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Action on Smoking and Health (ASH) Scotland	General	General	Please consult WHO Europe for info on nicotine and diabetes, which applies to tobacco and other nicotine products.	Thank you for this information.
Association of British Clinical Diabetologists (ABCD)	General	General	The document covers all major classes of non-insulin glucose lowering drugs relevant to the treatment of type 2 diabetes	Thank you for your comment
Association of British Clinical Diabetologists (ABCD)	General	General	The outcomes chosen are those that are most important to patients and also clinically important outcomes	Thank you for your comment
Association of British Clinical Diabetologists (ABCD)	007	026	When assessing cost effectiveness the committee should consider the requirement for glucose testing equipment (meters, test strips and lancets or intermittently scanned or real time continuous glucose monitoring devices) for drivers to meet DVLA requirements for fitness to drive	Thank you for your comment. The total resource use and costs associated with drugs will be considered when assessing cost effectiveness. This includes costs associated with glucose-testing and monitoring.
Association of British Clinical Diabetologists (ABCD)	008	017	Unplanned hospital admission should be considered as an outcome, this is particularly relevant for particular patient groups including those residing in care homes	Thank you for your comment. The outcome list in the scope is not exhaustive and the committee will discuss whether additional outcomes need to be added when writing the protocols for the review questions.
AstraZeneca	General	General	**References** 1. AstraZeneca Data on File. Clinical Study Report: A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney Disease (DAPA-CKD). 2020. 2. Wheeler DC, Stefánsson BV, Jongs N, et al. Effects of dapagliflozin on major adverse kidney and cardiovascular events in patients with diabetic and non-diabetic chronic kidney disease: a prespecified analysis from the DAPA-CKD	Thank you for this information.

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			trial. The Lancet Diabetes & Endocrinology. 2021;9(1):22-31. doi:10.1016/S2213-8587(20)30369-7 3. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. New England Journal of Medicine. 2019;380(24):2295-2306. doi:10.1056/NEJMoa1811744 4. AstraZeneca Data on File. REF-109687. Clinical Practice Research Datalink (CPRD) analyses conducted February 2021. Analysis of patients with CKD in the 12 months prior to May 2020. 2021. 5. QOF database. Data for Chronic kidney disease. Available at: https://www.gpcontract.co.uk/child/UK/CKD001/20 [Accessed: 28 October]. 6. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. New England Journal of Medicine. 2019;381(21):1995-2008. doi:10.1056/NEJMoa1911303 7. Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. Oct 8 2020;383(15):1413-1424. doi:10.1056/NEJMoa2022190 8. National Health Service (NHS). Quality and Outcomes Framework 2020-21: prevalence at regional and national level. Available at: https://digital.nhs.uk/data-and-information/publications/statistical/quality-and-outcomes-framework-achievement-prevalence-and-exceptions-data/2020-21 [accessed 28 October 2022]. 2021.	

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			9. Savarese G, Becher PM, Lund LH, et al. Global burden of heart failure: A comprehensive and updated review of epidemiology. Cardiovasc Res. 2022. 10. National Institute for Cardiovascular Outcomes Research (NICOR). About Heart Failure. Available at: https://www.nicor.org.uk/national-cardiac-audit-programme/about-heart-failure/#:~:text=Heart%20failure%20is%20a%20large,all%20emergency%20admissions%20to%20hospital [accessed 28 October 2022]. 11. Agha M, Agha R. The rising prevalence of obesity: part A: impact on public health. Int J Surg Oncol (N Y). 2017;2(7):e17. 12. Shah SJ, Borlaug BA, Kitzman DW, et al. Research Priorities for Heart Failure With Preserved Ejection Fraction: National Heart, Lung, and Blood Institute Working Group Summary. Circulation. 2020;141(12):1001-1026. 13. National Health Service (NHS). The NHS Long Term Plan. Available from: https://www.longtermplan.nhs.uk/publication/nhs-long-term-plan [accessed 28 October 2022]. 2019. 14. Olchanski N, Vest AR, Cohen JT, et al. Two-year outcomes and cost for heart failure patients following discharge from the hospital after an acute heart failure admission. Int J Cardiol. 2020;307:109-113. 15. Lam CSP, Wood R, Vaduganathan M, et al. Contemporary economic burden in a real-world heart failure	

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			population with Commercial and Medicare supplemental plans. Clin Cardiol. 2021;44(5):646-655. 16. Nguyen C, Zhang X, Evers T, et al. Real-World Treatment Patterns, Healthcare Resource Utilization, and Costs for Patients with Newly Diagnosed Systolic versus Diastolic Heart Failure. Am Health Drug Benefits. 2020;13(4):166-174. 17. Divino V, Ramasamy A, Anupindi VR, et al. Complication-specific direct medical costs by body mass index for 13 obesity-related complications: a retrospective database study. J Manag Care Spec Pharm. 2021;27(2):210-222. 18. Alghamdi A, Algarni E, Balkhi B, et al. Healthcare Expenditures Associated with Heart Failure in Saudi Arabia: A Cost of Illness Study. Healthcare (Basel). 2021;9(8).	
AstraZeneca	002	022 – 027	The draft scope currently does not put appropriate emphasis on the comorbid type 2 diabetes mellitus (T2DM) patients with chronic kidney disease (CKD) and heart failure. The recommendations across the whole treatment pathway need to reflect the differences in the strength of evidence, and consequently in licenced populations, of the Sodium-glucose-co-transporter-2 (SGLT2) inhibitors in specific patient subgroups such as those with high risk of cardiovascular disease (CVD), those with established heart failure (HF), and CKD	Thank you for your comment. People with heart failure and people with chronic kidney disease are listed as people who will be given specific consideration within the guideline in section 2.1 of the scope. The committee will consider all relevant populations when forming the protocol for this review and will consider these when making recommendations.
AstraZeneca	005	003 – 005	Ticagrelor for preventing cardiovascular events in people with type 2 diabetes and 3 coronary artery disease [ID1514]	Thank you this has been amended.

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			has been suspended since 2021 and therefore should be excluded from the list of related NICE guidance	
AstraZeneca	005	011 – 012	Canagliflozin for treating chronic kidney disease in people with type 2 diabetes 11 [ID1653] has been suspended since 2020 and therefore should be excluded from the list of related NICE guidance	Thank you this has been amended
AstraZeneca	005	018 – 019	Empagliflozin for reducing the risk of cardiovascular events in type 18 2 diabetes [ID1037] has been suspended since 2018 and therefore should be excluded from the list of related NICE guidance	Thank you this has been amended
AstraZeneca	006	012	The following technologies have been left off the NICE guidance that will be integrated into this guidance: • Dapagliflozin for treating chronic kidney disease [TA775], published 09 March 2022 AstraZeneca feel that the inclusion of patients with T2DM and CKD within the NG28 treatment algorithm is critical to ensuring optimal care for this sizable patient population, in which SGLT2 inhibitors have demonstrated clinical and cost effectiveness. The renal efficacy of SGLT2 inhibitors in patients with T2DM and CKD has been demonstrated in two dedicated renal outcomes trials: DAPA-CKD and CREDENCE. DAPA-CKD enrolled 2,906 (67.6%) patients with T2DM and CKD, and demonstrated that dapagliflozin significantly reduced the risk of the primary composite endpoint of sustained decline in estimated glomerular filtration rate (eGFR) ≥50%, end-stage kidney disease	Thank you for your comment. The list of related NICE guidance only includes those most closely related to the guideline topic, and therefore primarily relates to those for type 2 diabetes only. The guideline update will include people with type 2 diabetes and CKD, as listed in the groups that will be given specific consideration, and recommendations will be made accordingly on consideration of the evidence.

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			(ESKD) or death from renal or cardiovascular (CV) causes compared with placebo in this patient subgroup (10.4% versus 15.8%, respectively, hazard ratio [HR] 0.64; 95% confidence interval [CI]: 0.52, 0.79; [redacted]).[1,2] In CREDENCE, which enrolled 4,401 (100%) patients with T2DM and CKD, the relative risk of the primary composite outcome of ESKD, doubling of the serum creatinine level, or death from renal or CV causes was 30% lower in the canagliflozin group compared with the placebo group, with event rates of 43.2 and 61.2 per 1000 patient-years, respectively (HR: 0.70; 95%CI: 0.59, 0.82; p=0.00001).[3] AstraZeneca believes there to be approximately [redacted] patients with CKD and T2DM in England who would benefit substantially from treatment with an SGLT2 inhibitor.[4,5] Both treatment algorithms included in the current recommendations state that renal function should be assessed when choosing medicines for patients with T2DM, and highlights that options and doses of SGLT2 inhibitors may change if estimated glomerular filtration rate is <60 ml/min/1.73m^2 (i.e. in patients with CKD). As such, inclusion of this important patient population in which SGLT2 inhibitors have proven clinical benefit within the written recommendations and visual summaries of the guideline will help to simplify HCP decision making. This would also align these recommendations with the 2022 American Diabetes Association guidelines for the treatment of patients with T2DM, which are widely considered to represent the gold	

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			standard approach to risk stratification of the T2DM population and provide separate recommendations for diabetes patients with heart failure, atherosclerotic cardiovascular disease and CKD • Dapagliflozin for treating chronic heart failure with reduced ejection fraction (HFrEF) [TA679], published 24 February 2021 • Empagliflozin for treating chronic heart failure with (HFrEF) [TA773], published 09 March 2022 Importantly, only two of the currently available SGTL2 inhibitors (dapagliflozin and empagliflozin) have sufficient evidence of efficacy and safety in patients with HFrEF to support a marketing authorisation and reimbursement in this population in England. There is strong evidence for the treatment effect of dapagliflozin in HFrEF from the DAPA-HF trial. DAPA-HF was the first study of an SGLT2 inhibitor in patients with HFrEF, with or without T2DM. It was an event-driven, double-blind RCT with a median follow-up of 18.2 months which enrolled 4,744 patients and compared dapagliflozin (n=2,373) with placebo (n=2,371) for treatment of HFrEF, with patients also receiving current standard care for HFrEF in both arms. Overall, 42% of enrolled patients had T2DM. The results from DAPA-HF are summarised below:	

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			• Dapagliflozin significantly reduced the risk of the primary composite endpoint of CV death, hospitalisation for heart failure (hHF), or an urgent heart failure visit, compared with placebo (16.3% vs 21.2%, respectively, HR 0.74 [95% CI 0.65, 0.85; p<0.001]).[6]
			• Dapagliflozin also reduced the risk of each component of the composite endpoint, compared with placebo:
			  ○ hHF – HR 0.70 (95% CI 0.59, 0.83; p<0.001)
			  ○ Urgent heart failure visit – HR 0.43 (95% CI 0.20, 0.90; p=0.0213)
			  ○ CV death – HR 0.82 (95% CI 0.69, 0.98; p=0.0294)
			• Dapagliflozin was also superior to placebo for all secondary endpoints, including death from any cause (HR 0.83; 95% CI 0.71, 0.97; nominal p=0.022)
			
			There is also evidence for the treatment effect of empagliflozin in HFrEF from the EMPEROR- REDUCED trial (n=3,730; 49.8% of patients had T2DM) in which the risk of the primary composite outcome of CV death or hHF, was significantly reduced with empagliflozin (19.4%) compared to placebo (24.7%) (HR 0.75; 95% CI 0.65, 0.86, p < 0.001).[7]
			• CV death – HR 0.92 (95%CI: 0.75, 1.12)	

