National Institute for Health and Care Excellence

Final

# Type 2 diabetes in adults: management (Medicines update)

## Clinical protocol for subsequent pharmacological therapy for the management of type 2 diabetes

*Protocol*

*Final version for NICE website*

*May 2023*

*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, where appropriate, their carer or guardian.

Local commissioners and 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 All NICE guidance is subject to regular review and may be updated or withdrawn.

# Contents

# Appendices

# Appendix A: Review protocol

## Review protocol for *the subsequent pharmacological management of type 2 diabetes*

| ID | Field | Content |
|---|---|---|
| 0. | PROSPERO registration number | N/A |
| 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:<br>• medicines within the following classes biguanides, DPP-4 inhibitors, GLP-1 receptor agonist, insulin, sulfonylureas, SGLT2 inhibitors, and thiazolidinediones (but not limited to these),<br>• approaches to optimise treatment (including combination treatment, switching to different therapies, de-escalation and stopping previous therapies), and<br>• 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: |

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| | | • Cochrane Central Register of Controlled Trials (CENTRAL)<br>• Cochrane Database of Systematic Reviews (CDSR)<br>• Embase<br>• MEDLINE<br>• Epistemonikos<br><br>Searches will be restricted by:<br>• Study design RCT and SR filters will be applied<br>• No date limit will be set<br>• English language studies<br>• Human studies<br>• Conference abstracts will be excluded from the search results<br><br>Other searches:<br>• Inclusion lists of systematic reviews<br><br>The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant.<br><br>The full search strategies will be published in the final review.<br>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:<br>• Adults (age ≥18 years) with type 2 diabetes mellitus<br><br>The population will be stratified into different groups, these include:<br>• People with type 2 diabetes mellitus and heart failure<br>  ○ People with type 2 diabetes mellitus and heart failure |

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| | | ○ People with type 2 diabetes mellitus and no heart failure<br>○ Mixed population<br>○ Not stated/unclear<br>• People with type 2 diabetes mellitus and atherosclerotic cardiovascular disease<br>○ People with type 2 diabetes mellitus and atherosclerotic cardiovascular disease<br>○ People with type 2 diabetes mellitus and no atherosclerotic cardiovascular disease<br>○ Mixed population<br>○ Not stated/unclear<br>• People with type 2 diabetes mellitus and chronic kidney disease<br>○ People with type 2 diabetes mellitus and chronic kidney disease<br>○ People with type 2 diabetes mellitus and no chronic kidney disease<br>○ Mixed population<br>○ Not stated/unclear<br>• People with type 2 diabetes mellitus and high cardiovascular risk<br>○ People with type 2 diabetes mellitus and high cardiovascular risk<br>○ People with type 2 diabetes mellitus and not at high cardiovascular risk<br>○ Mixed population<br>○ Not stated/unclear<br><br>Exclusion:<br>• Children and young people (age <18 years) with type 2 diabetes mellitus<br>• Pregnant people with type 2 diabetes mellitus<br>• People with type 1 diabetes mellitus<br>• 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):<br>• Adding a new treatment (combining multiple therapies)<br>• Stopping a previous treatment<br>• 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)<br><br>Pharmacological therapies for people with type 2 diabetes. |

