National Institute for Health and Care Excellence

Draft for consultation

Type 2 diabetes in adults: management (medicines update)

[F2.1] Evidence reviews for subsequent pharmacological management of type 2 diabetes – Appendices A-C

NICE guideline GID-NG10336

Evidence reviews underpinning recommendations 1.8.6-1.8.32, 1.8.34,1.8.38-1.8.60 and recommendations for research in the NICE guideline

August 2025

Draft for Consultation

This evidence review was developed by NICE

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

ISBN:

Contents

Appendices

Appendix A Review protocols

A.1 Review protocol for the subsequent pharmacological management of type 2 diabetes

ID	Field	Content
0.	PROSPERO registration number	Not registered
1.	Review title	Which pharmacological therapies are most clinically and cost effective for the management of type 2 diabetes when current treatment has not given adequate response?
2.	Review question	Which pharmacological therapies are most clinically and cost effective for the management of type 2 diabetes when current treatment has not given adequate response, including: • medicines within the following classes biguanides, DPP-4 inhibitors, GLP-1 receptor agonist, insulin, sulfonylureas, SGLT2 inhibitors, and thiazolidinediones (but not limited to these), • approaches to optimise treatment (including combination treatment, switching to different therapies, de-escalation and stopping previous therapies), and • consideration of different population subgroups?
3.	Objective	Pharmacological treatment for type 2 diabetes has changed as more evidence has become available. As a more holistic approach to type 2 diabetes treatment has been adopted and more treatments have developed, more options have been available that may be better suited to different people at different times. This review will aim to ask what the best treatment approach is for people with type 2 diabetes in different population subgroups after initial therapy has not had an adequate response. This may include the initiation of new therapy, but could also include other approaches to optimising treatment (such as switching to different therapies, combining treatments and removing treatments that are not effective).
4.	Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos

		Searches will be restricted by: • Study design RCT and SR filters will be applied • No date limit will be set • English language studies • Human studies • Conference abstracts will be excluded from the search results Other searches: • Inclusion lists of systematic reviews The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Pharmacological treatments for people with type 2 diabetes mellitus

6.	Population	Inclusion:
		• Adults (age ≥18 years) with type 2 diabetes mellitus
		
		The population will be stratified into different groups, these include:
		• People with type 2 diabetes mellitus and heart failure
		  ○ People with type 2 diabetes mellitus and heart failure
		  ○ People with type 2 diabetes mellitus and no heart failure
		  ○ Mixed population
		  ○ Not stated/unclear
		• People with type 2 diabetes mellitus and atherosclerotic cardiovascular disease
		  ○ People with type 2 diabetes mellitus and atherosclerotic cardiovascular disease
		  ○ People with type 2 diabetes mellitus and no atherosclerotic cardiovascular disease

		○ Mixed population ○ Not stated/unclear • People with type 2 diabetes mellitus and chronic kidney disease ○ People with type 2 diabetes mellitus and chronic kidney disease ○ People with type 2 diabetes mellitus and no chronic kidney disease ○ Mixed population ○ Not stated/unclear • People with type 2 diabetes mellitus and high cardiovascular risk ○ People with type 2 diabetes mellitus and high cardiovascular risk ○ People with type 2 diabetes mellitus and not at high cardiovascular risk ○ Mixed population ○ Not stated/unclear After the protocol was submitted, it was agreed that five population models would be obtained from these stratifications: • People with type 2 diabetes and chronic heart failure • People with type 2 diabetes and atherosclerotic cardiovascular disease • People with type 2 diabetes and chronic kidney disease • People with type 2 diabetes and low cardiovascular risk with no other comorbidities • People with type 2 diabetes and high or mixed/unclear cardiovascular risk with no other comorbidities Exclusion: • Children and young people (age <18 years) with type 2 diabetes mellitus • Pregnant people with type 2 diabetes mellitus • People with type 1 diabetes mellitus • People with type 2 diabetes mellitus who are hyperglycaemic and require rescue treatment
7.	Intervention	Different strategies to optimise treatment (stratify trials by the strategy used in the trial): • Adding a new treatment (combining multiple therapies) • Stopping a previous treatment • Switching to a different treatment, which might include a different form of administration of the same drug (stopping a previous treatment and adding a new treatment simultaneously)

		Pharmacological therapies for people with type 2 diabetes. • All therapies will be examined on an individual drug level (rather than a class level). • All doses will be pooled together. • Biguanides o Metformin hydrochloride standard release o Metformin hydrochloride slow release • DPP-4 inhibitors o Alogliptin (Vipidia) o Linagliptin (Trajenta) o Saxagliptin (Onglyza) o Sitagliptin (Januvia) o Vildagliptin (Galvus) • GLP-1 receptor agonist o Dulaglutide (Trulicity) o Exenatide (Byetta) o Liraglutide (Victoza) o Lixisenatide (Lyxumia) o Semaglutide (Rybelsus, Ozempic) • Dual GIP/GLP-1 receptor co-agonists o Tirzepatide (Mounjaro) • SGLT2 inhibitors o Canagliflozin (Invokana) o Dapagliflozin (Forxiga) o Empagliflozin (Jardiance) o Ertugliflozin (Steglatro) • Sulfonylureas o Gliclazide o Glimepiride o Glipizide o Tolbutamide • Thiazolidinediones o Pioglitazone • Combinations of therapies listed above (combinations may include medicines being given separately or combination products) • After the protocol was submitted it was agreed that IDegLira (insulin degludec and liraglutide) and IGlarLixi (insulin glargine and lixisenatide) would be included as combinations that would be looked at in this category even though insulin is a comparator.
8.	Comparator	• Different strategies to optimise treatment • Different combinations of pharmacological therapies listed in the intervention section to each other

		• Different combination with an oral formulation of the same medication compared to a different combination with an injectable formulation of the same medication • Different combinations of pharmacological therapies listed in the intervention section and insulin (all types and doses of insulin pooled together in the same drug class) • Different combinations of pharmacological therapies listed in the intervention section and placebo
9.	Types of study to be included	Systematic reviews (SRs) of randomised-controlled trials Randomised-controlled trials (RCTs) Published NMAs and IPDs will be considered for inclusion.
10.	Other exclusion criteria	• Non-randomised trial evidence (including observational, cohort, case-control and case series studies, uncontrolled or single arm trials), narrative reviews, conference abstracts, letters, editorials and trial protocols. • Studies including a mixed population of people with type 1 and 2 diabetes, unless subgroup analyses were reported or 85% or more of the study population have type 2 diabetes. • Studies including a mixed population of people with and without diabetes will be excluded. • Comparisons with unlicensed modes of delivery (for example, inhaled insulin). • Crossover trials (a crossover trial will only be included if the duration of one or both interventions is at least 24 weeks and there is a washout period of at least 6 weeks between interventions). • Trials where there is unclear washout of existing drug treatments, where a proportion or all participants continued previous medicines that will likely confound study results (papers were excluded unless this represented a small proportion of patients that is less than 5%). • Trials that have a treatment and follow up period of less than 24 weeks. • Systematic reviews that did not include at least one RCT of at least 24 weeks duration. • Dose finding trials where both arms would be combined in a single node in the NMA. (Three arm trials may be included if they connect to the network and provide useful information.

