint ADA and EASD guideline was also cited as referring to low carbohydrate and low calorie diets. However, this guideline does not explicitly recommend these diets but states that 'advice should be given of the health benefits of weight loss and encouraged to engage in a programme of intensive lifestyle management, which may include food substitution'. NICE guideline NG28 already advises individualising recommendations for carbohydrate intake, and meal patterns. This encompasses a range of interventions, which may include low carbohydrate and low calorie diets. Please note that for the purposes of this surveillance review only Cochrane reviews, recent systematic reviews in priority areas, and RCTs are included, due to resource constraints and the volume of evidence. Therefore, studies submitted within other study designs were not included. The 2 year results of the DIRECT trial were included in the surveillance review. However, longer-term results of this study

		being in remission at 6 years. More recently, in the UK the use of Very Low Calorie Diets (VLCD) have been shown to 35.6% of participants maintaining remission at 2 years (4). One criticism that has been made of dietary advice for people with type 2 diabetes can be the lack of long term evidence. This can be view perhaps is more valid with respect to conventional dietary approaches, many of which have only been assessed as control interventions in the studies previously described. In addition to the 24-month data with respect to VLCD from DiRECT, similar data although not reporting on remission rates is available for low carbohydrate diets (5). With this and the combination of service user interest and growing evidence base, the British Dietetic Association published a Policy Statement on Low Carbohydrate Diet in 2018 (6). Therefore, based on the evidence that has become available since the last review of dietary guidelines for type 2 diabetes by NICE, both in terms of range of evidence based approaches and possible outcomes in the form of remission a new review is now clearly warranted not just in terms of clinical outcomes, but also cost effectiveness and quality of life. As a professional association we have a position statement and our members are using this approach with patients as it needs to be offered safely to help individuals gain control of their diabetes. The possibility of remission requires consideration, and as suggested, before do we need different thresholds for evidence for lifestyle compared to pharmaceutical and surgical therapeutic strategies. The following evidence supports our above comments: (1) Diabetes UK (2018) Evidence-based nutrition guidelines for the prevention and management of diabetes. Diabetes UK. London. UK.	(beyond 2 years), and other longer-term studies of low calorie and low carbohydrate diets are likely to be needed to establish any definite impact on the guideline. A joint working group of The Scientific Advisory Committee on Nutrition, NHS England and Diabetes UK, with input from the British Dental Association and Royal Colleges, is reviewing the evidence on low carbohydrate diets with publication expected in 2020. This will be tracked by the surveillance team and the results will be considered when available. We will also pass the collective feedback in this area to the development team working on the update of the NICE guideline on obesity (CG189) as the main study identified in this area (DiRECT) fed into the decision to update NICE guideline CG189.

		(2) Gregg. E W, Chen. H, Wagenknecht. L E et al (2012) Association of intensive lifestyle intervention with remission of type 2 diabetes. JAMA 208 (23) 2489-96. Doi:10.1001/jama.2012.67929 (3) Esposito. K, Maiorino. M I, Petrizzo. M et al (2014) The effects of a Mediterranean diet on the need for diabetes drugs and remission of newly diagnosed type 2 diabetes: follow-up of a randomized trial. Diabetes Care 27(7), 1834-30. doi:10.2337/dc13-2899. (4) Lean. M E J, Leslie. W S, Barnes. A C et al (2019). Durability of a 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*. 7 (5), 344 - 355. Accessed from: https://doi.org/10.1016/S2213-8587(19)30068-3 **(5) Tay. J, Thompspon. C H, Luscombe-Marsh N D et al. (2018). Effects of an energy-restricted low-carbohydrate, high unsaturated fat/low saturated fat diet versus a high-carbohydrate, low-fat diet in type 2 diabetes: A 2-year randomized clinical trial. *Diabetes Obesity and Metabolism*. 20 (4), 858-87. Accessed from: https://onlinelibrary.wiley.com/doi/abs/10.1111/dom.13164** (6) The British Dietetic Association (2018) Low Carbohydrate diets for the management of Type 2 Diabetes in adults. Policy statements.	