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			• All-cause mortality – HR 0.92 (95% CI: 0.77, 1.10, p >0.05) Therefore, AstraZeneca believes the strength of the available evidence in patients with HFrEF mean that these NICE recommendations should be included as part of the NG28 guideline update. • Dapagliflozin for treating chronic heart failure with preserved/mildly reduced ejection fraction (HFpEF/HFmrPEF) [ID1648], anticipated publication in 2023 • Empagliflozin for treating chronic heart failure with HFmrPEF/HFpEF [ID3945], anticipated publication in 2023 The prevalence of HF is estimated to be 0.91% in England[8] and is likely to rise in the future due to factors such as the ageing population in the UK and rising rates of obesity and T2DM.[9–11] AstraZeneca believes there to be approximately [redacted] patients with HF and LVEF >40% in primary or secondary care settings in England and Wales who would benefit substantially from treatment with an SGLT2 inhibitor. Without an efficacious, well-tolerated treatment, patients with HF and a left ventricular ejection fraction (LVEF) >40% (HFmrPEF and HFpEF) experience poor clinical outcomes	

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			and health related quality of life and face a life expectancy worse than patients with some cancers.[12] As such, clinical care is currently limited to symptomatic treatment and/or treatment for underlying co-morbidities, rather than treatments for HF and an LVEF >40%. There is therefore an urgent need for easily accessible new treatments which can reduce mortality and hospitalisation and improve disease symptoms and quality of life. Until SGLT2 inhibitors, there has been lack of any disease modifying therapies for patients with HFmrEF or HFpEF which have proven to be clinically effective in this population. There is now data for SGLT2 inhibitors which spans the entire ejection fraction spectrum for patients with HF. As a result, the MHRA has now granted empagliflozin a license for the treatment of adult patients with symptomatic HF with a license for dapagliflozin in the same population expected ([redacted]). Therefore, there is sufficient evidence to support the use of some SGLT2 inhibitors across the entire HF spectrum. Improving care in HF will support achieving one of the priorities of the NHS Long Term Plan, in which CVD has been identified as the single biggest area where lives can be saved by 2029 in England.[13] Given that HF and an LVEF >40% is associated with a substantial economic burden, primarily driven by high rates of hHF,[14–18] SGLT2 inhibitors offers a key opportunity to reduce healthcare resource use in HF, including HF events, for the NHS.	

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			Therefore, in anticipation of reimbursement in 2023, AstraZeneca believes the strength of the available evidence in patients with HFmrEF/HFpEF mean that these NICE recommendations should be included as part of the NG28 guideline update.	
AstraZeneca	007	006	It is not clear in the draft scope how the results will be stratified by specific risk groups (for example people with existing cardiovascular disease). Please may you provide clarity on how NICE will define the specific groups? In clinical practice, these group can be defined in numerous ways. International guidelines, such as the ADA/EASD consensus report (2022), divide specific risk groups into established ASCVD populations, HF populations, high CV risk populations and CKD populations with clear definitions for each subgroup.	Thank you for your comment. This will be considered by the committee when agreeing the protocols for the review questions and so we are not able to answer this question at this time, however we will provide clarification on this in the protocols. Your considerations will be taken into account when the committee discuss this issue.
AstraZeneca	007	026 – 028	It is not clear in the draft scope what the definition of 'adequate response is. Please may you provide clarity on what definition of adequate response will be used for this update? AstraZeneca would like to emphasise that is it important for NICE to ensure there is focus given to the 'response' of drugs on the prevention of cardiovascular disease and chronic kidney disease in type 2 diabetes, independently of glycaemic response. Such guidance is also supported by the international consensus from ADA and EASD.	Thank you for your comment. This will be considered by the committee when making the protocols for the review questions and so we are not able to answer this question at this time, however we will provide clarification on this in the protocols. Your considerations will be taken into account when the committee discuss this issue.

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			The recent update of the NG28 guidelines was a step-change in the management of patients with T2DM. It recognises the critical value of the recent clinical data that goes beyond the historical focus on glycaemic management alone, and how this is aligned with many NHS priorities, including the Core20PLUS5. It is imperative that this value is pulled through into the NG28 2024 update to ensure alignment with current clinical practice and NHS priorities.	
AstraZeneca	008	017 – 030	Given the above points relating to the inclusion heart failure and CKD in comorbid T2DM patients, AstraZeneca strongly suggest including clinical and non-clinical outcomes such as healthcare and dialysis resource use in relation to benefits associated with reductions in hHF, urgent heart failure visits and general NHS resources into the main outcomes for this guideline update. It is not clear from the draft scope what health related quality of life outcomes NICE will be using in this guideline, please may you therefore provide some additional clarity. In addition, AstraZeneca suggests that hospitalisation for heart failure should not be included as a major cardiovascular event but should be separated out to reflect the distinctness of these subpopulations.	Thank you for your comment. The outcome list in the scope is not exhaustive and the committee will discuss whether additional outcomes need to be added when writing the protocols for the review questions. The definition of outcomes will be discussed with the committee when defining the protocols for the review questions. It is expected that the major cardiovascular events will be both examined as aggregate scores and separated out into their individual events (therefore, hospitalisation for heart failure will be examined separately).
AstraZeneca	009	003 – 005	The current Quality Standards for Diabetes in Adults are out of date and do not reflect current clinical practice nor current evidence base. They do not take into consideration the importance of cardiovascular risk prevention or chronic	Thank you for your comment. As stated in the scope, Diabetes in adults (2016) NICE quality standard 6, may need to be revised or updated as a result of the update of this guideline.

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			kidney disease prevention and therefore do not align with key NHS priorities. It is therefore imperative that the NICE quality Standards for Diabetes are updated in line with this guideline update.	
Boehringer Ingelheim	General	General	We support a wide consultation on any updates to the guidelines, including involvement of both clinical and patient experts. All recommendations should align with clinical evidence and beliefs, to support their implementation.	Thank you for your comment. Stakeholder consultation and multidisciplinary guideline committees consisting of healthcare professionals and lay people are fundamental aspects of NICE guidelines as set out in the NICE guidelines manual. The manual also details how recommendations are made, using the best available evidence, in agreement with your comment.
Boehringer Ingelheim	General	General	A suggested topic is de-escalation or stopping of therapy. Currently limited guidance is offered to healthcare professionals (HCPs) on how to manage patients with an inadequate response to treatment.	Thank you for your comment. We agree this is important to consider. Draft review question 1.2 in the scope includes consideration of approaches to optimise treatment, including de-escalation and stopping previous therapies.
Boehringer Ingelheim	General	General	We suggest recommendations, in particular treatment algorithms, are as clear and simple as possible, to aid implementation for busy HCPs.	Thank you for your comment. We agree that producing clear recommendations that are useful and usable for healthcare professionals is an important aspect of this update and will be a consideration of the committee when agreeing the recommendations.
Boehringer Ingelheim	001	007 – 009	We welcome regular updates to clinical guidelines to ensure they are based on the best available evidence. However, we also suggest appropriate resource is made available to support implementation of the current guidance, as evidence suggests suboptimal prescribing of clinical and cost-effective options.	Thank you for your comment. The aim of the update will be to review the current evidence to inform recommendations on medicines for the management of type 2 diabetes. Implementation tools may be produced to support the guideline. This will be considered during the development of the update.

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			Based on the NG28 recommendations and the accompanying Resource Impact Template, an SGLT2 inhibitor with proven cardiovascular benefits should be offered to 34.8% of T2D patients (those with cardiovascular disease [CVD]) and considered or offered in 77.5% of T2D patients (those at high risk of or with CVD). However, evidence from a descriptive analysis of UK CPRD data suggests low usage of SGLT2 inhibitors. Despite a rise in use of SGLT2 inhibitors by patients with CVD between 2017 and 2019, it reached only 9.8% by the end of 2019,[1] and recent NHS prescribing data suggest adoption is still suboptimal vs the recommendations. There is clear evidence of the clinical and cost-effectiveness of SGLT2 inhibitors with proven cardiovascular benefit in addition to metformin for patients with or at high risk of CVD, as summarised in the NG28 Guidelines. We suggest support is offered to Integrated Care Systems (ICS) to implement the current guidelines to ensure the benefits are realised. 1. Farmer RE, et al. Clinical Therapeutics 2021;42:2:320–335.	
Boehringer Ingelheim	001	014 – 017	We welcome updates to clinical guidelines to ensure they are holistic and include all appropriate evidence on benefits beyond cardiovascular benefits. We trust the relative importance of each benefit will be handled using appropriate utilities and costs. We welcome	Thank you for your comment. Key outcomes that may be considered when searching for and assessing the evidence can be found in the scoping document. Model parameters including utilities and costs will be presented to the committee for consideration during development.

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			the opportunity to review the health economic model and draft reports.	
Boehringer Ingelheim	002	007 – 012	Regarding equality considerations, NHS prescribing data suggest that the adoption of SGLT2 inhibitors varies significantly between ICSs and this could serve to drive health inequalities in CV outcome. We suggest support is offered around implementation of the current guidelines, to reduce potential inequalities.	Thank you for your comment. Considering feasibility of implementation will be one of the factors taken into account during the development of the updated guideline. Implementation tools may be produced to aid this.
Boehringer Ingelheim	005	018 – 020	The guidance 'Empagliflozin for reducing the risk of cardiovascular events in type 2 diabetes [ID1037]' was suspended in 2018 and so not relevant. Further information is available on the relevant webpage: Project information | Empagliflozin for reducing the risk of cardiovascular events in type 2 diabetes [ID1037] | Guidance | NICE	Thank you this has been amended
Boehringer Ingelheim	007	001 – 002	Regarding the Health Economic Model that will be updated and expanded for this guideline update, we request that the results of the model are reported accurately, and in the context of the limitations to the different modelling approaches (including both the base case and the sensitivity analyses). We refer to the following statement published on page 41 of NG28 'Type 2 diabetes in adults: management': "…*The exception to this was dapagliflozin, which was cost effective at a threshold of £20,000 per quality-adjusted life year in the base-case analysis and across a range of model scenarios."*	Thank you for your comment. The examples cited relate to the previous guideline update which will be updated as part of the scope of this work.