		• Trials of Treatments which are not available, or no longer available, in the UK including:
		  ○ Glibenclamide
		  ○ Chlorpropamide
		  ○ Nateglinide
		  ○ Miglitol
		  ○ Omarigliptin
		  ○ Albiglutide
		  ○ Rosiglitazone
		• Trials of treatments that are rarely used in the UK, including:
		  ○ Repaglinide
		  ○ Acarbose
		• Trials of combinations of drugs which include one or more drug that is not available in the UK, no longer available in the UK.
		• Trials of a combined formulation of drugs which is not available in the UK.
		• Trials that were not reported in English.

11.	Context	The 2021 update focussed on the cardiovascular benefits of different pharmacological therapies for type 2 diabetes. The evidence included in this review will take a holistic view of the wider potential benefits of the treatments. This may affect which medicines should be offered, and which combinations should be used at each stage of treatment.

12.	Primary outcomes (critical outcomes)	Outcomes will be extracted in this review for inclusion in the review. The final time point (end point of the trial) reported will be extracted and used in the analysis where possible.
		
		Where outcomes are reported as time-to-event and dichotomous values, both time-to-event and dichotomous values will be extracted.
		
		Outcomes to be extracted for use in this review
		All outcomes are considered equally important for decision making and therefore have all been rated as critical:
		• Health-related quality of life (continuous outcomes):
		  ○ EQ-5D
		  ○ SF-6D
		  ○ SF-36
		  ○ SF-12
		  ○ Other utility measures (AQOL, HUI, 15D, QWB)

		○ HASMID-10 ○ Diabetes Quality of life ○ Diabetes Quality of life questionnaire ○ Diabetes Quality of life Clinical Trial Questionnaire ○ Audit of Diabetes Dependent Quality of Life ○ Diabetes-39 ○ Diabetes Health Profile ○ DAWN2 Impact of Diabetes Profile ○ Diabetes Impact Measurement Scales ○ QoLHYPO • All-cause mortality (time-to-event/dichotomous outcome) • Cardiovascular mortality (time-to-event/dichotomous outcome) • Major Cardiovascular Events (MACE) (where multiple MACE values are reported [for example: 3-item MACE and 4-item MACE], the highest number MACE value will be prioritised) (time-to-event/dichotomous outcome) ○ 3-item MACE ○ 4-item MACE ○ 5-item MACE • Events making up MACE (time-to-event/dichotomous outcomes): ○ Non-fatal stroke ○ Non-fatal myocardial infarction ○ Unstable angina ○ Hospitalisation for heart failure • Renal events (time-to-event/dichotomous outcome): ○ Acute kidney injury ○ Persistent signs of worsening kidney disease (including doubling of serum creatinine) ○ Development of end stage kidney disease (including need for renal replacement therapy and transplant) ○ Death from renal cause • Serious adverse events (time-to-event/dichotomous outcome): ○ Cardiac arrhythmia (including atrial fibrillation) ○ Diabetic ketoacidosis ○ Falls requiring hospitalisation

		• Progression of liver disease (to non-alcoholic fatty liver disease, to fibrosis, to cirrhosis, to end stage liver disease) (time-to-event/dichotomous outcome)
		• Remission (time-to-event/dichotomous outcome)
		• Acute diabetic complications (time-to-event/dichotomous outcome):
		  ○ Hypoglycaemia episodes
		  ○ At night hypoglycaemic episodes
		  ○ Severe hypoglycaemic episodes
		• Continuous outcomes:
		  ○ HbA1c change (absolute change scores prioritised over percentage change scores)
		  ○ Weight change
		  ○ BMI change

13.	Data extraction (selection and coding)	EndNote will be used for reference management, citations and bibliographies. All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. EPPI will be used for sifting. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow or equivalent. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
14.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0)

15.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager. Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. When different studies present continuous data measuring the same outcomes but using different numerical scales these outcomes will be converted to the same scale before meta-analysis is conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, this will be achieved using standardised mean differences (SMDs, Hedges' g). Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias will be considered with the guideline committee, and if suspected will be tested for when there are more than 5 studies for that outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ Network meta-analysis (NMAs) may be used to synthesise direct evidence about pairs of interventions that originate from two or more separate studies and indirect evidence. WinBUGS will be used for network meta-analysis, if possible given the data identified. The quality of the NMA networks will be assessed using a modified form of GRADE.

16.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present:
		
		• People with frailty
		  ○ People with frailty
		  ○ People without frailty
		  ○ Mixed population
		  ○ Not stated/unclear

		• Onset of type 2 diabetes mellitus ○ Early onset type 2 diabetes mellitus first diagnosed at age below 40 years of age ○ People with type 2 diabetes mellitus first diagnosed at age above 40 years of age ○ Mixed population ○ Not stated/unclear • People with non-alcoholic fatty liver disease ○ People with non-alcoholic fatty liver disease ○ People without non-alcoholic fatty liver disease ○ Mixed population ○ Not stated/unclear • People with obesity ○ People with obesity (for people with a South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean family background BMI ≥27.5, for people not in the groups listed before BMI ≥30) ○ People without obesity (for people with a South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean family background BMI <27.5, for people not in the groups listed before BMI <30) ○ Mixed population ○ Not stated/unclear • eGFR category at baseline ○ eGFR ≥30mL/min/1.73m^2 ○ eGFR 15-29mL/min/1.73m^2 ○ eGFR <15mL/min/1.73m^2 ○ Mixed population ○ Not stated/unclear • Albuminuria category at baseline ○ A1 (ACR <30mg/g or <3mg/mmol) ○ A2 (ACR 30-300 mg/g or 3-30mg/mmol) ○ A3 (ACR >300mg/g or >30mgmmol) ○ Mixed population ○ Not stated/unclear	
17.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
18.	Language	English	
19.	Country	England	

<table>
<tr><td>20.</td><td>Anticipated or actual start date</td><td colspan="3">10/01/2023</td></tr>
<tr><td>21.</td><td>Anticipated completion date</td><td colspan="3">01/12/2024</td></tr>
<tr><td rowspan="8">22.</td><td rowspan="8">Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td>Preliminary searches</td><td>☑</td><td>☑</td></tr>
<tr><td>Piloting of the study selection process</td><td>☑</td><td>☑</td></tr>
<tr><td>Formal screening of search results against eligibility criteria</td><td>☑</td><td>☑</td></tr>
<tr><td>Data extraction</td><td>☑</td><td>☑</td></tr>
<tr><td>Risk of bias (quality) assessment</td><td>☑</td><td>☑</td></tr>
<tr><td>Data analysis</td><td>☑</td><td>☑</td></tr>
<tr><td>23.</td><td>Named contact</td><td colspan="3">5a. Named contact
Guideline Development Team NGC