		Accessed from: https://www.bda.uk.com/improvinghealth/healthprofessionals/policy_statements/policy_statement_-_low_carbohydrate_diets_t2_diabetes	
Association of British Clinical Diabetologists	Yes	*There are however some areas where ABCD believes there is evidence to warrant updating, expanding or which have been over looked, namely;* o *Ultrafast acting insulins* o *Management of renal complications in light of CREDENCE trial data* o *Low/ v low calorie diets* o *Potential risks of SLG2 inhibitors: Fournier's gangrene, diabetic ketoacidosis & increased risk of lower limb amputation*	Thank you for your comment. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults, which includes drug therapy for blood glucose lowering and will incorporate fast acting insulins, CREDENCE trial data and adverse effects of SGLT-2 inhibitors. We retain our proposal not to update the guideline around very low calorie diets. Evidence submitted by stakeholders in relation to this area was not eligible due to indirectness of population (relating to obesity without T2D, and to prevention not treatment), out of scope study designs, and studies published outside the surveillance search period. The joint ADA and EASD guideline was also cited as referring to low carbohydrate and low calorie diets. However, this guideline does not explicitly recommend these diets but states that 'advice should be given of the health benefits of weight loss and encouraged to engage in a programme of intensive lifestyle management, which may include food substitution'. NICE guideline NG28 already advises individualising recommendations for carbohydrate intake, and meal patterns. This encompasses a range of interventions, which may include low carbohydrate and low calorie diets.

NHS England	Yes	**9. Periodontal and dental diseases should be included within the assessment of diabetes-related complications and other comorbidities that affect people with diabetes.** • (Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Medical Care in Diabetes d2019 Diabetes Care 2019;42(Suppl. 1):S34–S45). (Oral health: local authorities and partners Public health guideline Published: 22 October 2014 nice.org.uk/guidance/ph55) 1. Evidence suggests that periodontitis is more severe and more prevalent in patients with type 2 diabetes. • (Scientific evidence on the links between periodontal diseases and diabetes: Consensus report and guidelines of the joint workshop on periodontal diseases and diabetes by the International diabetes Federation and the European Federation of Periodontology. Sanz M, Ceriello A, Buysschaert M, Chapple I, Demmer RT, Graziani F, Herrera D, Jepsen S, Lione L, Madianos P, Mathur M, Montanya E, Shapira L, Tonetti M, Vegh D. Diabetes Res Clin Pract. 2018 Mar;137:231-241). • (Oral health: local authorities and partners Public health guideline Published: 22 October 2014 nice.org.uk/guidance/ph55) 3. When diagnosed in patients with diabetes, periodontitis is associated with increased risk of cardio-renal complications. • (Evidence summary: The relationship between oral diseases and diabetes. D'Aiuto F, Gable D, Syed Z, Allen Y, Wanyonyi KL, White S, Gallagher JE. Br Dent J. 2017 Jun 23;222(12):944-948). • (IDF Clinical Guidelines Task Force. IDF Guideline on oral health for people with diabetes. Brussels, Belgium: International Diabetes Federation (IDF); 2009. Available	Thank you for your comments. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults. Information obtained through the surveillance review, including feedback from stakeholders through this consultation, will be passed on to developers for consideration during the update of the guideline. Periodontal disease Thank you for your comment. The aetiology of diabetes is not within scope for NICE guideline NG17, NG18 or NG28 however NICE guideline NG18 cross-refers to NICE guideline CG19 on dental recall. This highlights diabetes as a risk factor for developing dental disease and notes that 'People with diabetes (both type I and type II) are at increased risk of developing destructive periodontal disease … individuals with diabetes may need a more frequent recall. Inadequate plaque control and the presence of other risk factors will modify the recall interval further.' This issue will be put forward for consideration for scoping discussions for NICE guidelines NG17 and NG28 as expert input is required to determine an appropriate way of highlighting oral health in people with diabetes. Thank you highlighting the evidence in this area. With the exception of Simpson et al (2015) and D'Aiuto et al (2018), the highlighted studies will not be added to Appendix A for the following reasons: - Diabetes Care 2019, Scottish Dental Clinical Effectiveness Programme, Canada Clinical Practice Guidelines (2018), Swedish National Guidelines for Diabetes Care, International Diabetes Federation and the European Federation of Periodontology: The surveillance team at