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			The statement is inaccurate and a misrepresentation of the results of the health economic model. We refer to the 'Health Economic Model Report', available at NG28 Health economic model report (nice.org.uk), in which there is a scenario in which empagliflozin is associated with an ICER of £15,427 as is ranked first in terms of net monetary benefit at £20,000. In this scenario, dapagliflozin is associated with an ICER of £21,233 and is ranked fourth in terms of net monetary benefit. (Table HE054, page 60). Thus, it is inappropriate to name dapagliflozin as an exception when it was not cost-effective across all scenarios. Furthermore, the overall message of the following paragraph on page 41 of NG28 'Type 2 diabetes in adults: management' is contradictory and potentially misleading: "*The evidence showed that SGLT2 inhibitors as a class of drugs were most likely to be cost effective in combination with metformin, although the incremental cost-effectiveness ratio (ICER) varied between different drugs in the class and in different scenarios in the model. The exception to this was dapagliflozin, which was cost effective at a threshold of £20,000 per quality-adjusted life year in the base-case analysis and across a range of model scenarios. However, the committee agreed there was too much uncertainty in the clinical data, and therefore the economic modelling, for them*	

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			to be confident that these different ICERs represented true underlying differences in cost effectiveness." The Committee concluded there was too much uncertainty to be confident there are true underlying differences in cost-effectiveness, and so it is inappropriate to suggest one drug may be the most cost effective.	
Boehringer Ingelheim	008	014 – 030	We welcome a more holistic update of the economic model, which should be based on robust empirical evidence, with appropriate weighting given to outcomes based on economic and clinical burden.	Thank you for your comment.
Cambridge University Hospitals NHS Foundation Trust	021 + general	General	The draft guidelines put the use of GLP-1 RA very far down the treatment pathway. This is wrong. This is against all of the current guidance of ADA/EASD. This is likely to lead to inferior management of patients who are overweight/obese (with or without significant cardiovascular disease). Indeed, there is seemingly limited scope for utilising GLP-1 RA in patients who are overweight/obese with NICE preferring to us weight positive agents seemingly (leading potentially to weight gain, more insulin resistance and co-morbidities). The guidelines could even put NICE at risk of being accused of weight bias because of how they have been constructed: as the first line intervention for patients with type 2 diabetes is lifestyle/weight loss, early initiation of weight positive drugs (eg sulphonylureas and pioglitazone and insulin) is likely to promote weight gain instead and be counter-productive in these patients, especially with increasing patient BMI..	Thank you for your comments. Consideration of treatment sequencing is included within the scope of the update. The update of these reviews may change these recommendations based on the clinical and economic evidence.

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			With NICE guidance being so far from current recognised international best practice this will likely to cause adverse impact on patient health as well as stresses on all health practitioners who prescribe for this patient population who would usually aim to prescribe according to recognised best practice.	
Cambridge University Hospitals NHS Foundation Trust	025 – 026	General	Excellent to see reference to periodontitis. Difficulties accessing dental care is a common issue facing patients with type 2 diabetes. Could there be specific reference to ensuring adequate access to oral health care and dental teams for patients with type 2 diabetes?	Thank you for your comment. Unfortunately we are not clear what this relates to in the current scope. Peridontitis is not referenced in this document.
CaReMe UK	007	001	Health economic model. We are encouraged that the committee will update and expand the economic model used in the February 2022 version of the guideline. However, we urge the committee to consider the holistic benefits of GLP1 receptor agonists beyond their influence on cardiovascular events in isolation. The previous analysis did not take into account the totality of evidence for GLP-RAs when the conclusion was reached that the class was not cost effective. We urge the committee to consider a holistic and patient-centred approach, including analysis of the benefits of glucose lowering, weight loss, risk of hypoglycaemia and CV benefits when assessing the cost effectiveness of GLP1-RAs. We also encourage the committee to consider cost-effectiveness of GLP1-RAs when SGLT inhibitors are not	Thank you for your comment. The aim of the update is to review the current clinical and economic evidence to update the recommendations on medicines for the management of type 2 diabetes. The committee will consider all relevant populations and evidence when forming their recommendations. They will also decide sequencing of treatment in any future modelling. The planned approaches will be set out in the systematic review protocols and economic plan. Your considerations will be taken into account when the committee discuss and agree these. For this update we will look at the full range of benefits associated with each drug type.

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			suitable or not tolerated in patients with cardiovascular disease or high cardiovascular risk. Finally, we are concerned that the base-case treatment paradigm used for economic modelling is founded on metformin, then addition of sulphonylurea then addition of insulin. This base-case scenario predisposes to exaggeration of the effects of hyopglycaemia when other classes of drugs are added. Such treatment escalation is an inappropriate baseline comparator for people with established cardiovascular disease, in whom exposure to hyopglycaemia should be avoided. It represents an outmoded treatment paradigm, which although inexpensive, unnecessarily exposes patients to hyopglycaemia and weight gain. We argue that in individuals with CVD, an escalation strategy based on metformin, SGLT2 inhibitor and GLP1-RA is much more appropriate so as to minimise risk of hyopglycaemia and facilitate weight management.	
CaReMe UK	007	012	The list of medication classes to be considered should include dual GLP-1 and GIP co-agonists ('twincretins')	Thank you for your comment. The list of medication classes provided is not exclusive and the committee will consider whether additional classes should be added when writing the protocols for the review questions, including whether dual GLP-1 and GIP co-agonists should be considered.
Diabetes UK	General	General	We welcome this update of the medicines section of this guideline and the expansion of the scope to look at a more holistic range of benefits following the most recent consultation, which was limited to cardiovascular benefits.	Thank you for your comment. It has been agreed that there is a need to update the medicines section of the guideline in full so that all treatments are compared to one another, rather than focussing on a subsection of the pathway. As the evidence base for medicines for type 2 diabetes is very large

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			There is a need for this update to ensure these guidelines are more consistent with clinical practice and align with recommendations in international guidelines such as the ADA/EASD consensus on the management of type 2 diabetes. However, we are also concerned about the length of time it may take to complete this update given the significant developments in this area that are not reflected in the guidelines currently, such as the increasing use of GLP-1s and other modern medicines earlier in the treatment line. We would therefore welcome more information about why this update is expected to conclude at the end of 2024. Reference: https://diabetesjournals.org/care/article/doi/10.2337/dci22-0034/147671/Management-of-Hyperglycemia-in-Type-2-Diabetes	and rapidly evolving we acknowledge this will take longer than focussing on a small section, however as part of this work a living guideline database will be produced to enable future updates to be conducted in more rapidly. This is an essential part of the work to ensure that NICE's aim of providing dynamic living guideline recommendations can be achieved on this topic.
Diabetes UK	General	General	We do not agree with the proposed approach and believe that the scope should consider the place of insulin in the treatment pathway. There is emerging evidence that some groups of people, such as those who are diagnosed with type 2 diabetes under the age of 40, would benefit from insulin being prescribed earlier than is recommended currently. Research indicates that earlier use of insulin can help to address the more rapid deterioration in glycaemic	Thank you for your comment. Following consideration of stakeholder comments NICE intend to commission a review of insulins as a separate piece of work. In this update, insulin will remain as a comparator intervention only. Comments about the timing of in the pathway have been acknowledged, but it is noted that this would not require an alteration in the pathway sequence, but instead more rapid escalation to treatments at later stages of the pathway for certain groups of people.

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			management seen in those who are diagnosed at younger ages. With increases in the number of people under 40 years old being diagnosed with diabetes who are less likely to achieve treatment targets and develop complications quicker, it is important that this update considers the most effective treatments for this group. Reference: https://onlinelibrary.wiley.com/doi/epdf/10.1111/dme.14940	
Diabetes UK	003	003 – 006	This scope may exclude women with type 2 diabetes who have unplanned pregnancies. The wording of this section could be read as implying that all pregnancies are planned when we know many pregnancies are unplanned, with only 6% of women with type 2 diabetes prepared for pregnancy, which results in poorer outcomes. Furthermore, the latest diabetes and pregnancy audit showed women with type 2 diabetes represent 54% of all diabetes pregnancies. This is likely to increase as the prevalence of type 2 diabetes is increases in the under-40 population. Whilst we appreciate the signpost to the 'Diabetes in Pregnancy' [NG3] guideline we think there is a gap in the guidance for women who have unplanned pregnancies. There is a need for safe glucose levels both before and during pregnancy in women with type 2 diabetes. As a result, we would suggest the addition of some text to the scope explaining the impact of unplanned pregnancies	Thank you for your comment. The population stated also includes those who are already pregnant, which would include unplanned pregnancies. NG3 covers all issues related to pregnancy for people with type 2 diabetes and therefore we do not agree this implies a gap in the population.

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			for women with type 2 and addressing the needs of this growing population. References: https://digital.nhs.uk/data-and-information/publications/statistical/national-pregnancy-in-diabetes-audit/2019-and-2020. https://diabetesjournals.org/care/article/45/5/1046/146906/Pregnancy-Outcomes-of-Young-Women-With-Type-2	
Diabetes UK	007	001 – 004	We reiterate that the new economic model developed for this consultation must look at evidence on the wider benefits of different treatments and reflect the broad scope of the update.	Thank you for your comment. Section 2.6 lists the key outcomes that may be considered during the guideline update, but is not exhaustive. The committee will consider whether any additional outcomes are required when agreeing the protocol for the review questions. The broad scope of the update will be reflected in the economic model.
Diabetes UK	008	014 - 030	Diabetes UK welcome the inclusion of remission as a key outcome in this scope. Remission has transformed the treatment landscape for many with diabetes and it is important that it is recognised within these guidelines.	Thank you for your comment.
Diabetes UK	008	014 – 030	We also welcome the inclusion of health-related quality of life as an outcome but think that more detail can be added to this list to refine it. This could be done, for example, by adding specific outcomes around patient tolerability and preferred methods of administration of medicines.	Thank you for your comment. The outcome list in the scope is not exhaustive and the committee will discuss what measures would be included within each broad outcome and whether additional outcomes need to be added when writing the protocols for the review questions.
Diabetes UK	008	014 – 030	It is important that the outcomes should also include the protective effects of medicines and this consultation should	Thank you for your comment. The outcome list in the scope is not exhaustive and the committee will discuss whether

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			review evidence on risk factor reduction as well as end points and major events.	additional outcomes need to be added when writing the protocols for the review questions.
Diabetes UK	008	014 – 030	As well as searching and assessing for evidence of HbA1c change we would encourage consideration of time in range as a marker of glycaemic management. The development and increasing use of CGM technology by people with type 2 diabetes - supported by the widening of access in the March 2022 update of this guideline - means that more can now track their time in range alongside HbA1c, providing an important additional measure of glycaemic management.	Thank you for your comment. The definition of outcomes will be discussed with the committee when defining the protocols for the review questions.
Eli Lilly and Company	General	General	Thank you for the opportunity to comment on the draft scope of the NICE guideline on type 2 diabetes in adults: management (medicines update).	Thank you for your comment.
Eli Lilly and Company	General	General	**ADA/EASD consensus report** The EASD and ADA have recently published an updated consensus report on the Management of hyperglycaemia in type 2 diabetes (T2D) (Davies et al., 2022) which is well respected and widely referred to in the UK. This should be used as a reference source for the NICE guideline development teams especially with regard to: • HbA1c (see below) • Weight loss • Earlier intensification • Considerations of T2D economic modelling analysis	Thank you for your comment. We are aware of the ADA/EASD. NICE follows a different process to this consensus report when making recommendations and will make recommendations based on the committee's interpretation of the clinical and cost-effectiveness evidence. The recommendations relating to the treatment algorithm will be revised accordingly as part of this update, based on the evidence reviewed.