5b Named contact e-mail
t2diabetesadults@nice.org.uk

5e Organisational affiliation of the review
National Institute for Health and Care Excellence (NICE)</td></tr>
<tr><td>24.</td><td>Review team members</td><td colspan="3">From NICE:
Serena Carville (Guideline lead)
George Wood (Medicines analyst)
Emily Terrazas-Cruz (Senior research fellow)
Tayyaba Mumtaz (Trainee technical analyst)
Nancy Pursey (Trainee technical analyst)
David Wonderling (Head of health economics)
Muksitur Rahman (Health economics analyst)
Joseph Runicles (Information specialist)
Sarah Glover (Information specialist)
Amy Crisp (Senior project manager)</td></tr>
<tr><td>25.</td><td>Funding sources/sponsor</td><td colspan="3">Development of this systematic review is being funded by NICE.</td></tr>
<tr><td>26.</td><td>Conflicts of interest</td><td colspan="3">All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing</td></tr>
</table>

		with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
27.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10336	
28.	Other registration details	N/A	
29.	Reference/URL for published protocol	N/A	
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
31.	Keywords	Adults; Biguanides; DPP-4 inhibitors; GLP-1 receptor agonists; Initial; Intervention; Pharmacological; SGLT2 inhibitors; Sulfonylureas; Thiazolidinediones; Type 2 Diabetes Mellitus	
32.	Details of existing review of same topic by same authors	N/A	
33.	Current review status	☐	Ongoing
		☒	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
34.	Additional information	N/A	
35.	Details of final publication	www.nice.org.uk	

1

A.2 Health economic review protocol

Below is the health economic review protocol. This sets out how published cost effectiveness evidence will be identified for the guideline and the criteria for inclusion/exclusion.

Table 1: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below. Databases searched: • Centre for Reviews and Dissemination NHS Economic Evaluations Database (NHS EED) – all years (closed to new records April 2015) • Centre for Reviews and Dissemination Health Technology Assessment database – all years (closed to new records March 2018) • International HTA database (INAHTA) – all years Medline and Embase – from 2014 (due to NHS EED closure)
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2008 (including those included in the previous guideline), abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2008 that were included in the previous guideline will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (https://www.nice.org.uk/process/pmg20/chapter/introduction) **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and

	methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2008 or later (including any such studies included in the previous guideline) but that depend on unit costs and resource data entirely or predominantly from before 2008 will be rated as 'Not applicable'. • Studies published before 2008 (including any such studies included in the previous guideline) will be excluded before being assessed for applicability and methodological limitations. *Number of interventions:* • Studies presenting results for multiple comparators of interest will be included in the review. • Studies presenting results of pair-wise analyses only will be excluded from the review. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

1

Appendix B Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual (NICE2014)

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies as these concepts may not be indexed or described in the title or abstract and are therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Q1.2 Which pharmacological therapies are most clinically and cost effective for the management of type 2 diabetes when current treatment has not given adequate response, including:

- medicines within the following classes biguanides, DPP-4 inhibitors, GLP-1 receptor agonist, insulin, sulfonylureas, SGLT2 inhibitors, and thiazolidinediones (but not limited to these),
- approaches to optimise treatment (including combination treatment, switching to different therapies, de-escalation and stopping previous therapies), and
- consideration of different population subgroups?

Table 2: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 21 March 2024	Randomised controlled trials Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 21 March 2024	Randomised controlled trials Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
The Cochrane Library (Wiley)	Cochrane Reviews to 2024 Issue 3 of 12 CENTRAL to 2024 Issue 3 of 12	Exclusions (clinical trials, conference abstracts)

Database	Dates searched	Search filter used
Epistemonikos (The Epistemonikos Foundation)	Inception to 21 March 2024	Systematic review studies Exclusions (Cochrane reviews) English language

Medline (Ovid) search terms

1.	exp Diabetes Mellitus, Type 2/
2.	(type adj4 ("2" or "II" or two) adj4 diabet*).tw.
3.	((matur* or adult* or slow*) adj4 onset* adj4 diabet*).tw.
4.	(("ketosis resistant" or "ketosis prone" or stable) adj4 diabet*).tw.
5.	(("non insulin" or noninsulin) adj4 depend* adj4 diabet*).tw.
6.	(NIDDM or T2DM or DM2).tw.
7.	or/1-6
8.	letter/
9.	editorial/
10.	news/
11.	exp historical article/
12.	Anecdotes as Topic/
13.	comment/
14.	case reports/
15.	(letter or comment*).ti.
16.	or/8-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animals/ not humans/
20.	exp Animals, Laboratory/
21.	exp Animal Experimentation/
22.	exp Models, Animal/
23.	exp Rodentia/
24.	(rat or rats or mouse or mice or rodent*).ti.
25.	or/18-24
26.	7 not 25
27.	limit 26 to english language
28.	exp Glucagon-Like Peptide 1/
29.	"glucagon like peptide 1".tw.
30.	("GLP 1" or "GLP1").tw.
31.	Exenatide/
32.	(Exenatide* or Byetta or Bydureon or Saxenda).tw.
33.	(Liraglutide* or Victoza).tw.
34.	(Dulaglutide* or Trulicity).tw.
35.	(Semaglutide* or Ozempic or Rybelsus).tw.
36.	(Lixisenatide* or Lyxumia).tw.
37.	(tirzepatide* or mounjaro).tw.

38.	Sodium-Glucose Transporter 2 Inhibitors/
39.	"Sodium-Glucose Transporter 2".tw.
40.	("Sodium-Glucose cotransporter 2" or "Sodium-Glucose co transporter 2").tw.
41.	(SGLT* or gliflozin*).tw.
42.	Canagliflozin/
43.	(Canagliflozin* or Invokana or Dapagliflozin or Forxiga or Ertugliflozin or Steglatro or Empagliflozin or Jardiance or Glyxambi).tw.
44.	exp Sulfonylurea Compounds/tu [Therapeutic Use]
45.	(Sulfonylurea* or Sulphonylurea*).tw.
46.	(Gliclazide* or Diamicron).tw.
47.	(Glimepiride* or Amaryl).tw.
48.	(Glipizide* or Minodiab).tw.
49.	Tolbutamide*.tw.
50.	Thiazolidinediones/
51.	(Thiazolidinedione* or Glitazone*).tw.
52.	Pioglitazone/
53.	(Pioglitazone* or Actos).tw.
54.	exp Dipeptidyl-Peptidase IV Inhibitors/ or Dipeptidyl Peptidase 4/
55.	("Dipeptidyl-Peptidase IV Inhibitor*" or "Dipeptidyl Peptidase 4 Inhibitor").tw.
56.	(DPP* adj2 ("4" or "iv")).tw.
57.	gliptin*.tw.
58.	(Saxagliptin* or Onglyza or Komboglyze or Qtern).tw.
59.	Vildagliptin/
60.	(Vildagliptin* or Galvus).tw.
61.	Sitagliptin/
62.	(Sitagliptin* or Januvia).tw.
63.	(Alogliptin* or Vipdomet).tw.
64.	Linagliptin/
65.	(Linagliptin* or Trajenta or Jentadueto).tw.
66.	Metformin/
67.	(Metformin* or Glucophage).tw.
68.	(Competact or Janumet or Eucreas or Synjardy or Vokanamet or Xigduo).tw.
69.	Biguanides/
70.	Biguanide*.tw.
71.	or/28-70
72.	randomized controlled trial.pt.
73.	controlled clinical trial.pt.
74.	randomi#ed.ti,ab.
75.	placebo.ab.
76.	randomly.ti,ab.
77.	Clinical Trials as topic.sh.
78.	trial.ti.
79.	or/72-78
80.	Meta-Analysis/