		from: https://www.idf.org/e-library/guidelines/83-oral-health-for -people-with-diabetes). 4. Treatment of periodontitis is associated with a mild but consistent improvement in glucose management over 3-4 months. • (Treatment of periodontal disease for glycaemic control in people with diabetes mellitus. Simpson TC, Weldon JC, Worthington HV, Needleman I, Wild SH, Moles DR, Stevenson B, Furness S, Iheozor-Ejiofor Z. Cochrane Database Syst Rev. 2015 Nov 6;(11):CD004714). 5. Recent evidence suggests that management of periodontitis is linked to improved metabolic outcomes, better vascular and kidney functions after 12 months. • (Systemic effects of periodontitis treatment in patients with type 2 diabetes: a 12 month, single-centre, investigator-masked, randomised trial. D'Aiuto F, Gkranias N, Bhowruth D, Khan T, Orlandi M, Suvan J, Masi S, Tsakos G, Hurel S, Hingorani AD, Donos N, Deanfield JE; TASTE Group. Lancet Diabetes Endocrinol. 2018 Dec;6(12):954-965). 6. Patients with diabetes should be referred to a dentist for comprehensive dental and periodontal examination. • (Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Medical Care in Diabetes d2019 Diabetes Care 2019;42(Suppl. 1):S34–S45). • (Scottish Dental Clinical Effectiveness Programme, 2014) • (Clinical Knowledge Summaries, Gingivitis and Periodontitis, https://cks.nice.org.uk/gingivitis-and-periodontitis#!scenario)	NICE do not consider guidelines from other organisations as an evidence type. - D'Aiuto et al (2017), Jeffcoat et al (2014), Solowiej-Wedderburn (2017), Nasseh et al (2017): Do not meet study type inclusion criteria. Due to the large volume of evidence available for this topic, this surveillance review focussed specifically on RCTs and Cochrane reviews.

Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees

		• (Oral health: local authorities and partners Public health guideline Published: 22 October 2014 nice.org.uk/guidance/ph55) • (2018 Clinical Practice Guidelines Introduction Diabetes Canada Clinical Practice Guidelines Expert Committee, Can J Diabetes 42 (2018) S1–S5) • (Swedish National Guidelines for Diabetes Care from the National Board of Health and Welfare – Support for governance and management. https://www.socialstyrelsen.se/publikationer2015/2015-4-12) 7. Oral health education should be provided to all patients with diabetes as part of their overall educational programme. • (Scientific evidence on the links between periodontal diseases and diabetes: Consensus report and guidelines of the joint workshop on periodontal diseases and diabetes by the International diabetes Federation and the European Federation of Periodontology. Sanz M, Ceriello A, Buysschaert M, Chapple I, Demmer RT, Graziani F, Herrera D, Jepsen S, Lione L, Madianos P, Mathur M, Montanya E, Shapira L, Tonetti M, Vegh D. Diabetes Res Clin Pract. 2018 Mar;137:231-241). • (Oral health: local authorities and partners Public health guideline Published: 22 October 2014 nice.org.uk/guidance/ph55) nice.org.uk/guidance/ph55) • (IDF Clinical Guidelines Task Force. IDF Guideline on oral health for people with diabetes. Brussels, Belgium: International Diabetes Federation (IDF); 2009. Available from: https://www.idf.org/e-library/guidelines/83-oral-health-for -people-with-diabetes). 8. Evidence from cost-effective analyses showed that promotion of oral health measure will lead to reduced medical costs in patients with diabetes.	