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			The ADA/EASD consensus report presents a particularly useful treatment algorithm for management of T2D (Figure 3) which helps clinicians individualise care based on patient characteristics and comorbidities. In 2020–21, only 50.4% of patients with T2D in England achieved an HbA1c <7.0% (53 mmol/mol) (*NHS National Diabetes Audit, 2020-21*). Please consider how the stepwise algorithm can be restructured to support clinicians in individualising care and reduce therapeutic inertia to enable more patients to achieve their HbA1c and weight loss targets.	
Eli Lilly and Company	General	General	**HbA1c target** As stated in the most recent ADA/EASD consensus report, achieving recommended glycaemic targets produces substantial and prolonged reductions in the onset and progression of microvascular complications and early intervention is essential. People with longer life expectancy have more to gain from early intensive glycaemic management. A reasonable HbA1c target for most non-pregnant adults with sufficient life expectancy to see microvascular benefits (generally ~10 years) is around 53 mmol/mol (7%) or less (Davies et al., 2022). A lower HbA1c target may be reasonable, particularly if it can be achieved safely without significant hypoglycaemia. This has not been reflected in the last NG28 update which linked lower targets directly with risk of hypoglycaemia which is not the same for all drug classes.	Thank you for your comment. The recommendations on HbA1c measurement and targets, included in section 1.6 on blood glucose management are not within the scope of the update at this time. This update focuses on drug treatment for management of type 2 diabetes.

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Eli Lilly and Company	General	General	**Weight loss** To make this guideline more relevant and up to date, weight loss should be included as a treatment goal for T2D patients. A higher magnitude of weight loss leads to better outcomes, and weight loss may exert benefits that extend beyond glycaemic management to improve risk factors for cardiometabolic disease and quality of life. As stated in the latest ADA/EASD consensus report, weight loss of 5–15% should be a primary target of management for many people living with T2D.	Thank you for your comment. Change in weight or BMI is included as one of the key outcomes for decision making specified in the scope. Although defining a treatment goal is not within the scope of the review questions for these questions, the effect of treatments on weight will be evaluated and will inform the committee's decisions when making recommendations.
Eli Lilly and Company	General	General	**References** Boye, K. S., Matza, L. S., Stewart, K. D., Jordan, J., Biricolti, G., Del Santo, S., Perez-Nieves, M., Federici, M. O., Gentilella, R., Losi, S., & Norrbacka, K. (2019). Patient preferences and health state utilities associated with dulaglutide and semaglutide injection devices among patients with type 2 diabetes in Italy. *Journal of Medical Economics*, *22*(8), 806–813. https://doi.org/10.1080/13696998.2019.1609482 Boye, K. S., Shinde, S., Kennedy-Martin, T., Robinson, S., & Thieu, V. T. (2022). Weight Change and the Association with Adherence and Persistence to Diabetes Therapy: A Narrative Review. *Patient Preference and Adherence*, *Volume 16*, 23–39. https://doi.org/10.2147/ppa.s328583 Davies, M. J., Aroda, V. R., Collins, B. S., Gabbay, R. A., Green, J., Maruthur, N. M., Rosas, S. E., Del Prato,	Thank you for this information.

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			S., Mathieu, C., Mingrone, G., Rossing, P., Tankova, T., Tsapas, A., & Buse, J. B. (2022). Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. https://doi.org/10.2337/dci22-0034 Divino, V., Boye, K. S., Lebrec, J., DeKoven, M., & Norrbacka, K. (2019). GLP-1 RA Treatment and Dosing Patterns Among Type 2 Diabetes Patients in Six Countries: A Retrospective Analysis of Pharmacy Claims Data. *Diabetes Therapy*, *10*(3), 1067–1088. https://doi.org/10.1007/s13300-019-0615-5 Fridman, M., Lucas, M. E., Paprocki, Y., Dang-Tan, T., & Iyer, N. N. (2020). Impact of Weight Change in Adults with Type 2 Diabetes Mellitus: A Literature Review and Critical Analysis. *ClinicoEconomics and Outcomes Research*, *Volume 12*, 555–566. https://doi.org/10.2147/ceor.s266873 Hayes, A. J., Leal, J., Gray, A. M., Holman, R. R., & Clarke, P. M. (2013). UKPDS Outcomes Model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82. *Diabetologia*, *56*(9), 1925–1933. https://doi.org/10.1007/s00125-013-2940-y	

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			Karkare, S., Fridman, M., Dang-Tan, T., Lu, J., Smolarz, B. G., DeKoven, M., & Iyer, N. N. (2019). Effect of Weight Change on Economic Outcomes Among Persons with Type 2 Diabetes Mellitus in the United States: Beyond Glycemic Control. *Journal of Managed Care &Amp; Specialty Pharmacy*, *25*(6), 658–668. https://doi.org/10.18553/jmcp.2019.18321 *National Diabetes Audit, 2020-21 Quarterly Report*. NHS Digital. Retrieved 31 October 2022, from https://digital.nhs.uk/data-and-information/publications/statistical/national-diabetes-audit/e4-data/ Palmer, A. J., Si, L., Tew, M., Hua, X., Willis, M. S., Asseburg, C., McEwan, P., Leal, J., Gray, A., Foos, V., Lamotte, M., Feenstra, T., O'Connor, P. J., Brandle, M., Smolen, H. J., Gahn, J. C., Valentine, W. J., Pollock, R. F., Breeze, P., Clarke, P. M. (2018). Computer Modeling of Diabetes and Its Transparency: A Report on the Eighth Mount Hood Challenge. *Value in Health*, *21*(6), 724–731. https://doi.org/10.1016/j.jval.2018.02.002	
Eli Lilly and Company	007	001 – 008	**Considerations for using UKPDS Outcomes Model 2** We are concerned that the model used in the February 2022 version of the guideline does not appropriately capture the key outcomes outlined in the EASD/ADA consensus report on newer T2D medicines. Many limitations were also highlighted during the previous consultation for NG28. The following should be considered in the revised model:	Thank you for your comment. Your considerations will be taken into account when the committee discuss how best to conduct any future modelling. The committee of experts will be involved in determining and agreeing all assumptions and approaches taken by the model.

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			Relevant risk factors Previous economic analysis for NG28 have not fully captured all relevant clinical risk factors other than HbA1c and weight loss. Risk factors such as systolic blood pressure, lipid levels (LDL, HDL) which are part of the UKPDS OM2, are missing in the main outcomes (Section 2.6) which will be considered when searching and assessing the evidence. These are predictors of disease progression for microvascular and macrovascular complications, mortality, health outcomes and costs (Hayes et al., 2013). Not including treatment effects on all relevant clinical risk factors would underestimate the benefit of T2D medications. ***Clinical validation and appropriate justification*** The transparency of modelling assumptions and approaches should be validated by clinical experts throughout the development of the guideline. An example from the previous modelling analysis in February 2022 were that patients were assumed to receive medication for the duration their lifetimes however this does not reflect clinical reality as shown in persistence data on GLP-1 RAs (Divino et al., 2019). ***Appropriateness of the standard of care (SoC) arm*** Similarly, the appropriateness of the SoC arm is difficult to interpret from the information provided in the HE report. No data are presented on changes in risk factors over time, the	A broader range of outcomes will be included in the model compared with the model developed for the February 2022 guideline. The revised model will provide a more detailed breakdown of results.

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			incidence of complications are also not reported. By presenting these results this would allow readers to judge how well the model reflects clinical reality. SoC should be revised and modelled correctly to reflect clinical practice in the NHS. ***Treatment intensification*** The impact of treatment intensification should not be assumed to be the same across all interventions as this will underestimate the benefits associated with good glycaemic control and weight loss. ***QoL utilities*** Regarding health-related quality of life, improvements of QoL associated with body weight reductions and device preference, are important for the long-term successful management of T2D. Weight loss in patients with T2D has been associated with improved clinical, economic, and patient-reported outcomes (Boye et al., 2022, Boye et al., 2019, Fridman et al., 2020, Karkare et al., 2019). This should therefore be considered in the updated economic analysis. In addition, in the previous NG28 update, injection-related disutility was applied to GLP-1 RAs but not to insulin treatment. Injection disutility should be applied to all relevant treatment (including insulin) if appropriate or strong rationale should be provided to exclude.	

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			Microvascular complications Microvascular complication rates such as diabetic retinopathy, diabetic neuropathy, foot amputations were not included in the previous modelling analysis in February 2022. Hazard ratios were only applied to macrovascular events, the full impact of new interventions on microvascular complications were not considered, underpredicting the efficacy of latest T2D medication. This underestimates the benefit of new treatments that would also affect progression of macrovascular complications and consequently does not fully capture all future healthcare costs and outcomes. ***Other shortcomings associated with the previous model*** • The appropriateness of the previous modelling analysis was hard to judge, as important data (changes in risk factors over time, incidence of complications) were not presented. As noted in the publications from Mount Hood Diabetes Modelling Meetings (that included the UKPDS Outcomes Model 2), assumptions around risk factor progression can play an important role in cost-effectiveness (Palmer et al., 2018). • Hazard ratios were held constant for the duration of the analysis, which may not be appropriate as there are many aspects that change over time that could affect risk (age, duration of diabetes, cumulative glycaemic exposure, etc.).	

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			Together, this means that the use of evidence from CVOTs in economic modelling has the potential to produce spurious results. For example, medications that have previously shown greater HbA1c and weight reductions in head-to-head clinical trials were associated with poorer outcomes in the previous NICE modelling analysis, which is not well aligned with published clinical evidence.	
Eli Lilly and Company	007 – 008	010 – 028 001 - 008	**Earlier intensification** The guidelines should provide guidance on how quickly to optimise treatment rather than remaining on initial therapy and evaluate the evidence which considers switching/adding/intensifying to more efficacious treatments/combinations and the optimum timeframe for doing it. Assumptions associated with treatment algorithms (i.e. sequence of treatments and decisions to intensify) will have an important impact on the economic modeling analysis along with assumptions on risk factor progression and the durability of treatment effects. It is important that these are aligned with current clinical practice in the UK and intended practice, as well as being communicated with stakeholders in the upcoming analysis.	Thank you for your comment. Methods of optimisation of treatment are planned to be considered within the review of the evidence, as noted in the draft review questions. The clinical and economic reviews and analyses undertaken in the guideline will inform the recommended treatment sequence and any assumptions made in the analyses will be detailed within the methods published with the guideline.
MSD (Merck Sharp and Dohme)	003	002	Section 2.1 which covers who is the focus of this guideline currently includes 'Patients with Obesity'. We feel this should include all patients with a raised BMI, as this is more reflective of the T2D population.	Thank you for your comment. Section 2.1 discusses populations requiring specific consideration. This is not an exhaustive list and does not exclude anyone from the guideline. The inclusion of this group was to specify that there may be different treatment effects and requirements for people with obesity than for people with a raised BMI who do not have obesity, and so this may be valuable to