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| | | • All therapies will be examined on an individual drug level (rather than a class level).<br>All doses will be pooled together.<br>• Biguanides<br>○ Metformin hydrochloride standard release<br>○ Metformin hydrochloride slow release<br>• DPP-4 inhibitors<br>○ Alogliptin (Vipidia)<br>○ Linagliptin (Trajenta)<br>○ Saxagliptin (Onglyza)<br>○ Sitagliptin (Januvia)<br>○ Vildagliptin (Galvus)<br>• GLP-1 receptor agonist<br>○ Dulaglutide (Trulicity)<br>○ Exenatide (Byetta)<br>○ Liraglutide (Victoza)<br>○ Lixisenatide (Lyxumia)<br>○ Semaglutide (Rybelsus, Ozempic)<br>• Dual GIP/GLP-1 receptor co-agonists<br>○ Tirzepatide (Mounjaro)<br>• SGLT2 inhibitors<br>○ Canagliflozin (Invokana)<br>○ Dapagliflozin (Forxiga)<br>○ Empagliflozin (Jardiance)<br>○ Ertugliflozin (Steglatro)<br>• Sulfonylureas<br>○ Gliclazide<br>○ Glimepiride<br>○ Glipizide<br>○ Tolbutamide<br>• Thiazolidinediones<br>○ Pioglitazone<br>• Combinations of therapies listed above (combinations may include medicines being given separately or combination products) |
| 8. | Comparator | • Different strategies to optimise treatment<br>• Different combinations of pharmacological therapies listed in the intervention section to each other<br>• Different combination with an oral formulation of the same medication compared to a different combination with an injectable formulation of the same medication<br>• Different combinations of pharmacological therapies listed in the intervention section and |

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| | | insulin (all types and doses of insulin pooled together in the same drug class)<br>• 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<br>Randomised-controlled trials (RCTs)<br>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.<br>• 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.<br>• Studies including a mixed population of people with and without diabetes will be excluded.<br>• Comparisons with unlicensed modes of delivery (for example, inhaled insulin).<br>• 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).<br>• 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%).<br>• Trials that have a treatment and follow up period of less than 24 weeks.<br>• Systematic reviews that did not include at least one RCT of at least 24 weeks duration.<br>• 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.<br>• Trials of treatments which are not available, or no longer available, in the UK including: |

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| | | ○ Glibenclamide<br>○ Chlorpropamide<br>○ Nateglinide<br>○ Miglitol<br>○ Omarigliptin<br>○ Albiglutide<br>○ Rosiglitazone<br>• Trials of treatments that are rarely used in the UK, including:<br>○ Repaglinide<br>○ Acarbose<br>• Trials of combinations of drugs which include one or more drug that is not available in the UK, no longer available in the UK.<br>• Trials of a combined formulation of drugs which is not available in the UK.<br>• 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.<br>Where outcomes are reported as time-to-event and dichotomous values, both time-to-event and dichotomous values will be extracted.<br><br>**Outcomes to be extracted for use in this review**<br>All outcomes are considered equally important for decision making and therefore have all been rated as critical:<br>• Health-related quality of life (continuous outcomes):<br>○ EQ-5D<br>○ SF-6D<br>○ SF-36<br>○ SF-12 |

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| | | ○ Other utility measures (AQOL, HUI, 15D, QWB)<br>○ HASMID-10<br>○ Diabetes Quality of life<br>○ Diabetes Quality of life questionnaire<br>○ Diabetes Quality of life Clinical Trial Questionnaire<br>○ Audit of Diabetes Dependent Quality of Life<br>○ Diabetes-39<br>○ Diabetes Health Profile<br>○ DAWN2 Impact of Diabetes Profile<br>○ Diabetes Impact Measurement Scales<br>○ QoLHYPO<br>○ Well-being questionnaire<br>○ Well-being Enquiry for Diabetics<br>○ Questionnaire on Stress in patients with Diabetes-Revised (QSD-R)<br>• All-cause mortality (time-to-event/dichotomous outcome)<br>• Cardiovascular mortality (time-to-event/dichotomous outcome)<br>• 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)<br>○ 3-item MACE<br>○ 4-item MACE<br>○ 5-item MACE<br>• Events making up MACE (time-to-event/dichotomous outcomes):<br>○ Non-fatal stroke<br>○ Non-fatal myocardial infarction<br>○ Unstable angina<br>○ Hospitalisation for heart failure<br>• Renal events (time-to-event/dichotomous outcome):<br>○ Acute kidney injury<br>○ Persistent signs of worsening kidney disease (including doubling of serum creatinine) |