		• (Swedish National Guidelines for Diabetes Care from the National Board of Health and Welfare – Support for governance and management. https://www.socialstyrelsen.se/publikationer2015/2015-4-12) • (The Relationship between Periodontal Interventions and Healthcare Costs and Utilization. Evidence from an Integrated Dental, Medical, and Pharmacy Commercial Claims Database. Nasseh K, Vujicic M, Glick M. Health Econ. 2017 Apr;26(4):519-527). • (Cost-effectiveness of non-surgical periodontal therapy for patients with type 2 diabetes in the UK. Solowiej-Wedderburn J, Ide M, Pennington M. J Clin Periodontol. 2017 Jul;44(7):700-707). • (Impact of periodontal therapy on general health: evidence from insurance data for five systemic conditions. Jeffcoat MK, Jeffcoat RL, Gladowski PA, Bramson JB, Blum JJ. Am J Prev Med. 2014 Aug;47(2):166-74). (SJH) There has been significant coverage in the media relating to diet and reversal of type 2 diabetes, it is probably that the public would be looking to the NICE guidance for further information on this subject area. This is not a specific area of clinical expertise for the CAHPO team, however we would encourage engagement with the College of Podiatry, The British Dietetic Association, The British and Irish Orthoptics Society and The British Association of Prosthetists and Orthotists if this has not already been considered, for further comment. (SC)	
Royal College of Physicians		We would like to endorse the responses submitted by the Diabetes Technology Network (DTN) and the Association of British Clinical Diabetologists (ABCD).	Thank you for your comment. Please see our response to the DTN and ABCD above.

Diabetes UK	Yes	**Dietary advice and remission** We strongly urge NICE to reconsider the decision not to review the recommendations surrounding dietary advice, which have not been updated since 2009, ten years ago. There has been research and a number of clinical trials which demonstrate the effectiveness of low-calorie or low-carbohydrate diets in putting Type 2 diabetes into remission for between 2 and 6 years. Crucially, there is data to show that the approach used in the DiRECT study would be cost-effective, leading to NHS England committing to piloting this across the country. The decision not to review this section of the guidelines fails to take account of the effect of remission upon the health of those concerned and the significant difference in adverse events during the second year of DiRECT also appears to have been overlooked. We suggest that without a proper review of the current data to inform the dietary advice section of the guidelines, an opportunity will be missed, thereby denying clinicians the opportunity to better support their patients with up to date information and a wider range of treatment options for those recently diagnosed with Type 2 diabetes, thus avoiding clinical inertia. Gregg et al. (2012), *Association of an intensive lifestyle intervention with remission of type 2 diabetes*. JAMA; 308(23): 2489-496 Esposito K et al. (2014) *The effects of a Mediterranean diet on the need for diabetes drugs and remission of newly diagnosed type 2 diabetes: follow-up of a randomized trial.* Diabetes Care;37(7):1824-30.	Thank you for your comments. Following consideration of new evidence identified in the surveillance review, we are retaining our proposal to partially update NICE's guideline on type 2 diabetes in adults. Information obtained through the surveillance review, including feedback from stakeholders through this consultation, will be passed on to developers for consideration during the update of the guideline. **Low Calorie diet** We retain our proposal not to update the guideline around very low calorie diets. Evidence submitted was not eligible due to indirectness of population (relating to obesity without T2D, and to prevention not treatment), out of scope study designs, and studies published outside the surveillance search period. The joint ADA and EASD guideline was also cited as referring to low carbohydrate and low calorie diets. However, this guideline does not explicitly recommend these diets but states that 'advice should be given of the health benefits of weight loss and encouraged to engage in a programme of intensive lifestyle management, which may include food substitution'. NICE guideline NG28 already advises individualising recommendations for carbohydrate intake, and meal patterns. This encompasses a range of interventions, which may include low carbohydrate and low calorie diets. The 2 year results of the DIRECT trial by Lean et al (2018) were included in the surveillance review. However, longer-term results of this study (beyond 2 years), and other longer-term studies of low calorie and low carbohydrate diets are likely to be needed to establish any definite impact on the guideline. A joint working group of The Scientific Advisory Committee on Nutrition, NHS England and Diabetes UK, with input from the British Dental Association and Royal Colleges, is reviewing the evidence on low carbohydrate diets