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				investigate as a separate population and may require different recommendations. The committee will consider whether this is important when making the protocol. People with a raised BMI, as this may be reflective of a larger proportion of people with type 2 diabetes mellitus, will be considered but not added to this section.
MSD (Merck Sharp and Dohme)	003	General	Again, Section 2.1 we feel an additional consideration should be made to patients with high blood pressure as hypertension is a common comorbidity associated with diabetes and has clinical implications such as renal pathology.	Thank you for your comment. Section 2.1 discusses populations requiring specific consideration and is not an exhaustive list. People with hypertension could be examples of people with long-term conditions. The committee will consider the inclusion of relevant groups when making the protocols for the reviews.
MSD (Merck Sharp and Dohme)	008	General	Section 2.6 (Main Outcomes). We feel that changes in blood pressure on T2D therapies should be an outcome that is considered when drafting guidelines.	Thank you for your comment. The outcome list in the scope is not exhaustive and the committee will discuss whether additional outcomes need to be added when writing the protocols for the review questions.
MSD (Merck Sharp and Dohme)	008	General	Again, Section 2.6 (Main Outcomes). We feel that cost effectiveness in patients with low CVD risk status and without commodities should be taken into consideration in this guideline.	Thank you for your comment. Section 2.1 discusses populations requiring specific consideration and is not an exhaustive list. The committee will consider population subgroups that they think are relevant to consider as a part of the review question and recommendations when making the protocols for the review.
NHS Bath and North East Somerset, Swindon and Wiltshire	General	General	We would prefer that you review on individual GLP1 **chemical substance** (instead of as a class) and their relevant probability of cost effectiveness by using as a combination agent at 2nd, 3rd, 4th line treatment? Our local diabetes teams are using GLP1s as a 2nd line treatment	Thank you for your comment. The draft review questions will be used to inform review protocols that will guide the development of the systematic reviews. Decisions such as whether to review drugs at a class or drug level will be made when the committee consider the protocols and will be

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Integrated Care Board (ICB)			outside of NICE and we don't believe it is cost-effective at that level.	specified within it. Stakeholder comments will be taken into account to help inform those decisions.
NHS Bath and North East Somerset, Swindon and Wiltshire Integrated Care Board (ICB)	General	General	Why is it taking until December 24 to actually publish this guidance- we need an answer on this now, not in 2 years time. GLP1 use is mushrooming outside of NICE and even publishing in 2023 is too late let alone 2024!	Thank you for your comment. It has been agreed that there is a need to update the medicines section of the guideline in full so that all treatments are compared to one another, rather than focussing on a subsection of the pathway. As the evidence base for medicines for type 2 diabetes is very large and rapidly evolving we acknowledge this will take longer than focussing on a small section, however as part of this work a living guideline database will be produced to enable future updates to be conducted in more rapidly. This is an essential part of the work to ensure that NICE's aim of providing dynamic living guideline recommendations can be achieved on this topic.
NHS England	002	General	Glad to see moderate and severe frailty in the list of specific considerations, also please be aware that (point 27) most people with dementia are also moderately to severely frail and so there is a big overlap between this cohort of patients. Services often focus on either the physical or cognitive elements of a person's condition, but this guidance brings an opportunity to get services to collaborate much closer together around the complex person rather then just focusing on conditions.	Thank you for your comment. Your comments will be taken into consideration when the committee consider the evidence to inform updated recommendations.
NHS England	008	019, 020 + 023	Taking a population health management approach to patients with other overlapping morbidities e.g. Renal or cardiovascular, so more collaborative MDT thinking	Thank you for your comment.

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			especially in secondary care between specialties so joined up plans are communicated to community and primary care	
NHS England	008	General	Multi-morbidity connected to moderate frailty and then the link between palliative care particularly in severe frailty (& the overlap with dementia – most people with dementia are frail). A lot of guidance is about diabetes in the younger person who may have diabetes as the only long term condition. In practice, many of the patients we see are older and complex which is not always reflected in QOF guidance & targets.	Thank you for your comment. People with moderate and severe frailty and people with dementia are people specified to require specific consideration in the guideline. The guideline will aim to provide guidance to help in this area.
NHS England	008	General	Clearly optimising drug treatments is important in improving diabetes outcomes, but so is having a reliable recall system particularly in primary care (linking this to QOF) especially if stratification tools are used (e.g. UCL Partners long term conditions stratification tool). There is variability about how practices recall and review patients some spreading it across the year (e.g. recall based on month of birth) but others leaving it until the last few months of the QOF year which is not the way to improve diabetes care. Perhaps your important and timely guidance can include this aspect of care.	Thank you for your comment. Reviewing the evidence for recall systems in primary care has not been prioritised for inclusion in the scope of the current update however.
NHS England	008	General	Health inequalities. Is there a way of looking at this aspect of care, perhaps looking at QOF exclusions for which there is a lot of variability between GP practices. This could run as a golden thread through the 30 points on page 8. It also links to my point above (point 4).	Thank you for your comment. Health inequalities issues will be considered as part of consideration of the evidence and when making recommendations for the guideline. However, looking at QOF exclusions is not within the remit of this guideline update.

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North Central London Joint Formulary Committee	003	023 - 024	The draft scope should include a review of insulins. There have been important developments since the original recommendation to use NPH: 1. Biosimilar insulin glargine 100 units/mL [iGlar100] is now available which has a lower acquisition cost than Lantus (the originator). The cost-effectiveness of glargine vs. NPH is now unknown. 2. Insulin glargine 300 units/mL [Toujeo; iGlar300] is now available. The cost-effectiveness of iGlar300 vs. NPH or iGlar100 is unknown 3. Insulin degludec [Tresiba; iDeg] is now available. The cost-effectiveness of iDeg vs. NPH or iGlar100 is unknown. Excluding these insulins means that that non-insulin therapies may be compared to a sub-optimal insulin regimen which will distort the cost-effectiveness assessment.	Thank you for your comment. Following consideration of stakeholder comments NICE intend to commission a review of insulins as a separate piece of work. In this update, insulin will remain as a comparator intervention only.
Northern Lincolnshire and Goole NHS Trust (NLAG)	General	General	Much of the guidance is good and positioning of SGLT2i is in keeping with evidence of glucose lowering, cardiovascular and renal protection (depending on the therapy).	Thank you for your comment.
Northern Lincolnshire and Goole NHS Trust (NLAG)	General	General	Positioning of GLP1 receptor agonists is poor and disregards years of clinical trial evidence since the publication of the LEADER study (2016).	Thank you for your comments. Consideration of treatment sequencing is included within the scope of the update. The update of these reviews may change these recommendations based on the clinical and economic evidence.
Northern Lincolnshire	General	General	Rather than immediately reviewing the whole NG28 guideline, surely it makes sense to update the GLP1 RA	Thank you for your comment. It has been agreed that there is a need to update the medicines section of the guideline in

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and Goole NHS Trust (NLAG)			positioning. The current proposed timeframe would mean these medicines have been available to prescribe for 6 years with no full review by NICE.	full so that all treatments are compared to one another, rather than focussing on a subsection of the pathway. Having a full update will enable the place of the GPR-1RA class in the pathway to be assessed, which would not be possible without comparing to all other treatment options. We acknowledge this will take longer than focussing on a small section, however as part of this work a living guideline database will be produced to enable future updates to be conducted in more rapidly. This is an essential part of the work to ensure that NICE's aim of providing dynamic living guideline recommendations can be achieved on this topic.
Northern Lincolnshire and Goole NHS Trust (NLAG)	General	General	Review of insulin usage in Type 2 Diabetes could surely be done as an addendum to this document – after the GLP1 review and positioning work. This would then make the document a 'rolling', current and evidenced-based dynamic document rather than guidance with an 'expiry date' that lapses further and further behind the evidence.	Thank you for your comment. Following consideration of stakeholder comments NICE intend to commission a review of insulins as a separate piece of work. In this update, insulin will remain as a comparator intervention only.
Northern Lincolnshire and Goole NHS Trust (NLAG)	General	General	I note that in the current NG28 guideline much of the references are for 2015 and update 2022 but in fact the wording of much of the GLP1 related items is that of 2009!	Thank you for your comment. The year associated with the recommendation denotes the year in which the evidence was reviewed and recommendation considered by the committee. In some cases the committee may consider the evidence and agree that it still supports the wording of the previous recommendation. The date will still be updated in this case to highlight that this evidence has been updated and reconsidered by the committee and the recommendation is current at that stated date.
Northern Lincolnshire	General	General	Many clinicians feel they should be following NICE guidance, but guidance needs to be current and in several respects	Thank you for your comment. It has been agreed that there is a need to update the guidelines on medicines for

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and Goole NHS Trust (NLAG)			(predominantly GLP1 RA usage) this guidance is already outdated and set for review for a further 2 years (in my view at least). Clinicians find the ADA EASD guidance workable, pragmatic and evidence-based and I think practitioners will feel that is they wish to Practice within a current evidence base, then they will defer to ADA EASD instead.	management of type 2 diabetes in full to ensure the recommendations produced are based on all of the best available evidence. As part of this work a living guideline database will be produced to enable future updates to be conducted in more rapidly. This is an essential part of the work to ensure that NICE's aim of providing dynamic living guideline recommendations can be achieved on this topic.
Northern Lincolnshire and Goole NHS Trust (NLAG)	General	General	In terms of cost savings – the focus needs to be on complications reduction. Committee members will be well aware that around 80% of diabetes costs are complications related and we have evidence from STENO (2008) and much more recently that to reduce costs we must encourage use of therapies with evidence of complications reduction.	Thank you for your comment. In general, cost-utility analyses will weigh up the costs and benefits of each treatment and this usually factors in the consequences of disease or treatment complications. The committee will decide what complications are relevant for inclusion in any cost-related analyses. The economic modelling will include a broader range of outcomes than the model used for the February 2022 update.
Novo Nordisk	General	General	1.Thank you for the opportunity to comment on this draft scope. We agree with the importance of giving specific consideration to people with individual and clinical characteristics.	Thank you for your comment.
Novo Nordisk	005	006 – 009	2.There are inaccuracies on this page with regards related NICE guidance in development. There is no technology appraisal guidance in development for either semaglutide or dulaglutide and including this incorrect information within this scope is likely to cause confusion. We recommend that the guidance in development section is fully reviewed to ensure it is accurate and updated as needed.	Thank you this has been amended.

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Novo Nordisk	007	001 – 008	3.Novo Nordisk has significant concerns about the proposal within this scope relating to the economic model. Concerns about this proposal were also raised by other participants during the scoping workshop on 6th September and were in fact shared by a member of the NICE guideline committee during the workshop who acknowledged the size of the challenge in developing a model to meet the proposed requirements. • Whilst we welcome the ambition to assess CV and various sub-populations within the health economic (HE) model to reflect the changing aspects of the management of type 2 diabetes, there were significant flaws with the economic modelling approach used for the recent update of the CV recommendations for diabetes medicines. • Medicines recommendations in NG28 have been heavily reliant on HE modelling. There are significant complexities in modelling CV outcomes in diabetes, which have been widely published and discussed[1]. • There is a lack of published evidence presenting models which have incorporated CV outcomes into diabetes modelling – owing to how complex a task it is. We have concerns with the modelling approach used in NG28 - to simply use CVOT data in a model	Thank you for your comment. Section 2.4 states that the previous guideline model will be updated and expanded for this update. Part of this update will involve incorporating clinical outcomes from the updated systematic review. The committee will decide what outcomes are most relevant upon finalisation of the protocols. The scope also states that NICE intend to use this model for future NICE guidance. Collaboration with external bodies is something that NICE may explore as part of this update. If agreed, details of any such collaborations will be included in the methodology chapter published with the guideline.

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			developed to model glycaemic endpoints is methodologically incorrect and does not adequately capture the full nature of the disease. • The diabetes community is unique compared to other therapy areas due to the existence of an independent group of expert health economic modellers. The group is called the MountHood Diabetes Network, who are experts from across academia who collaborate to address several health economic specific modelling issues. • Given NICE plans to use this model for future rapid updates of new medicines, we highly recommend that NICE seek expertise from the MountHood Diabetes Network, to advise on the development of any new model. Given the complexities of diabetes economic modelling we propose NICE commits to an approach which involves external diabetes modelling experts supporting the development and validation of a new health economic model. **Reference** 1. Si L, Willis M, Asseburg C, Nilsson A, Tew M, Clarke P, Lamotte M, Ramos M, Shao H, Shi L, Zhang P, McEwan P, Ye W, Herman W, Kuo S, Isaman D, Schramm W, Sailer F, Brennan A, Pollard D, Smolen H, Leal J, Gray A, Patel R, Feenstra T, Palmer A. Evaluating the Ability of Economic	

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			Models of Diabetes to Simulate New Cardiovascular Outcomes Trials: A Report on the Ninth Mount Hood Diabetes Challenge, Value in Health, Volume 23, Issue 9,2020, Pages 1163-1170, ISSN 1098-3015. doi.org/10.1016/j.jval.2020.04.1832.	
Novo Nordisk	007 – 008	026 – 028 001 – 008	4.We suggest uniformity in wording of the review questions. They currently lack consistency and may confuse. We suggest the second review question reflects the wording of the first review question.	Thank you for your comment. The wording of the draft review questions has been reconsidered, but the original wording has been retained in the scope as these are drafts to illustrate the broad intention of the questions that will be further refined in the review protocols. The review protocols will provide more detailed information as to how the reviews will be carried out and will be publicly available once agreed by the committee.
Novo Nordisk	008	010 – 011	5."Current NICE technology appraisal recommendations will be integrated into the guideline within the clinical context" The intent in this sentence is unclear and requires clarification. Technology appraisals often cover a very targeted review of a medicine whereas guidelines cover medicines sequencing. It is not clear how easily this can be done if the clinical guideline update cannot keep pace with the technology appraisal programme, as it potentially creates the need for a re-evaluation of individual medicines' clinical and cost effectiveness or historically has resulted in a lack of up-to-date review of the clinical and cost effectiveness for some medicines.	Thank you for your comment. We have amended the wording to clarify that the treatments in these appraisals will be included in the comparative analysis that is undertaken. This will allow the treatments to be ordered in a care pathway. NICE is exploring how to integrate technology appraisals into NICE guidelines and will engage with stakeholders regarding any decisions on individual technology appraisals Alongside the work to develop this update, a living guideline database will be created to enable future updates to this topic to be carried out more rapidly, on discrete areas as appropriate. This will enable more dynamic living guidelines

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			Novo Nordisk has several medicines that will become available during this period that are unlikely to be reviewed by the Technology Appraisal programme, how will they fit into the guideline? We recommend that further clarification is needed on the integration of NICE-approved recommendations within this guideline update scope.	to be produced in future in response to new evidence when that is likely to impact on the recommendations.
Novo Nordisk	009	007	6.This scope is counter to NICE 5-year strategy to 'provide dynamic, living guideline recommendations that are useful, useable, and used, and incorporate the latest evidence and newly recommended technologies to help speed up access for patients'. • The timeframe for this update is more than two years and the review scope includes evidence which has never been assessed by NICE, despite being published more than 7 years ago. • Medicines in the GLP-1RA class with significant new data have been available to prescribe in the UK since January 2015 but as their full evidence base has never been reviewed by NICE, recommendations on their use are restricted by the existing 2015 guideline which relies on an evidence base dating back to 2012. • In comparison with all the other classes of medicines for type 2 diabetes, the biggest evidence	Thank you for your comment. It has been agreed that there is a need to update the medicines section of the guideline in full so that all treatments are compared to one another, rather than focussing on a subsection of the pathway. Having a full update will enable the place of the GPR-1RA class in the pathway to be assessed, which would not be possible without comparing to all other treatment options. We acknowledge this will take longer than focussing on a small section, however as part of this work a living guideline database will be produced to enable future updates to be conducted in more rapidly. This is an essential part of the work to ensure that NICE's aim of providing dynamic living guideline recommendations can be achieved on this topic.

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			gap in the guideline relates to the GLP-1RA class. The current proposed timeline would mean these medicines have been available to prescribe for 6 years with no full review by NICE. We propose that this update is organised into two phases whereby the first phase focuses on an accelerated review of the GLP-1 class of medicines and provides recommendations on their use within the existing NG28 guideline and the second phase focuses on building an effective economic model to assess the best individual and combination treatments to include the wider individual and clinical characteristics for people with type 2 diabetes for new medicines now and in the future. This will enable best use of NICE resources as well as publishing new recommendations for treatment within a reasonable timeframe.	
Perspectum Ltd	002	023	Page 002 of the draft scope states "*The draft scope includes people with long term conditions for example … non-alcoholic fatty liver disease"* The draft scope should clarify the spectrum of disease comprised by non-alcoholic fatty liver disease (NAFLD) and what the difference in disease definition means to patients. Non-alcoholic fatty liver disease is spectrum of disease spanning from isolated steatosis or fatty infiltration that is asymptomatic and often benign through to non-alcoholic steatohepatitis (NASH). The risk factors that cause the	Thank you for your comment. The scope provides high level information to inform the broad remit of the update. The specific details of included populations may be included within the evidence reviews and protocols as relevant, but is beyond the level of detail included in the scope.

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			progression from NAFLD to NASH are unclear, and since the progression of the disease is "silent", a diagnosis of NASH is often only made at a late stage of the disease. NASH is an important diagnosis to make, since it is associated with development of cirrhosis, liver cancer (NHS website), and is the fastest growing cause of liver transplants (Pais et al. 2016). References: Pais et al. (2017). NAFLD and transplantation: Current burden and expected challenges. Journal of Hepatology; 65(6): 1245-1257	
Perspectum Ltd	003	009	Page 003 of the draft scope states that the settings that will be covered include "*All settings where NHS-funded care is provided*". **We would like to support this criteria and request that this scope criteria includes NHS Community Diagnostic Centres (CDCs).** Some NHS CDCs are run on behalf of the NHS by external stakeholders, who often provide a more efficient model of care within a community setting. In line with the priorities set by the NHS Long Term Plan, shifting patients away from hospitals and towards community care addresses the huge backlog and long waiting lists associated with acute hospital sites. These CDCs are likely to become increasingly central to the assessment and management of chronic conditions	Thank you for your comment. NHS community diagnostic centres would be covered by the setting for this scope, as they provide NHS-funded care.

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			including T2D. CDCs will improve flow in patient groups and facilitate one stop outpatient assessment and imaging (Richards, 2020), which can be applied to long term conditions including T2D. For example, CDCs are an appropriate setting to perform the nine care processes as well as other non-invasive assessments and tests for other co-prevalent diseases such as NAFLD (Dai et al. 2017; Friedman et al. 2018; Younossi et al. 2019). *References* (1) Dai W. et al. (2017). Prevalence of nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus: A meta-analysis. Medicine, 96(39), e8179–e8179. (2) Friedman S. Neuschwander-Tetri B. Rinella M. and Sanyal A. (2018). Mechanisms of NAFLD development and therapeutic strategies. Nature Medicine, 24(7), 908–922. (3) Richards, M. (2020). Diagnostics: Recovery and renewal. Report of the Independent Review of Diagnostic Services for NHS England. Publication approval reference: PAR242 (4) Younossi et al. (2019) The Global epidemiology of NAFLD and NASH in patients with Type 2 diabetes: a systematic review and met-analysis: JHepatology; 71(4) P793-801.	
Perspectum Ltd	003	017	Page 003 of the draft scope states "..*guideline recommendations will normally fall within licensed*	Thank you for your comment. People with non-alcoholic fatty liver disease has been specified in the list of people to be

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			indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended." There is a 60% co-prevalence of NAFLD and T2D (Dai et al., 2017; Friedman et al. 2018). Meta-analyses have also shown that patients with co-prevalent NAFLD and T2DM are also at higher risk of liver-related outcomes (Wang et al. 2012; Bazick et al. 2015). **We urge NICE to consider the use of medicines off-label in patients living with T2D and NASH overlap.** The evidence outlining the clinical benefit to people with T2D and NASH is growing. Given the significant length of time it will take to complete this guideline update, there will likely be further evidence published to support the use of GLP-1 RAs in these patients. (1) NICE should consider recommending GLP-1 receptor agonists (GLP-1 RAs) in people with T2D and NASH overlap because GLP-1 RAs have demonstrated significant clinical benefit to patients with comorbid T2DM and NASH (Dickson, 2021; Garber et al., 2018). Specifically, studies of semaglutide have shown promise in this cohort: a 72-week study with semaglutide resulted in 59% of patients obtaining NASH resolution without	given specific consideration in section 2.1. The committee will consider population subgroups that they think are relevant to consider as a part of the review question and recommendations when making the protocol. The committee will consider medication and whether recommendations are required for any medicines outside of their licensed use as appropriate.

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			worsening of fibrosis at doses of 0.4mg semaglutide per day vs. 17% on placebo (Newsome et al., 2021). (2) The use of GLP-1 RAs in T2D and NASH overlap is supported by the most recent updates to clinical guidelines using evidence-based recommendations regarding the diagnosis and management of NAFLD and NASH to endocrinologists recommends (R3.31b): "*Clinicians must consider treating diabetes with pioglitazone and/or GLP-1 RAs when there is an elevated probability of having NASH based on elevated plasma aminotransferase levels and noninvasive tests*" This recommendation was supported by evidence graded Grade A, with best level of evidence Level 1. (Cusi et al. 2022). Evidence supporting (1) and (2): Pioglitazone was the first diabetes agent to show efficacy in an early RCT in 55 individuals with prediabetes or diabetes and biopsy-proven NASH (Belfort et al. 2006). A 2016 single-centre study in 101 persons with obesity, and either prediabetes or T2D, confirmed its sustained benefit on glucose and lipid metabolism and NASH over 36 months of follow-up (Cusi et al. 2016). With pioglitazone treatment (45 mg), 58% of individuals achieved the primary outcome of a reduction of at least 2 points in NAS, while 51% had resolution of NASH (treatment difference of 41% and 32% vs placebo, respectively;	

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			both P < .001 vs placebo). There was also improvement in the mean fibrosis score (P=.039) (Cusi et al. 2016). A 2017 meta-analysis of available pioglitazone RCTs in persons with biopsy- proven NASH noted a significant improvement versus placebo for NASH resolution (OR, 3.22; 95% CI, 2.17-4.79; P < .001) and for any stage of fibrosis (OR, 1.66; 95% CI, 1.12-2.47; P = .01), with even greater ORs for the effect on advanced fibrosis (OR, 3.15; 95% CI, 1.25-7.93; P = .01), with similar results for those with and without T2D (Musso et al. 2017). A 2020 incremental cost-effectiveness ratio analysis that added a more recent 2019 study combining pioglitazone with vitamin E confirmed the aforementioned findings (Rind et al. 2020). Studies agree that GLP-1 RAs normalise plasma aminotransferase levels and reduce liver fat content on imaging in individuals with NAFLD (Stefan et al. 2019, Cusi 2019, Patel et al. 2022). A small (n=52) 2016 proof-of-concept RCT suggested that liraglutide improved some features of liver histology in persons with NASH, including delaying fibrosis progression versus placebo (Armstrong et al. 2016). In 2021, a phase 2 RCT compared the doses of 0.1, 0.2, and 0.4 mg of semaglutide daily with placebo in 320 persons with NASH (of whom 230 had stage F2 or F3 fibrosis). Resolution of steatohepatitis was found in 40% of those in the 0.1-mg group, 36% of	