81.	exp Meta-Analysis as Topic/
82.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
83.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
84.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
85.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
86.	(search* adj4 literature).ab.
87.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
88.	cochrane.jw.
89.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
90.	or/80-89
91.	27 and 71
92.	91 and (79 or 90)

Embase (Ovid) search terms

1.	non insulin dependent diabetes mellitus/
2.	(type adj4 ("2" or "II" or two) adj4 diabet*).tw.
3.	((matur* or adult* or slow*) adj4 onset* adj4 diabet*).tw.
4.	(("ketosis resistant" or "ketosis prone" or stable) adj4 diabet*).tw.
5.	(("non insulin" or noninsulin) adj4 depend* adj4 diabet*).tw.
6.	(NIDDM or T2DM or DM2).tw.
7.	or/1-6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	case report/ or case study/
12.	(letter or comment*).ti.
13.	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
14.	or/8-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animal/ not human/
18.	nonhuman/
19.	exp Animal Experiment/
20.	exp Experimental Animal/
21.	animal model/
22.	exp Rodent/
23.	(rat or rats or mouse or mice or rodent*).ti.
24.	or/16-23
25.	7 not 24

26.	limit 25 to english language
27.	"glucagon like peptide 1".tw.
28.	*glucagon like peptide 1/
29.	("GLP 1" or "GLP1").tw.
30.	*exendin 4/
31.	(Exenatide* or Byetta or Bydureon or Saxenda).tw.
32.	*liraglutide/
33.	(Liraglutide* or Victoza).tw.
34.	*dulaglutide/
35.	(Dulaglutide* or Trulicity).tw.
36.	*semaglutide/
37.	(Semaglutide* or Ozempic or Rybelsus).tw.
38.	*lixisenatide/
39.	(Lixisenatide* or Lyxumia).tw.
40.	*tirzepatide/
41.	(tirzepatide* or mounjaro).tw.
42.	*sodium glucose cotransporter 2 Inhibitor/
43.	"Sodium-Glucose Transporter 2".tw.
44.	("Sodium-Glucose cotransporter 2" or "Sodium-Glucose co transporter 2").tw.
45.	(SGLT* or gliflozin*).tw.
46.	*canagliflozin/
47.	(Canagliflozin* or Invokana or Dapagliflozin or Forxiga or Ertugliflozin or Steglatro or Empagliflozin or Jardiance or Glyxambi).tw.
48.	sulfonylurea derivative/dt [Drug Therapy]
49.	(Sulfonylurea* or Sulphonylurea*).tw.
50.	*gliclazide/
51.	(Gliclazide* or Diamicron).tw.
52.	*glimepiride/
53.	(Glimepiride* or Amaryl).tw.
54.	*glipizide/
55.	(Glipizide* or Minodiab).tw.
56.	*tolbutamide/
57.	Tolbutamide*.tw.
58.	*2,4 thiazolidinedione derivative/ or *Glitazone derivative/
59.	(Thiazolidinedione* or Glitazone*).tw.
60.	*pioglitazone/
61.	(Pioglitazone* or Actos).tw.
62.	*dipeptidyl peptidase IV inhibitor/
63.	*dipeptidyl peptidase IV/
64.	("Dipeptidyl-Peptidase IV Inhibitor*" or "Dipeptidyl Peptidase 4 Inhibitor").tw.
65.	(DPP* adj2 ("4" or "iv")).tw.
66.	gliptin*.tw.
67.	*saxagliptin/
68.	(Saxagliptin* or Onglyza or Komboglyze or Qtern).tw.

69.	*vildagliptin/
70.	(Vildagliptin* or Galvus).tw.
71.	*sitagliptin/
72.	(Sitagliptin* or Januvia).tw.
73.	*alogliptin/
74.	(Alogliptin* or Vipdomet).tw.
75.	*linagliptin/
76.	(Linagliptin* or Trajenta or Jentadueto).tw.
77.	*metformin/
78.	*dapagliflozin plus metformin/ or *linagliptin plus metformin/ or *metformin/ or *dapagliflozin plus metformin plus saxagliptin/ or *ertugliflozin plus metformin/ or *glipizide plus metformin/ or *metformin plus pioglitazone/ or *metformin plus vildagliptin/ or *metformin plus saxagliptin/ or *empagliflozin plus linagliptin plus metformin/ or *alogliptin plus metformin/ or *glimepiride plus metformin/ or *empagliflozin plus metformin/ or *metformin plus sitagliptin/ or *canagliflozin plus metformin/
79.	(Metformin* or Glucophage).tw.
80.	(Competact or Janumet or Eucreas or Synjardy or Vokanamet or Xigduo).tw.
81.	*biguanide derivative/
82.	Biguanide*.tw.
83.	or/27-82
84.	random*.ti,ab.
85.	factorial*.ti,ab.
86.	(crossover* or cross over*).ti,ab.
87.	((doubl* or singl*) adj blind*).ti,ab.
88.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
89.	crossover procedure/
90.	single blind procedure/
91.	randomized controlled trial/
92.	double blind procedure/
93.	or/84-92
94.	systematic review/
95.	meta-analysis/
96.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
97.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
98.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
99.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
100.	(search* adj4 literature).ab.
101.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
102.	cochrane.jw.
103.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
104.	or/94-103
105.	26 and 83