		Lean et al. (2019). Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. Lancet Diabetes Endocrinol;7(5):344-355. Remission is life-changing for people with Type 2 diabetes. It affects their insurance premiums, and major insurers are already interested in adding diabetes remission to their criteria for calculating their premiums. Remission can give people with Type 2 diabetes realistic hope. Of all the issues affecting people with Type 2 diabetes, the question of whether diabetes can be 'reversed' is hugely important and has the potential to change the perception of Type 2 diabetes from a progressive condition managed with either medicine or insulin, to one that is treatable and reversible. People living with Type 2 diabetes want more information on remission and the option of having NHS support to achieve this. Diabetes UK (2017). Your priorities for Type 2 diabetes research: The top 10 https://www.diabetes.org.uk/resources-s3/2017-0/1196_PSP%20lay%20report_DIGITAL%20SPREADS.pdf GP systems already have a read-code for Type 2 diabetes remission. But unfortunately, this is not being used consistently partly because there is no consensus on defining remission. We are currently working with the American Diabetes Association (ADA) and the European	with publication expected in 2020. This will be tracked by the surveillance team and the results will be considered when available. We will also pass the collective feedback in this area to the development team working on the update of the NICE guideline on obesity (CG189) as the main study identified in this area (DiRECT) fed into the decision to update NICE guideline CG189. Please note that the studies by Esposito K et al. (2014) and Gregg et al (2012) preceded the surveillance search period and were therefore not included. **Bariatric surgery** Bariatric surgery is covered in NICE's guideline on Obesity which includes specific advice for T2D, and is cross referred to by NICE guideline NG28.

Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees

		Association for the Study of Diabetes (EASD) to develop an international consensus that will be published in the autumn 2019 which may help NICE inform its own guidelines surrounding remission. We suggest that remission should be included in the guidelines as a realistic treatment outcome for some people with Type 2 diabetes and we are concerned that the decision not to review the dietary advice section of NG28 could have an adverse impact on quality of care and treatment for people living with Type 2 diabetes. Since the last publication of the NICE Type 2 diabetes guidelines, major diabetes organisations have updated their nutrition guidelines to reflect current evidence. Since 2018 we, Diabetes Canada and the ADA have published new nutritional guidelines which highlight that there are different approaches to dietary management of Type 2 diabetes and recognise individualised approaches to dietary choices. In addition, all three have also recognised the potential to put Type 2 diabetes into remission. We suggest that not reviewing the guidelines surrounding dietary advice and updating them to reflect the growing evidence base surrounding remission would be a significant missed opportunity for NICE. Sievenpiper JL, Chan CB, Dworatzek PD, Freeze C, Williams SL. Diabetes Canada Clinical Practice Guidelines Expert Committee. Nutrition Therapy. Can J Diabetes 42 (2018) S64–S79 Dyson PA, Twenefour D, Breen C, Duncan A, Elvin E, Goff L, Hill A, Kalsi P, Marsland N, McArdle P, Mellor D, Oliver L, Watson K. Diabetes UK evidence-based nutrition guidelines for the prevention and management of diabetes. Diabet Med. 2018 May;35(5):541-547. Full guidelines here https://diabetes-resources-production.s3.eu-west-	

		1.amazonaws.com/resources-s3/2018-03/1373_Nutrition%20guidelines_0.pdf Evert AB, Dennison M, Gardner CD, Garvey WT, Lau KHK, MacLeod J, Mitri J, Pereira RF, Rawlings K, Robinson S, Saslow L, Uelmen S, Urbanski PB, Yancy WS Jr. Nutrition Therapy for Adults With Diabetes or Prediabetes: A Consensus Report. Diabetes Care. 2019 May;42(5):731-754 **Bariatric (metabolic) surgery** There is now more data on the effect of bariatric (metabolic) surgery on Type 2 diabetes with evidence of surgery putting Type 2 diabetes into remission and this lasting up to 15 years, with a reduction of diabetes complications. Current access to bariatric surgery services is very varied, with low numbers accessing it. There is a lack of understanding amongst healthcare professionals of the role of metabolic surgery in treating hyperglycaemia and its potentially significant role in inducing Type 2 diabetes remission. We suggest that NICE now has the opportunity to provide clarity on this by producing evidence-based guidelines that reflect the most up-to-date data and we would urge NICE to consider doing this. Rubino F, Nathan DM, Eckel RH, Schauer PR, Alberti KG, Zimmet PZ, Del Prato S, Ji L, Sadikot SM, Herman WH, Amiel SA, Kaplan LM, Taroncher-Oldenburg G, Cummings DE; Delegates of the 2nd Diabetes Surgery Summit. Metabolic Surgery in the Treatment Algorithm for Type 2	