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			those in the 0.2-mg group, 59% of those in the 0.4-mg group, and 17% of those in the placebo group (P < .001 for semaglutide 0.4 mg vs placebo) in the context of significant weight loss (13% in the 0.4-mg group vs 1% in the placebo group) (Newsome et al. 2021). There were no significant between-group differences in the percentage of individuals with an improvement in fibrosis stage, but progression of liver fibrosis was significantly less with the highest dose of the GLP-1 RA (4.9%) versus placebo (18.8%). *References* (1) Bazick et al. (2015). Clinical Model for NASH and Advanced Fibrosis in Adult Patients With Diabetes and NAFLD: Guidelines for Referral in NAFLD. Diabetes Care, 38:1347–1355. (2) Belfort R, Harrison SA, Brown K, et al. A placebo-controlled trial of pioglita- zone in subjects with nonalcoholic steatohepatitis. N Engl J Med. 2006;355(22):2297e2307. (3) Cusi K et al. (2022) American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings. Endocrine Practice; 28: 528-56. (4) Cusi K, Orsak B, Bril F, et al. Long-term pioglitazone treatment for patients with nonalcoholic	

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			steatohepatitis and prediabetes or type 2 diabetes mellitus: a randomized trial. Ann Intern Med. 2016;165(5):305e315. (5) Cusi K. Incretin-based therapies for the management of nonalcoholic fatty liver disease in patients with type 2 diabetes. Hepatology. 2019;69(6): 2318e2322. (6) Dai W. et al. (2017). Prevalence of nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus: A meta-analysis. Medicine, 96(39), e8179–e8179. (7) Dickson, I. (2021). Semaglutide is safe and efficacious for NASH resolution. Nat. Rev. Gastroenterol. Hepatol. 18, 6–6. (8) Friedman S. Neuschwander-Tetri B. Rinella M. and Sanyal A. (2018). Mechanisms of NAFLD development and therapeutic strategies. Nature Medicine, 24(7), 908–922. (9) Garber, A.J. et al. (2018). Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm – 2018 Executive Summary. Endocr. Pract. 24, 91–121. (10) Musso G, Cassader M, Paschetta E, Gambino R. Thiazolidinediones and advanced liver fibrosis in nonalcoholic steatohepatitis: a meta-analysis. JAMA Intern Med. 2017;177(5):633e640.	

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			(11)Newsome, P.N. et al. (2021). A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. N. Engl. J. Med. 384, 1113–1124. (12)Patel Chavez C, Cusi K, Kadiyala S. The emerging role of glucagon-like peptide- 1 receptor agonists for the management of NAFLD. J Clin Endocrinol Metab. 2022;107(1):29e38. (13)Rind DM, Hansen R, Guzauskas G, Beinfeld M, Chapman R, Bradt P, Pearson SD. Obeticholic acid for the treatment of nonalcoholic steatohepatitis with fibrosis: effectiveness and value. Institute for Clinical and Economic Review, July 21,2020. (14)Stefan N, Ha,Ç¨ring HU, Cusi K. Non-alcoholic fatty liver disease: causes, diag- nosis, cardiometabolic consequences, and treatment strategies. Lancet Diabetes Endocrinol. 2019;7(4):313e324. (15)Wang et al. (2012) Increased risk of hepatocellular carcinoma in patients with diabetes mellitus: a systematic review and meta-analysis of cohort studies. Int J Cancer, 130:1639–1648.	
Perspectum Ltd	004	005	Page 004 of the draft scope includes a list of cross-referenced "*Related NICE guidance*". **We request that the NICE guideline NG49 'Non-alcoholic fatty liver disease (NAFLD): assessment and management' is added to this list of related NICE guidance.** NG49 includes several references to patients with T2D including the co-prevalence with NAFLD and the	Thank you this has been added.

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			diagnosis and pharmacological treatment of NAFLD and T2D, and therefore should be cross-referenced accordingly.	
Perspectum Ltd	006	013	Page 006 of the draft scope includes a list of NICE guidelines that will be updated by this guideline. Considering the overlap between T2D and NAFLD, and that this draft scope includes NAFLD as special considerations group, **we request that the NICE guidelines related to NAFLD are added to the list of NICE guidelines that will be updated following this programme.** **(1)** The global prevalence of NAFLD and NASH amongst individuals with T2D is estimated to be 60% and ~37%, respectively (Dai et al. 2017; Friedman et al. 2018; Younossi et al. 2019). This is supported in the NICE NG49 guideline; Recommendation 1.1.1. which states that NAFLD is more common in people who have T2D or metabolic syndrome. (2) Related NAFLD guidelines to be updated should include the NICE guideline NG49 and the guideline In development GID-DG10045 'MRI-based technologies for assessing non-alcoholic fatty liver disease' which makes recommendations on the diagnosis, assessment, and management of non-alcoholic fatty liver disease (NAFLD), including NASH.	Thank you this has been added.

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			References (1) Dai W. et al. (2017). Prevalence of nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus: A meta-analysis. Medicine, 96(39), e8179–e8179. (2) Friedman S. Neuschwander-Tetri B. Rinella M. and Sanyal A. (2018). Mechanisms of NAFLD development and therapeutic strategies. Nature Medicine, 24(7), 908–922. (3) Younossi et al. (2019) The Global epidemiology of NAFLD and NASH in patients with Type 2 diabetes: a systematic review and met-analysis: JHepatology; 71(4) P793-801.	
Perspectum Ltd	007	006	Page 007 of the draft scope states that the economic results "*will be stratified by line of treatment and specific risk groups (for example people with existing cardiovascular disease)*.". In line with the groups of people that NICE has listed in the specific considerations (page 002, line 23), **we request that the specific risk groups that the economic results will be stratified by should include those with NAFLD**.	Thank you for your comment. The groups that are listed for specific consideration apply throughout the guideline evidence reviews and recommendation making and therefore also apply to the economic analyses.
Perspectum Ltd	008	014	Page 008 of the draft scope lists the main outcomes "*that may be considered when searching for and assessing the evidence*". In line with NAFLD being included as a specific considerations group within this NICE scope (page 002, line 23), **we propose that the list of main outcomes (page**	Thank you for your comment. The list of outcomes is not exhaustive, and the committee will consider whether any additional outcomes are required when writing the protocol for the review questions.

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			008, line 014) is extended to include liver related outcomes in addition to cardiovascular and renal outcomes. (1) Meta-analyses have also shown that patients with co-prevalent NAFLD and T2DM are also at higher risk of both liver-related (Wang et al. 2012; Bazick et al. 2015) in addition to non-liver comorbidities, mainly cardiovascular (Targher et al. 2016, Khalid et al. 2020) and renal (Musso et al. 2014; Mantovani et al. 2018). (2) Based on published evidence from drug efficacy trials, from regulatory bodies or from clinical guidelines we propose that the liver related outcomes should include: • Liver related complications and events (including: cirrhosis, decompensation events, MELD score, listing for liver transplant, mortality) (EMA 2018, FDA 2018) • Resolution of NASH without worsening of fibrosis (FDA 2018) • Improvement in fibrosis stage without worsening of NASH (FDA 2018) • Resolution of NASH and improvement in fibrosis (EMA 2018)	

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			• Reduction in liver enzymes or algorithms (ALT, FIB-4 and NFS) (Newsome et al. 2021) • Reduction in liver fat (histological and or imaging) (Marjot et al. 2019, Gastaldelli et al. 2022, Harrison et al 2021) • Reduction in liver disease activity (Imaging biomarkers corrected T1, cT1) (Harrison et al 2020, Harrison et al 2019). Unlike FIB4 or AST and ALT, cT1 biomarker has also been independently associated with major adverse cardiovascular events (Roca-Fernandez et al. 2022). *References* (1) Bazick et al. (2015) Clinical Model for NASH and Advanced Fibrosis in Adult Patients With Diabetes and NAFLD: Guidelines for Referral in NAFLD. Diabetes Care, 38:1347–1355. (2) Committee for Medicinal Products for Human Use. Reflection paper on regulatory requirements for the development of medicinal products for chronic non-infectious liver diseases (PBC, PSC, NASH) [draft]. European Medicines Agency. Published November 15, 2018. Available at: https://www.ema.europa.eu/en/draft-reflection-	

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			paper-regulatory-requirements-development-medicinal-products-chronic-non-infectious. (3) Gastaldelli A, Cusi K, Landó LF, Bray R, Brouwers B, Rodríguez Á. Effect of tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in people with type 2 diabetes (SURPASS-3 MRI): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial. The Lancet Diabetes & Endocrinology. 2022 Jun 1;10(6):393–406. (4) Harrison SA, Ruane PJ, Freilich BL, Neff G, Patil R, Behling CA, et al. Efruxifermin in non-alcoholic steatohepatitis: a randomized, double-blind, placebo-controlled, phase 2a trial. Nat Med. 2021 Jul;27(7):1262–71 (5) Harrison SA, Rossi SJ, Paredes AH, Trotter JF, Bashir MR, Guy CD, et al. NGM282 Improves Liver Fibrosis and Histology in 12 Weeks in Patients With Nonalcoholic Steatohepatitis. Hepatology. 2020 Apr;71(4):1198–212 (6) Harrison SA et al. (2019) Resmetirom (MGL-3196) for the treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet. 394(10213); (2012-2024) (7) Khalid et al. (2020) Increased cardiovascular events and mortality in females with NAFLD: a meta-analysis. Am J Cardiovasc Dis, 10:258–271.	

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			(8) Loomba R, Ratziu V, Harrison S. (2021) Expert Panel Review to Compare FDA and EMA Guidance on Drug Development and Endpoints in Nonalcoholic Steatohepatitis. Gastroenterology; 162(3) (9) Marjot et al. (2019). Sodium-glucose cotransporter 2 inhibition does not reduce hepatic steatosis in overweight, insulin-resistant patients without type 2 diabetes. JGH open an open access J Gastroenterol Hepatol 2019;4:433–440 (10) Mantovani et al. (2018) Nonalcoholic fatty liver disease increases risk of incident chronic kidney disease: A systematic review and meta-analysis. Metab - Clin Exp, 79:64–76. (11) Musso et al. (2014) Association of non-alcoholic fatty liver disease with chronic kidney disease: a systematic review and meta-analysis. PLoS Med, 11:e1001680–e1001680. (12) Newsome P, Francque S, Harrison S, et al. Effect of semaglutide on liver enzymes and markers of inflammation in subjects with type 2 diabetes and/or obesity. Aliment Pharmacol Ther 2019;50:193–203 (13) Roca-Fernandez, A, et al. (2022). NAFLD is associated with significantly higher risk of cardiovascular outcomes in the absence of fibrosis. EASL Summit	

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			(14)Targher et al. (2016) Non-alcoholic fatty liver disease and risk of incident cardiovascular disease: A meta-analysis. J Hepatol, 65:589–600. (15)US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Noncirrhotic nonalcoholic steatohepatitis with liver fibrosis: developing drugs for treatment. Guidance for industry [draft guidance]. US Food and Drug Administration. Published December 2018. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/noncirrhotic-nonalcoholic-steatohepatitis-liver-fibrosis-developing-drugs-treatment. Wang et al. (2012) Increased risk of hepatocellular carcinoma in patients with diabetes mellitus: a systematic review and meta-analysis of cohort studies. Int J Cancer, 130:1639–1648.	
Primary Care Cardiovascular Society	008	017 – 030	2.6 - The focus needs to be on these elements, looking at diabetes holistically from the patient perspective and reflecting the overall risk: benefit profile. The downgrading of GLP1s in previous guidance puts NICE at odds with international recommendations and may lead to unnecessary combat between medicines management and clinicians. Clinicians are already prescribing GLP1s and will continue to do so, making NICE guidance appear less relevant to real life practice	Thank you for your comments. Consideration of treatment sequencing is included within the scope of the update. The update of these reviews (based on outcomes listed in 2.6 and those agreed by the committee) may change these recommendations based on the clinical and economic evidence.

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Royal College of Ophthalmologists	008	025	Please ensure worsening of diabetic retinopathy is considered under serious adverse events as we feel it is important is not left out.	Thank you for your comment. The outcome list in the scope is not exhaustive and the committee will discuss whether additional outcomes need to be added when writing the protocols for the review questions.
Royal College of Physicians	General	General	The RCP is grateful for the opportunity to respond to the above consultation. We would like to endorse the response submitted by the Association of British Clinical Diabetologists (ABCD)	Thank you for your comment.
Ruddington Medical Centre	General	General	This scope is against the principle of NICE 5-year strategy to 'provide dynamic, living guideline recommendations that are useful, useable, and used, and incorporate the latest evidence and newly-recommended technologies to help speed up access for patients'. This would not be considered as a 'live document'	Thank you for your comment. It has been agreed that there is a need to update the guidelines on medicines for management of type 2 diabetes in full to ensure the recommendations produced are based on all of the best available evidence. As part of this work a living guideline database will be produced to enable future updates to be conducted in more rapidly. This is an essential part of the work to ensure that NICE's aim of providing dynamic living guideline recommendations can be achieved on this topic.
Ruddington Medical Centre	015	014 – 015	1.7.1 cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost). [2015, amended 2022] This is incorrect as lowest acquisition cost among SGLT2 inhibitors is Ertugliflozin which does not have any evidence in its impact on MACE in patients with Type2 Diabetes and established Cardiovascular disease. In February 2022, using	Thank you for your comment. This recommendation is within the scope of this update and may change based on the updated clinical and economic evidence.

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			ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off-label and lacks data to support this.	
Ruddington Medical Centre	017	008 – 009	1.7.9If they have chronic heart failure or established atherosclerotic cardiovascular disease, offer an SGLT2 inhibitor with proven cardiovascular benefit.- What would be options available if patient has contra-indications to use of SGLT2 inhibitors, intolerant to SGLT2 inhibitors- I do believe GLP1-mimetics should be mentioned here as they have cardiovascular benefit as well	Thank you for your comments. Consideration of appropriate pharmacological treatment options for different population subgroups is included within the scope of the update. The update of these reviews may change these recommendations based on the clinical and economic evidence.
Ruddington Medical Centre	021	010	1.7.19 For adults with type 2 diabetes, if dual therapy with metformin and another oral drug has not continued to control HbA1c to below the person's individually agreed threshold for further intervention consider either: • triple therapy by adding a DPP-4 inhibitor, pioglitazone or a sulfonylurea or an SGLT2 inhibitor for people who meet the criteria in I do believe GLP1 mimetic need mention here as one of choices as its potential to reduce HBAIC is far greater than DPP4 inhibitor or Pioglitazone. It does independent of metformin or any other combination. It should be offered at the onset of triple therapy especially where greater magnitude of HBAIC reduction is required rather than after other triple therapy has not be tolerated or ontraindicated..	Thank you for your comments. Consideration of treatment sequencing is included within the scope of the update. The update of these reviews may change these recommendations based on the clinical and economic evidence.
Sanofi	General	General	Insulin therapies should be included in this draft scope to provide a more holistic consideration of type-2 diabetes care. As part of an analysis of cost and clinical effectiveness it may be prudent to include timely initiation of insulin	Thank you for your comment. Following consideration of stakeholder comments NICE intend to commission a review of insulins as a separate piece of work. In this update, insulin will remain as a comparator intervention only.

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			therapy upon disease progression and/or failure of OADs and GLP-1 therapy in lowering HbA1c	
Sanofi	General	General	Should Insulin therapy be included in a future review - Alongside a clinical and cost-effective review of data, a personalised approach to insulin management should be considered, taking into account the pharmacokinetic and pharmacodynamic profiles of the available insulins and the matching of the dose and timing to an individual's requirements.	Thank you for your comment. Following consideration of stakeholder comments NICE intend to commission a review of insulins as a separate piece of work. In this update, insulin will remain as a comparator intervention only.
Sanofi	General	General	The use of flash and continuous glucose monitoring in line with previous NICE guidance should be included in relation to Insulin use. This may be particularly relevant to the at-risk groups who are given special consideration within this draft scope.	Thank you for your comment. Glucose monitoring is not within the scope of this guideline update, which is focussed on the use of antidiabetic medicines apart from insulin.
Sanofi	007	012	The draft scope does not specifically mention insulins and consider insulin therapies. Given the scope - including those with frailty, cognitive impairment, learning disabilities where insulins with lower hypoglycaemia and longer duration of action may be beneficial (and in those with youth onset T2DM where longer action and stability of profile may be of benefit), we feel that the guideline should include more details on insulin therapies for such groups including second generation basal insulins.	Thank you for your comment. Following consideration of stakeholder comments NICE intend to commission a review of insulins as a separate piece of work. In this update, insulin will be included as a comparator intervention only.
The Dirac Foundation	General	General	I do not see mention of the need to monitor T2D for increased pancreatitis risk. T2D patients need increased monitoring by lipase/amylase for pancreatitis type 2 diabetic patients in view of risk factor for pancreatitis given type 2	Thank you for your comment. The focus of this update is medicines for management of diabetes. Other sections of the guideline, such as management of complications, are not being updated at this time.

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			diabetes due to bidirectional causal effects pancreatitis -> T2D, T2D -> pancreatitis (e.g. by gallstones). At least, the pancreatitis should order tests in cases of any indefinite lower back or abdominal pain in a type 2 diabetic patient. Aune D, Mahamat-Saleh Y, Norat T, Riboli E. Diabetes mellitus and the risk of pancreatitis: A systematic review and meta-analysis of cohort studies. Pancreatology. 2020, Aune D, Vatten LJ. Diabetes mellitus and the risk of gallbladder disease: A systematic review and meta-analysis of prospective studies. J Diabetes Complicat. 2016;30(2):368-73. Cao C, Yang S, Zhou Z. GLP-1 receptor agonists and pancreatic safety concerns in type 2 diabetic patients: data from cardiovascular outcome trials. Endocrine. 2020; Gonzalez-perez A, Schlienger RG, Rodríguez LA. Acute pancreatitis in association with type 2 diabetes and antidiabetic drugs: a population-based cohort study. Diabetes Care. 2010;33(12):2580-5. Hartz JC, De ferranti S, Gidding S. Hypertriglyceridemia in Diabetes Mellitus: Implications for Pediatric Care. J Endocr Soc. 2018;2(6):497-512. Mikó A, Farkas N, Garami A, et al. Preexisting Diabetes Elevates Risk of Local and Systemic Complications in Acute Pancreatitis: Systematic Review and Meta-analysis. Pancreas. 2018;47(8):917-923. Singh S, Chang HY, Richards TM, Weiner JP, Clark JM, Segal JB. Glucagonlike peptide 1-based therapies and risk	

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			of hospitalization for acute pancreatitis in type 2 diabetes mellitus: a population-based matched case-control study. JAMA Intern Med. 2013;173(7):534-9. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. Lancet. 2016;387(10027):1513-1530.	
University Hospitals of North Midlands NHS Trust	General	General	1.7.18 - GLP-1 therapy should be considered earlier when thinking about improving treatment post SGLT-2 and Biguanides. This is something that should be included earlier with the improvements in weight and CV disease risks.	Thank you for your comments. Consideration of treatment sequencing is included within the scope of the update. The update of these reviews may change these recommendations based on the clinical and economic evidence.
University of Liverpool	008	014 – 030	The SCORE-IT study developed a core outcome set for use in trials for the management of type 2 diabetes in adults. This study had input from health professionals, researchers, and people with type 2 diabetes. We have reviewed the core outcome set against the outcomes included in the scope and whilst many are included, sometimes under a broader outcome, there are three core outcomes that are not specifically included. These are: • Visual deterioration or blindness - if someone's eyesight gets worse or if they have loss of vision including blindness. • Neuropathy - damage to the nerves caused by high glucose. This can lead to tingling and pain or	Thank you for your comment. The outcomes listed in the scope were those defined in the stakeholder workshops and scoping process as the key outcomes likely to be included in the reviews. The outcome list in the scope is not exhaustive and the committee will discuss whether additional outcomes need to be added when writing the protocols for the review questions. As part of this work a living guideline database will be produced to enable future updates to be conducted in more rapidly. This database will include a broader set of outcomes, and the SCORE-IT core outcome set (including the outcomes specified) has been considered for deciding any outcomes that may need extracting for this.

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			numbness in the feet or legs. It can also affect bowel control; stomach emptying and sexual function. • Having gangrene or having an amputation of the leg, foot or toe. We feel that these outcomes should be included as they are considered core by health professionals, researchers and people with type 2 diabetes. It would be helpful to understand how the outcomes in the scope were chosen and if there is a reason that these outcomes cannot be included. SCORE-IT final report- http://dx.doi.org/10.1136/bmjdrc-2019-000700	
University of Liverpool	008	017	The SCORE-IT study identified both quality of life and activities of daily living as core outcomes. Will the scope recommend that health related quality of life includes a measure of activities of daily living?	Thank you for your comment. The definition of outcomes will be discussed with the committee when defining the protocols for the review questions.
University of Liverpool	008	025	The SCORE-IT study specifically included three core outcomes that might be considered serous adverse events. We feel that these should be specifically listed: How often someone is admitted to hospital because of their diabetes. Hyperglycaemic emergencies (to include diabetic ketoacidosis and hyperosmolar hyperglycaemic state).	Thank you for your comment. The outcome list in the scope is not exhaustive and the committee will discuss whether additional outcomes need to be added when writing the protocols for the review questions. The definition of outcomes will be discussed with the committee when defining the protocols for the review questions.

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			Side effects of treatment- any unwanted effects of the treatment.	
University of Liverpool	008	028	We identified both glycaemic control and hyperglycaemia as core outcomes in the SCORE-IT study. HbA1c is a measure of overall glycaemic control but may not reflect the frequency of hyperglycaemia and associated symptoms. Will hyperglycaemia also be considered under this outcome?	Thank you for your comment. The definition of outcomes will be discussed with the committee when defining the protocols for the review questions.