106.	105 and (93 or 104)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Diabetes Mellitus, Type 2] explode all trees
#2.	(type near/4 ("2" or "II" or two) near/4 diabet*):ti,ab
#3.	((matur* or adult* or slow*) near/4 onset* near/4 diabet*):ti,ab
#4.	(("ketosis resistant" or "ketosis prone" or stable) near/4 diabet*):ti,ab
#5.	(("non insulin" or noninsulin) near/4 depend* near/4 diabet*):ti,ab
#6.	(NIDDM or T2DM or DM2):ti,ab
#7.	(or #1-#6)
#8.	MeSH descriptor: [Glucagon-Like Peptide 1] explode all trees
#9.	"glucagon like peptide 1":ti,ab
#10.	("GLP 1" or "GLP1"):ti,ab
#11.	MeSH descriptor: [Exenatide] this term only
#12.	(Exenatide* or Byetta or Bydureon or Saxenda):ti,ab
#13.	(Liraglutide* or Victoza):ti,ab
#14.	(Dulaglutide* or Trulicity):ti,ab
#15.	(Semaglutide* or Ozempic or Rybelsus):ti,ab
#16.	(Lixisenatide* or Lyxumia):ti,ab
#17.	(tirzepatide* or mounjaro):ti,ab
#18.	MeSH descriptor: [Sodium-Glucose Transporter 2 Inhibitors] this term only
#19.	"Sodium-Glucose Transporter 2":ti,ab
#20.	("Sodium-Glucose cotransporter 2" or "Sodium-Glucose co transporter 2"):ti,ab
#21.	(SGLT* or gliflozin*):ti,ab
#22.	MeSH descriptor: [Canagliflozin] this term only
#23.	(Canagliflozin* or Invokana or Dapagliflozin or Forxiga or Ertugliflozin or Steglatro or Empagliflozin or Jardiance or Glyxambi):ti,ab
#24.	MeSH descriptor: [Sulfonylurea Compounds] explode all trees
#25.	(Sulfonylurea* or Sulphonylurea*):ti,ab
#26.	(Gliclazide* or Diamicron):ti,ab
#27.	(Glimepiride* or Amaryl):ti,ab
#28.	(Glipizide* or Minodiab):ti,ab
#29.	Tolbutamide*:ti,ab
#30.	MeSH descriptor: [Thiazolidinediones] this term only
#31.	(Thiazolidinedione* or Glitazone*):ti,ab
#32.	MeSH descriptor: [Pioglitazone] this term only
#33.	(Pioglitazone* or Actos):ti,ab
#34.	MeSH descriptor: [Dipeptidyl-Peptidase IV Inhibitors] explode all trees
#35.	MeSH descriptor: [Dipeptidyl Peptidase 4] this term only
#36.	(Dipeptidyl NEXT Peptidase NEXT IV NEXT Inhibitor* or Dipeptidyl NEXT Peptidase NEXT 4 NEXT Inhibitor*):ti,ab
#37.	(DPP* NEAR/2 ("4" or "iv")):ti,ab
#38.	gliptin*:ti,ab

#39.	(Saxagliptin* or Onglyza or Komboglyze or Qtern):ti,ab
#40.	MeSH descriptor: [Vildagliptin] this term only
#41.	(Vildagliptin* or Galvus):ti,ab
#42.	MeSH descriptor: [Sitagliptin Phosphate] this term only
#43.	(Sitagliptin* or Januvia):ti,ab
#44.	(Alogliptin* or Vipdomet):ti,ab
#45.	MeSH descriptor: [Linagliptin] this term only
#46.	(Linagliptin* or Trajenta or Jentadueto):ti,ab
#47.	MeSH descriptor: [Metformin] this term only
#48.	(Metformin* or Glucophage):ti,ab
#49.	(Competact or Janumet or Eucreas or Synjardy or Vokanamet or Xigduo):ti,ab
#50.	MeSH descriptor: [Biguanides] this term only
#51.	Biguanide*:ti,ab
#52.	(or #8-#51)
#53.	#7 and #52
#54.	((clinicaltrials or trialsearch* or trial-registry or trials-registry or clinicalstudies or trialsregister* or trialregister* or trial-number* or studyregister* or study-register* or controlled-trials-com or current-controlled-trial or AMCTR or ANZCTR or ChiCTR* or CRiS or CTIS or CTRI* or DRKS* or EU-CTR* or EUCTR* or eudract* or ICTRP or IRCT* or JAPIC* or JMCTR* or JRCT or ISRCTN* or LBCTR* or NTR* or ReBec* or REPEC* or RPCEC* or SLCTR or TCTR* or UMIN*):so or (ctgov or ictrp)):an
#55.	#53 not #54
#56.	conference:pt
#57.	#55 not #56 with Cochrane Library publication date Between Oct 2023 and Mar 2024, in Cochrane Reviews, Cochrane Protocols, Trials

Epistemonikos search terms

1.	(title:((type AND ("2" OR "II" OR two) AND diabet*)) OR abstract:((type AND ("2" OR "II" OR two) AND diabet*))) OR (title:(((matur* OR adult* OR slow*) AND onset* AND diabet*)) OR abstract:(((matur* OR adult* OR slow*) AND onset* AND diabet*))) OR (title:((("ketosis resistant" OR "ketosis prone" OR stable) AND diabet*)) OR abstract:((("ketosis resistant" OR "ketosis prone" OR stable) AND diabet*))) OR (title:((("non insulin" OR noninsulin) AND depend* AND diabet*)) OR abstract:((("non insulin" OR noninsulin) AND depend* AND diabet*))) OR (title:((NIDDM OR T2DM OR DM2)) OR abstract:((NIDDM OR T2DM OR DM2)))
2.	(title:("glucagon like peptide 1") OR abstract:("glucagon like peptide 1")) OR (title:(("GLP 1" OR "GLP1")) OR abstract:(("GLP 1" OR "GLP1"))) OR (title:((Exenatide* OR Byetta OR Bydureon OR Saxenda)) OR abstract:((Exenatide* OR Byetta OR Bydureon OR Saxenda))) OR (title:((Liraglutide* OR Victoza)) OR abstract:((Liraglutide* OR Victoza))) OR (title:((Dulaglutide* OR Trulicity)) OR abstract:((Dulaglutide* OR Trulicity))) OR (title:((Semaglutide* OR Ozempic OR Rybelsus)) OR abstract:((Semaglutide* OR Ozempic OR Rybelsus))) OR (title:((Lixisenatide* OR Lyxumia)) OR abstract:((Lixisenatide* OR Lyxumia))) OR (title:((tirzepatide* OR mounjaro)) OR abstract:((tirzepatide* OR mounjaro))) OR (title:("Sodium-Glucose Transporter 2") OR abstract:("Sodium-Glucose Transporter 2")) OR (title:(("Sodium-Glucose cotransporter 2" OR "Sodium-Glucose co transporter 2")) OR abstract:(("Sodium-Glucose cotransporter 2" OR "Sodium-Glucose co transporter 2"))) OR (title:((SGLT* OR gliflozin*)) OR abstract:((SGLT* OR gliflozin*))) OR (title:((Canagliflozin* OR Invokana OR Dapagliflozin OR Forxiga OR Ertugliflozin OR Steglatro OR Empagliflozin OR Jardiance OR Glyxambi)) OR abstract:((Canagliflozin* OR Invokana OR Dapagliflozin OR Forxiga OR Ertugliflozin OR Steglatro OR Empagliflozin OR Jardiance OR Glyxambi))) OR (title:((Sulfonylurea* OR