		Diabetes: a Joint Statement by International Diabetes Organizations. Obes Surg. 2017 Jan;27(1):2-21 Madsen LR, Baggesen LM, Richelsen B, Thomsen RW. Effect of Roux-en-Y gastric bypass surgery on diabetes remission and complications in individuals with type 2 diabetes: a Danish population-based matched cohort study. Diabetologia. 2019 Apr;62(4):611-620. Sjöström L, Peltonen M, Jacobson P, Ahlin S, Andersson-Assarsson J, Anveden Å, Bouchard C3, Carlsson B, Karason K, Lönroth H, Näslund I, Sjöström E, Taube M, Wedel H, Svensson PA1, Sjöholm K, Carlsson LM. Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications. JAMA. 2014 Jun 11;311(22):2297-304.	

Do you have any comments on equalities issues?			
Stakeholder	**Overall response**	**Comments**	**NICE response**
Surrey Downs CCG	No	No comments provided.	Thank you.
NHS Leeds CCG	No	No comments provided.	Thank you.

South Sefton Clinical Commissioning Group	No	No comments provided.	Thank you.
British Dental Associaiton	No	No comments provided.	Thank you.
Total Diet and Meal Replacements (TDMR) Europe	No	No comments provided.	Thank you.
Digital Diabetes Media Ltd	No	No comments provided.	Thank you.
UK Clinical Pharmacy Association (UKCPA) Diabetes and Endocrinology Group	No	No comments provided.	Thank you.
Merck Sharp & Dohme Limited	No	No comments provided.	Thank you.
Diabetes Research Unit Cymru (Wales) (DRUC)	No	No comments provided.	Thank you.
Abbott Diabetes Care	No	No comments provided.	Thank you.
Royal College of Ophthalmologists	No	No comments provided.	Thank you.
UK Renal association	No	No comments provided.	Thank you.

Elcena Jeffers Foundation	Yes	The access to let us contribute on the work of NICE	Thank you for your comment. Stakeholders will be informed when the guidance in development page is available, with details of how to contribute to the update.
Novo Nordisk	No	No comments provided.	Thank you.
British Society of Periodontology	No	No comments provided.	Thank you.
X-PERT Health	No	No comments provided.	Thank you.
AstraZeneca Ltd. (UK)	No	No comments provided.	Thank you.
Eli Lilly and Company Ltd	No	No comments provided	Thank you.
UCL Eastman Dental Institute	No	No comments provided	Thank you.
Gilead Sciences	No	No comments provided	Thank you.
MedTech Europe	No	No comments provided	Thank you.
Bayer plc		There are two ongoing phase 3 trials for Finerenone in subjects with type 2 diabetes mellitus and diabetic kidney disease (FIDELIO-DKD https://clinicaltrials.bayer.com/study/1963 and FIGARO-	Thank you for your comment. **Diabetic kidney disease**

		DKD https://clinicaltrials.bayer.com/study/2098), from which results are expected to be available within the anticipated timeframe of the update to this guideline. Evidence from these trials should be considered when conducting the update. We agree that recommendations regarding the treatment of diabetic eye disease should be updated. As part of this update we agree that the recommendations from NICE technology appraisal 346, Aflibercept for treating diabetic macular oedema, should be incorporated into the guideline in accordance with the procedure outlined in the guidelines manual.	The highlighted ongoing trials will be tracked by the surveillance team and the results considered when available. **Diabetic eye disease** Given the growing evidence base in this area and the related NICE technology appraisal guidance on treatments for diabetic macular oedema, including aflibercept, there may be a need for new recommendations to be developed with specialist ophthalmic input. However, please note that the surveillance proposal does not include incorporating technology appraisal 346, although this will be considered as part of the update, in accordance with the NICE guidelines manual.
Association for Clinical Biochemistry and Laboratory Medicine	No	No comments provided	Thank you.
Takeda UK Ltd	No	No comments provided	Thank you.
Boehringer Ingelheim Ltd.	Yes	Compared with the white population, Type 2 diabetes is up to six times more common in people of South Asian descent and up to three times more common in those of African and African-Caribbean descent. It is also more common in people of Chinese descent and other non-Caucasian groups. The average age at diagnosis is also comparatively younger in these groups. Type 2 diabetes is more prevalent among less affluent populations. Those in the most deprived one-fifth of the population are one-and-a-half times more likely than average to have diabetes at any given age. The risk of death from diabetes is between	Thank you for your comment. The points highlighted have been noted for consideration of inequalities in the update process.