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| | | ○ Development of end stage kidney disease (including need for renal replacement therapy and transplant)<br>○ Death from renal cause<br>• Serious adverse events (time-to-event/dichotomous outcome):<br>○ Cardiac arrhythmia (including atrial fibrillation)<br>○ Diabetic ketoacidosis<br>○ Falls requiring hospitalisation<br>• Progression of liver disease (to non-alcoholic fatty liver disease, to fibrosis, to cirrhosis, to end stage liver disease) (time-to-event/dichotomous outcome)<br>• Remission (time-to-event/dichotomous outcome)<br>• Acute diabetic complications (time-to-event/dichotomous outcome):<br>○ Hypoglycaemia episodes<br>○ At night hypoglycaemic episodes<br>○ Severe hypoglycaemic episodes<br>• Continuous outcomes:<br>○ HbA1c change (absolute change scores prioritised over percentage change scores, % units prioritised over mmol/dL units)<br>○ Weight change<br>○ BMI change |
| 13. | Data extraction (selection and coding) | EndNote will be used for reference management, citations and bibliographies.<br>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.<br>10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.<br>The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above.<br>A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4).<br>10% of all evidence reviews are quality assured by a senior research fellow or equivalent. This includes checking: |

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| | | • papers were included /excluded appropriately<br>• a sample of the data extractions<br>• correct methods are used to synthesise data<br>• a sample of the risk of bias assessments<br>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.<br>• Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS)<br>• 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).<br>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.<br>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. |

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| | | 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/<br><br>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.<br><br>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:<br><br>• People with frailty<br>  ○ People with frailty<br>  ○ People without frailty<br>  ○ Mixed<br>  ○ Not stated/unclear<br><br>• Onset of type 2 diabetes mellitus<br>  ○ Early onset type 2 diabetes mellitus first diagnosed at age below 40 years of age<br>  ○ People with type 2 diabetes mellitus first diagnosed at age above 40 years of age<br>  ○ Mixed population<br>  ○ Not stated/unclear<br>• People with non-alcoholic fatty liver disease<br>  ○ People with non-alcoholic fatty liver disease<br>  ○ People without non-alcoholic fatty liver disease<br>  ○ Mixed population<br>  ○ Not stated/unclear<br>• People with obesity<br>  ○ 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)<br>  ○ 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)<br>  ○ Mixed population<br>  ○ Not stated/unclear<br>• eGFR category at baseline<br>  ○ eGFR ≥30mL/min/1.73m$^2$<br>  ○ eGFR 15-29mL/min/1.73m$^2$<br>  ○ eGFR <15mL/min/1.73m$^2$ |

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○ Mixed population<br>
○ Not stated/unclear<br>
• Albuminuria category at baseline<br>
○ A1 (ACR <30mg/g or <3mg/mmol)<br>
○ A2 (ACR 30-300 mg/g or 3-30mg/mmol)<br>
○ A3 (ACR >300mg/g or >30mgmmol)<br>
○ Mixed population<br>
○ Not stated/unclear
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<tr><td>☐</td><td colspan="2">Diagnostic</td></tr>
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<tr><td>20.</td><td>Anticipated or actual start date</td><td colspan="3">10/01/2023</td></tr>
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<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>
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<tr><td>23.</td><td>Named contact</td><td colspan="3">5a. Named contact<br>Guideline Development Team NGC<br><br>5b Named contact e-mail<br>t2diabetesadults@nice.org.uk<br><br>5e Organisational affiliation of the review</td></tr>
</table>

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| | | National Institute for Health and Care Excellence (NICE) |
| 24. | Review team members | From NICE:<br>Serena Carville (Guideline lead)<br>George Wood (Medicines analyst)<br>Emily Terrazas-Cruz (Senior research fellow)<br>Tayyaba Mumtaz (Trainee technical analyst)<br>Nancy Pursey (Trainee technical analyst)<br>David Wonderling (Head of health economics)<br>Muksitur Rahman (Health economics analyst)<br>Joseph Runicles (Information specialist)<br>Sarah Glover (Information specialist)<br>Amy Crisp (Senior project manager) |
| 25. | Funding sources/sponsor | Development of this systematic review is being funded by NICE. |
| 26. | Conflicts of interest | 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 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: |

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| | | • notifying registered stakeholders of publication<br>• publicising the guideline through NICE's newsletter and alerts<br>• 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 | |