	Sulphonylurea*)) OR abstract:((Sulfonylurea* OR Sulphonylurea*))) OR (title:((Gliclazide* OR Diamicron)) OR abstract:((Gliclazide* OR Diamicron))) OR (title:((Glimepiride* OR Amaryl)) OR abstract:((Glimepiride* OR Amaryl))) OR (title:((Glipizide* OR Minodiab)) OR abstract:((Glipizide* OR Minodiab))) OR (title:(Tolbutamide*) OR abstract:(Tolbutamide*)) OR (title:((Thiazolidinedione* OR Glitazone*)) OR abstract:((Thiazolidinedione* OR Glitazone*))) OR (title:((Pioglitazone* OR Actos)) OR abstract:((Pioglitazone* OR Actos))) OR (title:((Dipeptidyl*)) OR abstract:((Dipeptidyl*))) OR (title:((DPP* AND ("4" OR "iv"))) OR abstract:((DPP* AND ("4" OR "iv")))) OR (title:(gliptin*) OR abstract:(gliptin*)) OR (title:((Saxagliptin* OR Onglyza OR Komboglyze OR Qtern)) OR abstract:((Saxagliptin* OR Onglyza OR Komboglyze OR Qtern))) OR (title:((Vildagliptin* OR Galvus)) OR abstract:((Vildagliptin* OR Galvus))) OR (title:((Sitagliptin* OR Januvia)) OR abstract:((Sitagliptin* OR Januvia))) OR (title:((Alogliptin* OR Vipdomet)) OR abstract:((Alogliptin* OR Vipdomet))) OR (title:((Linagliptin* OR Trajenta OR Jentadueto)) OR abstract:((Linagliptin* OR Trajenta OR Jentadueto))) OR (title:((Metformin* OR Glucophage)) OR abstract:((Metformin* OR Glucophage))) OR (title:((Competact OR Janumet OR Eucreas OR Synjardy OR Vokanamet OR Xigduo)) OR abstract:((Competact OR Janumet OR Eucreas OR Synjardy OR Vokanamet OR Xigduo))) OR (title:(Biguanide*) OR abstract:(Biguanide*)))))
3.	1 AND 2

B.1.2 Health Economics literature search strategy

Health economic evidence was identified by conducting searches using terms for a broad type 2 diabetes population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics, and all years for quality-of-life studies.

Table 2: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1 January 2014 – 08 November 2022	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
	Quality of Life 1946 – 08 November 2022	
Embase (OVID)	Health Economics 1 January 2014 – 08 November 2022	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials,

Database	Dates searched	Search filters and limits applied
	Quality of Life 1974 – 08 November 2022	case studies/reports, conference abstracts) English language
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31st March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31st March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception - 08 November 2022	English language

Medline (Ovid) search terms

1.	exp Diabetes Mellitus, Type 2/
2.	(Type* adj4 ("2" or "II" or two*) adj4 (diabete* or diabetic*)).tw.
3.	((Maturit* or adult* or slow*) adj4 onset* adj4 (diabete* or diabetic*)).tw.
4.	((Ketosis-resistant* or stable*) adj4 (diabete* or diabetic*)).tw.
5.	((Non-insulin* or Non insulin* or Noninsulin*) adj4 depend* adj4 (diabete* or diabetic*)).tw.
6.	NIDDM.tw.
7.	or/1-6
8.	letter/
9.	editorial/
10.	news/
11.	exp historical article/
12.	Anecdotes as Topic/
13.	comment/
14.	case report/
15.	(letter or comment*).ti.
16.	or/8-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animals/ not humans/

20.	exp Animals, Laboratory/
21.	exp Animal Experimentation/
22.	exp Models, Animal/
23.	exp Rodentia/
24.	(rat or rats or mouse or mice or rodent*).ti.
25.	or/18-24
26.	7 not 25
27.	limit 26 to english language
28.	exp Glucagon-Like Peptide 1/
29.	(Glucagon* adj Like adj Peptide adj "1").tw.
30.	(GLP* adj "1").tw.
31.	GLP1*.tw.
32.	Exenatide/
33.	(Exenatide* or Byetta* or Bydureon* or Saxenda*).tw.
34.	(Liraglutide* or Victoza*).tw.
35.	(Dulaglutide* or Trulicity*).tw.
36.	(Semaglutide* or Ozempic* or Rybelsus*).tw.
37.	(Lixisenatide* or Lyxumia*).tw.
38.	(tirzepatide* or Mounjaro).tw.
39.	Sodium-Glucose Transporter 2/
40.	(Sodium* adj4 Glucose* adj4 Transporter* adj4 "2").tw.
41.	(Sodium* adj4 Glucose* adj4 (co-transporter* or cotransporter* or co transporter*) adj4 "2").tw.
42.	(SGLT* or gliflozin*).tw.
43.	Canagliflozin/
44.	(Canagliflozin* or Invokana* or Dapagliflozin* or Forxiga* or Ertugliflozin* or Steglatro* or Empagliflozin* or Jardiance* or Glyxambi*).tw.
45.	exp Sulfonylurea Compounds/tu [Therapeutic Use]
46.	(Sulfonylurea* or Sulphonylurea*).tw.
47.	(Gliclazide* or Diamicron*).tw.
48.	(Glimepiride* or Amaryl*).tw.
49.	(Glipizide* or Minodiab*).tw.
50.	Tolbutamide*.tw.
51.	Thiazolidinediones/
52.	(Thiazolidinedione* or Glitazone*).tw.
53.	Pioglitazone/
54.	(Pioglitazone* or Actos*).tw.
55.	exp Dipeptidyl-Peptidase IV Inhibitors/ or Dipeptidyl Peptidase 4/
56.	(Dipeptidyl* adj2 Peptidase* adj2 ("4" or "iv") adj Inhibitor*).tw.
57.	(DPP* adj2 ("4" or "iv")).tw.

58.	gliptin*.tw.
59.	(Saxagliptin* or Onglyza* or Komboglyze* or Qtern*).tw.
60.	(Vildagliptin* or Galvus*).tw.
61.	(Sitagliptin* or Januvia*).tw.
62.	(Alogliptin* or Vipdomet*).tw.
63.	(Linagliptin* or Trajenta* or Jentadueto*).tw.
64.	Metformin/
65.	(Metformin* or Glucophage*).tw.
66.	(Competact* or Janumet* or Eucreas* or Synjardy* or Vokanamet* or Xigduo*).tw.
67.	Biguanides/
68.	Biguanide*.tw.
69.	exp Glycoside Hydrolase Inhibitors/
70.	glycosid*.tw.
71.	(glycosyl adj4 hydrolases).tw.
72.	(((intestinal adj4 alpha adj4 amylase adj4 inhibitor*) or intestinal) adj4 alpha-amylase adj4 inhibitor*).tw.
73.	((pancreatic adj4 alpha adj4 amylase adj4 inhibitor*) or (pancreatic adj4 alpha-amylase adj4 inhibitor*)).tw.
74.	Acarbose/
75.	(Acarbose* or Glucobay*).tw.
76.	exp Insulins/ad, tu [Administration & Dosage, Therapeutic Use]
77.	exp Insulin/ad, tu [Administration & Dosage, Therapeutic Use]
78.	Insulin Infusion Systems/
79.	(Insulin* adj4 (treat* or therap* or administrat* or dos* or human* or analogue* or biphasic* or basal* or protamine* or isophane* or inject* or pen* or deliver* or device* or system* or pump* or syringe* or needle* or infusion*)).tw.
80.	(Insulin* adj4 (Intermediate* or shortact* or short-act* or short act* or longact* or long-act* or long act* or ultralong* or ultra-long* or ultra long* or rapidact* or rapid-act* or rapid act*)).tw.
81.	(Actrapid* or Humulin* or Hypurin*).tw.
82.	Aspart*.tw.
83.	(Glulisine* or Apidra*).tw.
84.	(Lispro* or Humalog*).tw.
85.	(Insulin* adj4 zinc* adj4 (suspension* or protamine*)).tw.
86.	(Detemir* or Levemir*).tw.
87.	(Glargine* or Lantus* or Toujeo*).tw.
88.	(Degludec* or Tresiba*).tw.
89.	(Isophane* or Insulatard* or Insuman* or Novomix*).tw.
90.	(Fiasp* or Lyumjev* or Suliqua* or Xultophy* or NovoRapid*).tw.
91.	(LY2963016 or Abasaglar* or MYK-1501D or MYK1501D or Semglee*).tw.
92.	Biosimilar pharmaceuticals/
93.	(biosimilar* or biologics).tw.

94.	Nateglinide/
95.	(Meglitinide* or Repaglinide* or Nateglinide*).tw.
96.	or/28-94
97.	Economics/
98.	Value of life/
99.	exp "Costs and Cost Analysis"/
100.	exp Economics, Hospital/
101.	exp Economics, Medical/
102.	Economics, Nursing/
103.	Economics, Pharmaceutical/
104.	exp "Fees and Charges"/
105.	exp Budgets/
106.	budget*.ti,ab.
107.	cost*.ti.
108.	(economic* or pharmaco?economic*).ti.
109.	(price* or pricing*).ti,ab.
110.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
111.	(financ* or fee or fees).ti,ab.
112.	(value adj2 (money or monetary)).ti,ab.
113.	or/97-112
114.	quality-adjusted life years/
115.	sickness impact profile/
116.	(quality adj2 (wellbeing or well being)).ti,ab.
117.	sickness impact profile.ti,ab.
118.	disability adjusted life.ti,ab.
119.	(qal* or qtime* or qwb* or daly*).ti,ab.
120.	(euroqol* or eq5d* or eq 5*).ti,ab.
121.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
122.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
123.	(hui or hui1 or hui2 or hui3).ti,ab.
124.	(health* year* equivalent* or hye or hyes).ti,ab.
125.	discrete choice*.ti,ab.
126.	rosser.ti,ab.
127.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
128.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
129.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
130.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
131.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.

132.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
133.	or/114-132
134.	27 and 96
135.	113 and 134
136.	133 and 134

Embase (Ovid) search terms

1.	exp Diabetes Mellitus, Type 2/
2.	(Type* adj4 ("2" or "II" or two*) adj4 (diabete* or diabetic*)).tw.
3.	((Maturit* or adult* or slow*) adj4 onset* adj4 (diabete* or diabetic*)).tw.
4.	((Ketosis-resistant* or stable*) adj4 (diabete* or diabetic*)).tw.
5.	((Non-insulin* or Non insulin* or Noninsulin*) adj4 depend* adj4 (diabete* or diabetic*)).tw.
6.	NIDDM.tw.
7.	or/1-6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	case report/ or case study/
12.	(letter or comment*).ti.
13.	(conference abstract or conference paper).pt.
14.	or/8-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animal/ not human/
18.	nonhuman/
19.	exp Animal Experiment/
20.	exp Experimental Animal/
21.	animal model/
22.	exp Rodent/
23.	(rat or rats or mouse or mice or rodent*).ti.
24.	or/16-23
25.	7 not 24
26.	limit 25 to english language
27.	*Glucagon Like Peptide 1/
28.	(Glucagon* adj Like adj Peptide adj "1").tw.
29.	(GLP* adj "1").tw.
30.	GLP1*.tw.
31.	*Exenatide/
32.	*Exendin 4/

33.	(Exenatide* or Byetta* or Bydureon* or Saxenda*).tw.
34.	*Liraglutide/
35.	(Liraglutide* or Victoza*).tw.
36.	*Dulaglutide/
37.	(Dulaglutide* or Trulicity*).tw.
38.	*Semaglutide/
39.	(Semaglutide* or Ozempic* or Rybelsus*).tw.
40.	*Lixisenatide/
41.	(Lixisenatide* or Lyxumia*).tw.
42.	(tirzepatide* or Mounjaro).tw.
43.	*Sodium-Glucose Cotransporter 2/
44.	(Sodium* adj4 Glucose* adj4 Transporter* adj4 "2").tw.
45.	(Sodium* adj4 Glucose* adj4 (co-transporter* or cotransporter* or co transporter*) adj4 "2").tw.
46.	(SGLT* or gliflozin*).tw.
47.	*Canagliflozin/ or *Dapagliflozin/ or *dapagliflozin plus saxagliptin/ or *dapagliflozin plus metformin plus saxagliptin/ or *Empagliflozin/ or *Empagliflozin plus Metformin/
48.	(Canagliflozin* or Invokana* or Dapagliflozin* or Forxiga* or Ertugliflozin* or Steglatro* or Empagliflozin* or Jardiance* or Glyxambi*).tw.
49.	exp *Sulfonylurea Derivative/dt [Drug Therapy]
50.	(Sulfonylurea* or Sulphonylurea*).tw.
51.	(Gliclazide* or Diamicron*).tw.
52.	(Glimepiride* or Amaryl*).tw.
53.	(Glipizide* or Minodiab*).tw.
54.	Tolbutamide*.tw.
55.	*2,4 Thiazolidinedione Derivative/ or *Glitazone Derivative/
56.	(Thiazolidinedione* or Glitazone*).tw.
57.	*Pioglitazone/ or *pioglitazone plus sitagliptin/
58.	(Pioglitazone* or Actos*).tw.
59.	*Dipeptidyl Peptidase IV Inhibitor/
60.	(Dipeptidyl* adj2 Peptidase* adj2 ("4" or "iv") adj Inhibitor*).tw.
61.	(DPP* adj2 ("4" or "iv")).tw.
62.	gliptin*.tw.
63.	*Saxagliptin/
64.	(Saxagliptin* or Onglyza* or Komboglyze* or Qtern*).tw.
65.	*Vildagliptin/ or *Metformin plus Vildagliptin/
66.	(Vildagliptin* or Galvus*).tw.
67.	*Sitagliptin/ or *metformin plus sitagliptin/ or *simvastatin plus sitagliptin/ or *pioglitazone plus sitagliptin/ or *ertugliflozin plus sitagliptin/
68.	(Sitagliptin* or Januvia*).tw.
69.	*Alogliptin/ or *alogliptin plus metformin/ or *alogliptin plus pioglitazone/

70.	(Alogliptin* or Vipdomet*).tw.
71.	*Linagliptin/ or *empagliflozin plus linagliptin/ or *linagliptin plus metformin/
72.	(Linagliptin* or Trajenta* or Jentadueto*).tw.
73.	*Metformin/ or *metformin plus sitagliptin/ or *metformin plus repaglinide/ or *metformin plus vildagliptin/ or *metformin plus pioglitazone/ or *metformin plus rosiglitazone/ or *metformin 4 chlorophenoxyacetate/ or *metformin plus saxagliptin/ or *metformin embonate/ or *metformin glycinate/
74.	(Metformin* or Glucophage*).tw.
75.	(Competact* or Janumet* or Eucreas* or Synjardy* or Vokanamet* or Xigduo*).tw.
76.	*Biguanide Derivative/
77.	Biguanide*.tw.
78.	exp *glycosidase inhibitor/
79.	glycosid*.tw.
80.	(glycosyl adj4 hydrolases).tw.
81.	((intestinal adj4 alpha adj4 amylase adj4 inhibitor*) or (intestinal adj4 alpha-amylase adj4 inhibitor*)).tw.
82.	((pancreatic adj4 alpha adj4 amylase adj4 inhibitor*) or (pancreatic adj4 alpha-amylase adj4 inhibitor*)).tw.
83.	*Acarbose/
84.	(Acarbose* or Glucobay*).tw.
85.	exp *insulin/ad, do [Drug Administration, Drug Dose]
86.	exp *Insulin Derivative/ad, do [Drug Administration, Drug Dose]
87.	*Insulin Infusion/
88.	insulin aspart plus insulin degludec/ or insulin degludec plus liraglutide/ or insulin aspart/ or insulin glulisine/ or insulin lispro/ or insulin detemir/ or insulin glargine plus lixisenatide/ or insulin glargine/ or insulin glargine plus lixisenatide/ or insulin glargine/
89.	(Insulin* adj4 (treat* or therap* or administrat* or dos* or human* or analogue* or biphasic* or basal* or protamine* or isophane* or inject* or pen* or deliver* or device* or system* or pump* or syringe* or needle* or infusion*)).tw.
90.	(Insulin* adj4 (Intermediate* or shortact* or short-act* or short act* or longact* or long-act* or long act* or ultralong* or ultra-long* or ultra long* or rapidact* or rapid-act* or rapid act*)).tw.
91.	(Actrapid* or Humulin* or Hypurin*).tw.
92.	Aspart*.tw.
93.	(Glulisine* or Apidra*).tw.
94.	(Lispro* or Humalog*).tw.
95.	(Insulin* adj4 zinc* adj4 (suspension* or protamine*)).tw.
96.	(Detemir* or Levemir*).tw.
97.	(Glargine* or Lantus* or Toujeo*).tw.
98.	(Degludec* or Tresiba*).tw.
99.	(Isophane* or Insulatard* or Insuman* or Novomix*).tw.
100.	(Fiasp* or Lyumjev* or Suliqua* or Xultophy* or NovoRapid*).tw.
101.	(LY2963016 or Abasaglar* or MYK-1501D or MYK1501D or Semglee*).tw.
102.	*Biosimilar Agent/

103.	(biosimilar* or biologics).tw.
104.	*Meglitinide/ or *Repaglinide/ or *Nateglinide/
105.	(Meglitinide* or Repaglinide* or Nateglinide*).tw.
106.	or/27-105
107.	26 and 106
108.	health economics/
109.	exp economic evaluation/
110.	exp health care cost/
111.	exp fee/
112.	budget/
113.	funding/
114.	budget*.ti,ab.
115.	cost*.ti.
116.	(economic* or pharmaco?economic*).ti.
117.	(price* or pricing*).ti,ab.
118.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
119.	(financ* or fee or fees).ti,ab.
120.	(value adj2 (money or monetary)).ti,ab.
121.	or/108-120
122.	quality adjusted life year/
123.	"quality of life index"/
124.	short form 12/ or short form 20/ or short form 36/ or short form 8/
125.	sickness impact profile/
126.	(quality adj2 (wellbeing or well being)).ti,ab.
127.	sickness impact profile.ti,ab.
128.	disability adjusted life.ti,ab.
129.	(qal* or qtime* or qwb* or daly*).ti,ab.
130.	(euroqol* or eq5d* or eq 5*).ti,ab.
131.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
132.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
133.	(hui or hui1 or hui2 or hui3).ti,ab.
134.	(health* year* equivalent* or hye or hyes).ti,ab.
135.	discrete choice*.ti,ab.
136.	rosser.ti,ab.
137.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
138.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
139.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
140.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.

141.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
142.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
143.	or/122-142
144.	107 and 121
145.	107 and 143

NHS EED and HTA (CRD) search terms

#1.	(MeSH DESCRIPTOR Diabetes Mellitus, Type 2 EXPLODE ALL TREES)
#2.	((Type*) NEAR4 ("2" or "II" or two*) NEAR4 (diabete* or diabetic*))
#3.	((Maturit* or adult* or slow*) NEAR4 (onset*) NEAR4 (diabete* or diabetic*))
#4.	((Ketosis-resistant* or stable*) NEAR4 (diabete* or diabetic*))
#5.	((Non-insulin* or Non insulin* or Noninsulin*) NEAR4 (depend*) NEAR4 (diabete* or diabetic*))
#6.	((NIDDM))
#7.	(#1 OR #2 OR #3 OR #4 OR #5 OR #6)

INAHTA search terms

1.	((Type* AND ("2" or "II" or two*) AND (diabete* or diabetic*))) OR (Diabetes Mellitus, Type 2)[mh] OR (((Maturit* or adult* or slow*) AND onset* AND (diabete* or diabetic*))) OR (((Ketosis-resistant* or stable*) AND (diabete* or diabetic*))) OR (((Non-insulin* or Non insulin* or Noninsulin*) AND depend* AND (diabete* or diabetic*))) OR (NIDDM)
2.	limit English language 2015-2022

Appendix C Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review