		three and six times higher, with these groups also being particularly susceptible to the cardiovascular and renal complications of diabetes. Increasing health inequalities across England and Wales continues to be reported and is a major public health issue. The NHS Long Term Plan sets out a range of improvements for those at risk of Type 2 diabetes and living with Type 2 diabetes. Prevention, access to appropriate multi-disciplinary teams, and self-management form integral parts of the Long Term Plan specifically relating to diabetes and reducing inequalities. It is therefore an important consideration for NICE that whilst a guideline update will be helpful it must be implemented with an acknowledgement and specific consideration of inequalities and consistent implementation. We would urge NICE to work with all relevant stakeholders to specifically address adherence to the guidelines due to the serious and significant impact of Type 2 diabetes on public health. This guideline may lend itself to an innovative pilot programme to support more consistent access and uptake.	
Perspectum Diagnostics	No	No comments provided	Thank you.
South Asian Health Foundation	Yes	As above – the older adult with diabetes would need a specific section or focus as they form a particularly unique population. The evidence needs to look at ethnic minorities in more detail particularly in terms of looking at different cut-offs for medications such as GLP-1 analogues in terms of BMI. In terms of risk factors for cardiovascular disease	Thank you for your comment. The points highlighted have been noted for consideration of inequalities in the update process.

		we should exercise caution when generalizing the results of trials to own practice, with regard to the ethnicity of individuals. Efforts should be made to improve reporting of ethnicity and improve diversity in trial recruitment, although we acknowledge that there are challenges that must be overcome to make this a reality.	
Roche Diabetes Care, Ltd	No	No comments provided	Thank you.
Medtronic Ltd	No	No comments provided.	Thank you.
Primary Care Diabetes Society	No	No comments provided.	Thank you.
Royal College of Nursing	No	No comments provided.	Thank you.
Napp Pharmaceuticals Ltd.	No	No comments provided.	Thank you.
Dexcom Operating Ltd	YES	The proposed scope has the potential to create an inequality for people with suboptimal HbA1c and those vulnerable patients in greatest need of a customised therapeutic intervention. To remove any inequality, rt-CGM should be added to the scope for people with suboptimal HbA1c so that these patients, too, are able to access the appropriate technology.	Thank you for your comment. Please see the earlier response to the comments on continuous glucose monitoring. Addressing potential inequity in access due to suboptimal HbA1c will be considered as part of the update.
Newcastle University	Yes	The low socio-economic groups were very well represented in DiRECT and remission of diabetes was similar across these groups.	Thank you for your comment.

			The points highlighted have been noted for consideration of inequalities in the update process.
The British Dietetic Association	No	No comments provided.	Thank you.
Association of British Clinical Diabetologists	No	No comments provided.	Thank you.
NHS England	No	No comments provided.	Thank you.
Royal College of Physicians		We would like to endorse the responses submitted by the Diabetes Technology Network (DTN) and the Association of British Clinical Diabetologists (ABCD).	Thank you for your comment. Please see our response to the DTN and ABCD above.
Diabetes UK	Yes	Language throughout the whole of NG28 should be amended to reflect the NHS England position statement 'Language Matters'. This should help to ensure that all people living with Type 2 diabetes are able to access the best possible care available regardless of their age, sex, gender, disability, religion, race, ethnicity or socio-economic status. NHS England (2018) https://www.england.nhs.uk/publication/language-matters-language-and-diabetes/	Thank you for your comment about the language used within NICE guideline NG28. All NICE guidelines and related products are developed with editors to ensure they are written and presented in a way that is clear and accessible to a range of different audiences. Further details can be found on the Language page of the NICE website.

Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees

Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees