Type 2 diabetes in adults: management - SGLT2 inhibitors for chronic kidney disease (update)

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AstraZeneca	Evidence Review	225	General	Section I.3.2 of the evidence review details that treatment effects of SGLT2 inhibitors on eGFR and log (ACR) were considered in the model as well as cardiovascular and mortality risk improvements via hazard ratios (HR). However, no information is provided related to the consideration of weight lowering effects and glycaemic improvements offered by SGLT2 inhibitors. In cost effectiveness evaluation, however, it is mandatory to consider all treatment benefits when full drug acquisition costs are applied. Having considered only incremental benefits represents a biased approach that is likely to underestimate the cost effectiveness. This is especially relevant since weight lowering effects of SGLT2 inhibitor represent a strong driver in cost effectiveness evaluations due to the consideration of body mass index (BMI) related utility decrements (e.g. in NG28, a utility decrement of -0.0061 was assumed per 1 unit increase in BMI above 25kg/m^2).[33] Regarding glycaemic improvements, we acknowledge the reduced glycaemic efficacy of SGLT2 inhibitor at low levels of eGFR. However, we believe that the consideration of residual efficacy would be an appropriate approach. For example, for dapagliflozin, the residual glucose lowering efficacy in patients with mild (eGFR between 60 and 90 ml/min) and moderate (eGFR between 30 and 59 ml/min) decline in renal function was estimated at 78% and 57%.[34] This approach to modelling attenuating glycaemic efficacy has been ratified by clinical and health economic experts during the development of a novel T2DM cost-effectiveness model by AstraZeneca.	Thank you for your comment. Recommendations for the use of SGLT2 inhibitors in people with Type 2 diabetes without CKD are covered in the current guideline update on management of Type 2 diabetes, which is supported by an economic model that includes treatment effect on weight and glycaemic control. The focus of this review was to consider whether SGLT2 inhibitors are associated with any additional renal protection benefits in the population with Type 2 diabetes and CKD. The committee did not identify weight or glycaemic control as key outcomes for the assessment of additional benefits of SGLT2 inhibitors in this population and so they were not included in the review protocol or economic model. The SPCs for licensed SGLT2 inhibitors note reduced glucose lowering effects in people with CKD and diabetes. The effects on renal outcomes were considered more important for this population than the effect on weight, though cardiovascular outcomes were incorporated which may be influenced by the effect on weight indirectly. Further to this, the economic analysis was based on a model developed by Willis et al. which did not include weight and glycaemic control as baseline characteristics or treatment outcomes. It would therefore not have been feasible to incorporate these outcomes into the analysis.
AstraZeneca	Evidence Review	229	General	In Section I.3.4.2 of the evidence review it states that the cost-effectiveness model developed by NICE excludes the long-term costs of dialysis, in line with the approach taken in the previous	Thank you for your comment. The base-case analysis has been updated to include dialysis costs. This has not changed the cost-effectiveness of SGLT2 inhibitors in this population.

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				NICE CKD guideline and in the NICE guideline on renal replacement therapy. This assumption was made in the context of assessing the cost effectiveness of dialysis treatment compared to no dialysis. Since dialysis represents an essential intervention and no treatment would result in death, total costs of dialysis and a one-year life extension (with a quality-of-life weight of 0.7) in the dialysis arm would be compared to zero costs and QALYs in the non-dialysis arm. It is therefore highly unlikely that dialysis would be considered cost effective by usual NICE criteria. While we understand the rationale for excluding dialysis costs in the above context, we believe that such considerations cannot be transferred to cost effectiveness evaluations of therapies such as SGLT2 inhibitors that are proven to slow down the progression of CKD and prevent or delay the onset of dialysis.[1] Dialysis costs have been included in the cost-effectiveness model submitted for the ongoing STA of dapagliflozin for treating CKD [ID3866], and this approach has been accepted by the Evidence Review Group (ERG) and NICE technical team. As such, there appears to be no justification for excluding dialysis costs from the present economic evaluation. This is inconsistent with previously accepted approaches and fails to capture significant cost savings that may be achieved on an NHS system level. The exclusion of dialysis costs therefore represents a biased approach that may have led to a considerable underestimation of the cost effectiveness associated with SGLT2 inhibitors.	
AstraZeneca	Evidence Review	General	General	AstraZeneca understands that the health economic model used in this review was adapted from the model used in Willis et al. (2021) (i.e. canagliflozin cost effectiveness model) and that model inputs were derived from data from the CREDENCE trial.[35] The adapted model was used to support the committee's consideration of the cost effectiveness of SGLT inhibitors as a	The baseline risk equations in the economic model were developed using individual patient data from CREDENCE by developers who had access to this data source. Since we do not have access to IPD from the dapagliflozin clinical trials, we are unable to develop similar equations from these sources, as this would be required to undertake the regression analysis and

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				class for adults with CKD and T2DM. However, AstraZeneca believes that data from dapagliflozin clinical trials should be used to inform health economic modelling for UK guideline recommendations given the breadth and strength of the evidence in both patients with and without T2DM and the existing indications for dapagliflozin for the treatment of T2DM, HFrEF and CKD in the UK, whilst less trial data is available for canagliflozin across fewer patient populations and it is licenced only for the treatment of T2DM.[8]	select the patient population relevant to this review question. Nevertheless, we would expect that risk equations developed from each source would be relatively consistent, once the appropriate (DKD-specific) populations were accounted for. Data from the dapagliflozin clinical trials were included in the evidence review and were used to inform the treatment effect of SGLT2 inhibitors on key endpoints.
AstraZeneca	Guideline	002	General	On page 2 of the Guideline, in the "Related guidance" section, it states the following: "We are developing a technology appraisal on canagliflozin for treating chronic kidney disease in people with type 2 diabetes." According to the NICE website and supported by confirmation from the relevant NICE team, the technology appraisal of canagliflozin for the treatment of CKD in people with T2DM has been suspended and will in due course be terminated.[32] A significant new therapeutic indication was not granted for canagliflozin in June 2020, and instead the SmPC was simply updated with renal outcomes data from the CREDENCE trial and no new indication was issued. There is, however, an ongoing NICE technology appraisal of dapagliflozin for the treatment of CKD, which considers both patients with and without T2DM. It would be more appropriate to reference this ongoing appraisal here and remove the mention of the technology appraisal for canagliflozin which is no longer going ahead.	Thank you for your comment. This has now been corrected to refer to the ongoing technology appraisal of dapagliflozin for the treatment of CKD: https://www.nice.org.uk/guidance/indevelopment/gid-ta10808
AstraZeneca	Guideline	General	General	**SUMMARY OF KEY COMMENTS**	Thank you for your comment. We have responded to the individual points below.

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				AstraZeneca would like to thank NICE for its commitment to advancing clinical care for patients with chronic kidney disease (CKD). AstraZeneca also continues to be fully committed to advancing care for patients across the spectrum of cardiovascular (CV), renal and metabolic conditions. With this shared ambition and commitment to improve the lives of patients with these long-term conditions in mind, AstraZeneca welcomes the opportunity to respond to the draft sodium glucose co-transporter 2 (SGLT2) inhibitors for CKD guideline update (GID-NG10246). AstraZeneca agrees with many of the recommendations set out by the committee in the draft SGLT2 inhibitors for CKD guideline (GID-NG10246), particularly the decision to recommend the use of SGLT2 inhibitors for patients with CKD and type 2 diabetes mellitus (T2DM) with an albumin creatine ratio (ACR) over 30 mg/mmol and who meet the criteria in the marketing authorisation. However, we strongly feel that there are areas of the draft SGLT2 inhibitors for CKD guideline update which represent significant missed opportunities to further improve the lives of patients and address areas of inequality of care. The main areas of concern include: 1. The proposed recommendation to only "consider" SGLT2 inhibitors in people with T2DM and an ACR of between 3 and 30 mg/mmol does not reflect the evidence of clinical benefit for SGLT2 inhibitors in this patient population, nor how cost-effective these therapies are when all relevant costs are considered.	

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				The large body of evidence now available supports the strengthening of this to "offer" instead of "consider". 2. Currently, there is no consideration given in either the recently published CKD guideline (NG203) nor this SGLT2 inhibitors for CKD guideline for the use of SGLT2 inhibitors to treat CKD in patients **without** diabetes. There remains an extremely high unmet medical need in this sizeable patient population and compelling clinical evidence now exists that demonstrates the efficacy and safety of an SGLT2 inhibitor in these patients. Whilst AstraZeneca appreciates that patients with CKD without comorbid T2DM are outside the scope of the current guideline update, we urge the NICE Guideline Committee to initiate a separate consultation on this topic to consider the available evidence and create clear written recommendations for the use of SGLT2 inhibitors in CKD patients without T2DM that can be fully incorporated into NG203. a. Renal benefits have been observed for the SGLT2 inhibitor class in their respective cardiovascular outcomes trials (CVOTs), as well as in the DAPA-CKD trial (which was stopped early upon the recommendation of the independent data monitoring committee [IDMC] due to overwhelming efficacy). This trial was the first SGLT2 inhibitor trial to assess the efficacy and safety of an SGLT2 inhibitor in patients with CKD irrespective of the diabetes status. The results of this trial demonstrated a clinically meaningful, statistically significant,	

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				improvement in renal outcomes which were consistent irrespective of diabetes status. As such, there is no clinical rationale for excluding a recommendation for patients with CKD without comorbid T2DM and such a lack of recommendation may drive inequalities of care for patients across the UK. 3. The requirement for angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) to be titrated to the highest dose that patients can tolerate may unnecessarily delay initiation of an SGLT2 inhibitor in patients with CKD and T2DM, and clarity is required for clinicians initiating first-line treatment for patients newly presenting with CKD and T2DM that ACE inhibitor/ARB titration should not delay treatment initiation with SGLT2 inhibitors. As an alternative, we propose that the recommendations should be updated to simply state that an SGLT2 inhibitor should be offered in addition to an ACE inhibitor or ARB therapy, unless contraindicated or not tolerated. The evidence for these concerns and suggested changes to the recommendations are outlined in detail in the sections below, as well as some additional more specific concerns. AstraZeneca respectfully requests the Committee to consider these important additions with a view to improving the speed and quality of care for patients with CKD in the UK.	
AstraZeneca	Guideline	General	General	**Concern** The wording of the recommendation for SGLT2 inhibitors in people with T2DM and an ACR of between 3 and 30 mg/mmol (30-300 mg/g; [microalbuminuria; A2]) does not reflect the	Thank you for your comment. It is NICE style to use 'offer' and 'consider' to reflect the relative strength or quality of the underpinning evidence and the trade-off between benefits and harms. The box above section 1.1 contains a link to Making

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				strength of the evidence available for the efficacy of SGLT2 inhibitors in this population, and should be updated to "offer" instead of "consider" to reflect the large body of available evidence for SGLT2 inhibitors in this population. We further feel that the wording currently suggested by NICE for recommendations which have some residual uncertainty is unclear and doesn't provide enough guidance to the clinical community to inform their prescribing decisions. We strongly feel that the wording used by NICE should be consistent with that used by KDIGO, who base their wording on the strength of the available evidence as guided by GRADE. Specifically, recommendations which have strong evidence are worded as '*we recommend*', whilst those with weaker or conditional evidence are worded as '*we suggest*' rather than 'consider', as currently used throughout the recently published NICE guidelines. Rationale Data from the DAPA-CKD and DECLARE-TIMI 58 trials provide evidence of a consistent treatment effect for dapagliflozin irrespective of ACR. Firstly, the DAPA-CKD trial demonstrates a significant treatment effect of dapagliflozin across a range of renal and CV outcome measures in patients with an ACR of 20–500 mg/mmol (approximately 200 to 5000 mg/g).[1] A pre-specified subgroup analysis of the primary endpoint investigated patients with ACR above and below 100 mg/mmol (approximately 1,000 mg/g) and showed no significant between-group difference [This text was identified as confidential and has been removed], indicating consistency of treatment effect across the ACR spectrum included in the trial.[1] In the Committee's discussion and interpretation of the evidence the following comment is made regarding the evidence available	decisions using NICE guidelines which explains this. It is also outlined in our guidelines manual how we assess and critically appraise the strength of evidence including the use of GRADE. As outlined in the committee discussion section of the evidence review, a 'consider' recommendation was made for the A2 population because of the greater uncertainty in the clinical and cost effectiveness evidence for this group. When stratified by ACR, the hazard ratio for the renal composite outcome in the A2 population is 0.87 but the 95% confidence intervals cross the line of no effect (0.63-1.19). This is shown to be similar in other outcomes in the A2 population including CV 3-point MACE but also the individual outcomes of all-cause mortality, and CV death. The evidence you highlight from Declare-TIMI trial refers to a composite outcome not included in our review. A renal composite (end stage kidney disease, doubling of serum creatinine and renal death) was included as it matched the definition of CKD progression in the review protocol and was commonly reported across studies. Other renal composite outcomes were not included in the review. Individual outcomes were favoured over composites because composite outcomes combine data across outcomes with very different clinical consequences and costs. Individual outcomes were used for economic modelling and were preferred for decision making. Additionally, we do not think that the absence of an interaction effect across groups should be interpreted as evidence for the equivalence of effect, because a lack of interaction effect could arise because of uncertainty in the effect estimates as well as true equivalence across groups. In relation to the meta-analysis you highlight (Cardiovascular and Kidney Outcomes in Patients With Type 2 Diabetes – McGuire 2021), it includes data from trials that included people with and

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				from DAPA-CKD "*The DAPA-CKD study recruited participants with an ACR of greater than 20 mg/mol which was between the A2 and A3 categories. However, the median ACR for the group with type 2 diabetes (that met the inclusion criteria for this review) was 116 mg/mol (IQR 53 to 23), and so most participants in this trial would have fallen into the A3 category*." The Committee goes on to conclude that "*There was less certainty in the clinical evidence of benefit and evidence for cost effectiveness for an A2 population (people with ACR between 3 and 30 mg/mol), therefore a weaker 'consider' recommendation was made for this group*." AstraZeneca would like to highlight the further clinical evidence available to support the efficacy of dapagliflozin in the A2 population (ACR 3–30 mg/mmol [30-300 mg/g]) available from the DECLARE-TIMI 58 trial (N=17,160), which investigated dapagliflozin in patients with T2DM and established atherosclerotic CVD or multiple CV risk factors.[2] The majority of patients enrolled in this trial had normoalbuminuria (ACR <3 mg/mmol [<30 mg/g]; n=11,644 [69.1%]) or microalbuminuria (ACR 3-30 mg/mmol [30-300 mg/g]; n=4,030 [23.9%]).[2] The positive treatment effect of dapagliflozin on the renal endpoint without CV death (sustained decline of ≥40% in estimated glomerular filtration rate [eGFR] to less than 60 mL/min per 1.73m^2, end-stage kidney disease [ESKD], or death from renal causes) was consistent irrespective of ACR category. Dapagliflozin reduced the risk of this secondary outcome by 47% (HR 0.53; 95% CI: 0.43–0.66; p-value<0.0001) in the overall population, with the treatment effect consistent across all ACR categories (A1 vs A2 vs A3; p-value for interaction=0.30) and clear evidence of benefit in the group of patients in the A2 population (3-30 mg/mmol [30-300 mg/g]; HR 0.59; 95% CI: 0.39–0.87).[2]	without CKD. Our review specifically included studies (or subgroup analyses from larger studies) that included people with both CKD and type 2 diabetes. Therefore this study was not included in the review. The economic analysis has now been updated to include the cost of dialysis in the base case and all scenarios. The addition of these costs does not alter the conclusion of the analysis. When the unpublished subgroup results come out, this recommendation may change if it strengthens the evidence. This is likely to be considered in future updates of the guideline.

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				Although the p value for interaction fell below 0.05 for the cardiorenal endpoint of ≥40% eGFR decline, ESKD, renal death or CV death in a subgroup analysis by ACR category (A1 vs A2 vs A3; p value for interaction=0.02), this could be a chance finding as these analyses have not been adjusted for multiple testing.[2] Regardless of the p value for interaction, a clear treatment benefit was observed in the ACR 3-30 mg/mmol (30-300 mg/g) subgroup (HR=0.73; 95% CI 0.57-0.94).[2] Furthermore, results from a "DECLARE$_{CKD}$" dataset of patients enrolled in the DECLARE-TIMI 58 trial who meet the criteria for a formal diagnosis of CKD (i.e. those with an eGFR ≥60 ml/min/1.73m² and uACR of ≥30 mg/mmol [≥3 mg/g]). **[This text was identified as confidential and has been removed].** Additionally, whilst not all SGLT2i's are currently licenced for the treatment of adults with CKD, a recently published meta-analysis evaluating the efficacy on cardiovascular and kidney outcomes across all four available SGLT2i's in patients with T2DM demonstrated a statistically significant improvement in kidney outcomes at a class level (HR 0.62 [95% CI: 0.56—0.70]). **[This text was identified as confidential and has been removed].** *Health economic evidence* The justification provided by NICE for the recommendation to "consider" the use of SGLT2 inhibitors in patients with an ACR 3–30 mg/mmol (30 mg/g–300 mg/g) was based on results of economic modelling showing that SGLT2 inhibitors were still likely to be both more effective and cost saving in people with a baseline ACR of 3–30 mg/mmol (30–300 mg/g) compared with standard treatment. However, there was more uncertainty around the clinical and cost effectiveness in this group than in people	

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				with macroalbuminuria (A3; ACR >30 mg/mmol [300 mg/g]). The exploratory subgroup analysis conducted by NICE to investigate the cost-effectiveness of patients with ACR 3-30 mg/mmol (30–300 mg/g) only included the treatment effect on all-cause mortality and HF, as no other relevant published studies were identified in the clinical review (DECLARE-TIMI 58 data were excluded since not all enrolled patients had an eGFR<60 **[This text was identified as confidential and has been removed].** The remaining outcomes in the model were based on evidence for patients with macroalbuminuria (A3; ACR>30 mg/mmol [>300 mg/g]). Furthermore, the baseline characteristics of this patient subgroup are assumed to be the same as in the base case analysis. These issues are stated as major limitations of the model and clearly contribute to the uncertainty referenced by NICE in the rationale for recommendation SGLT2 inhibitors are only "considered" in this groups rather than offered. As outlined above, AstraZeneca feels there is additional clinical evidence for SGLT2 inhibitors from the DAPA-CKD trial as well as the DECLARE-TIMI 58 trial that has not been considered in the NICE subgroup analysis to evaluate populations with microalbuminuria (A2; ACR 3-30 mg/mmol [30-300 mg/g]).[1, 2] Data from these studies have presented a consistent treatment effect of dapagliflozin in patients T2DM and comorbid CKD across the range of ACR categories and provide data for the outcomes included in the NICE cost-effectiveness model. AstraZeneca have conducted economic evaluations to assess the cost effectiveness of dapagliflozin in patients with lower ACR (<20 mg/mmol [<200 mg/g]) in order to provide the Committee with further evidence to support the cost-effectiveness of SGLT2 inhibitors in this patient population and increase the certainty on this topic. Details of the economic evaluation are briefly explained	

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				below but further information can be found in the summary modelling report that is submitted alongside this consultation response. The "Broad Population Model" used for these analyses was originally developed to estimate cost-effectiveness outcomes in a population below the threshold for the ACR inclusion criteria of the DAPA-CKD trial criteria (see summary modelling report for more information). The model was developed to support the ongoing NICE technology appraisal of dapagliflozin for the treatment of CKD and uses data from the DAPA-CKD trial as well as DECLARE-TIMI 58 to assess the health economic impact associated with the introduction of dapagliflozin versus placebo in patients with elevated ACR (≥20 mg/mmol [≥200 mg/g]) and low ACR (<20 mg/mmol [<200 mg/g]). The model was applied to compare dapagliflozin vs. standard of care (SOC) in patients with T2DM and low ACR (<20 mg/mmol [<200 mg/g]). Evidence for the treatment effect of dapagliflozin in patients with low ACR was sourced from a pooled dataset that combined a subset of DECLARE-TIMI 58 patients who had CKD (eGFR ≤60 ml/min/1.73m^2]) and DAPA-CKD patients who had a lower ACR. Additional modelling inputs (cost inputs, utility values, time horizon etc.) were adopted from the economic modelling approach as described in the NICE evidence review to support the review question. One adaptation made to the NICE modelling inputs was the cost of dialysis, which the NICE modelling team has set at zero in the current model. AstraZeneca feels this is an extremely important cost to include in the model since delays to ESKD, at which point the costs of dialysis are commonly incurred, is an important outcome for the SGLT2 inhibitor class (see comment 8 below for more details).	

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				[This table was identified as confidential and has been removed]. This analysis did not include the beneficial treatment effects of dapagliflozin on weight lowering and glucose control (further details related to this limitation are provided in comment 6 of this consultation response). Therefore, the outcomes presented above can be considered as conservative estimates of the cost effectiveness. <u>Summary</u> Overall, these data support a stronger recommendation to "offer"' an SGLT2 inhibitor in patients with a ACR of 3–30 mg/mmol (30–300 mg/g; microalbuminuria). Based on an analysis using Clinical Practice Research Datalink (CPRD) and QOF data, currently in England there are approximately [redacted] (people with CKD and T2DM who have an ACR between 3 and 30 mg/mmol (30-300 mg/g) who could potentially benefit from treatment with dapagliflozin.[4, 5] The use of effective new CKD therapies as early in the disease pathway as possible to prevent irreversible kidney damage and avoid a range of costly CV and renal events is a major priority for the NHS,[6] and every effort should be made to achieve this. Provision of effective treatment as early in the disease process as possible is particularly critical for people from lower socioeconomic groups and many Black, Asian and minority ethnic communities, who are more likely to develop CKD and are also at increased risk of fast progression to more severe stages of the disease compared with those in higher socioeconomic groups or a White ethnic background.[7] It is therefore important ensure and encourage early usage of SGLT2 inhibitor to prevent disease progression in	

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				these disproportionately affected patients groups. Recommendations reflecting the full population in which clinical value has been observed in clinical trials, and in which cost-effectiveness has been demonstrated beyond any reasonable doubt, would ensure all patients covered by the trial evidence from DAPA-CKD and DECLARE-58 TIMI, including those with less severe disease as reflected by their ACR category, can benefit from effective therapies. Furthermore, the MHRA, EMA and FDA have all granted a marketing authorisation for the use of dapagliflozin to treat adults with CKD, without any restrictions based on ACR, irrespective of diabetes status.[8, 9] The MHRA (and independently, the EMA) determined that the available evidence was sufficient to robustly demonstrate the renal efficacy of dapagliflozin in patients outside of the DAPA-CKD trial, including in patients with low ACR. The MHRA clinical assessor stated the following: **[This text was identified as confidential and has been removed].** In addition, the UK Kidney Associated recently published their draft guideline on the use of SGLT2i's in adults with kidney disease, within which they make the following recommendation for patients with T2DM: *'In people with T2DM and an eGFR ≥25 mL/mim/1.73m^2:* *(a) We suggest initiation SGLT2i in those with a uACR of ≥25 mg/mmol attributable to a non-diabetic cause* *(b) We suggest initiating SGLT2i to modify cardiovascular risk in those with an eGFR 25—60 mL/min/1.73m^2 and uACR <25 mg/mmol, recognising effects on glycaemic control will be limited'*	

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				Therefore, the UKKA make a strong recommendation for the use of SGLT2i at a uACR lower than that currently suggested by NICE. As the UKKA clinical guidelines are accredited by NICE we urge the NICE committee to reconsider the strength of the recommendation made in patients with a lower uACR. **AstraZeneca requests the Committee to consider reflecting the full breadth of evidence with the following recommendation (proposed changes in red):** 1.1.3 For adults with type 2 diabetes and CKD, ~~consider~~ **offer** an SGLT-2i, in addition to an ARB or an ACEi (titrated to highest dose that they can tolerate), if: • ACR is between 3 and 30 mg/mmol AND • They meet criteria in the marketing authorisation (including relevant eGFR thresholds) Monitor for volume depletion and eGFR decline.	
AstraZeneca	Guideline	General	General	As we mentioned in our response to the NICE CKD guideline consultation [NG203], AstraZeneca has become aware of considerable concern amongst nephrologists over the Committee's recommendation to monitor eGFR decline following the initiation of an SGLT2 inhibitor in patients with T2DM. The mechanism of action of SGLT2 inhibitors causes an initial decline in eGFR, due to a reduction in glomerular pressure following vasoconstriction in the afferent arteriole induced by SGLT2 inhibition. In the long term, this helps to protect the glomerulus from damage caused by the high intra-glomerular pressure common to patients with CKD.[10] eGFR subsequently increases again over several months and henceforth the SGLT2 inhibitor treatment slows progressive eGFR decline as compared with individuals not taking SGLT2 inhibitors. In the DAPA-CKD	Thank you for your comment. In response to comments from stakeholders pointing out that the monitoring requirements may differ between SGLT2 inhibitors, we have removed the sentence about monitoring for eGFR decline and volume depletion from the recommendation. Practitioners should follow advice in the Summary of Product Characteristics and the BNF on monitoring according to the particular SGLT2 inhibitor being prescribed. These resources should always be consulted when prescribing medicines, as set out at the start of the recommendations section in the guideline (see: making decisions using NICE guidelines)

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				trial, a greater initial drop in eGFR was observed with dapagliflozin vs. placebo (-3.97(± 0.15) vs. –0.82 ± 0.15 ml/minute/1.73 m^2) after two weeks of treatment. Thereafter, the annual change in the mean eGFR was smaller with dapagliflozin than with placebo (–1.67 ± 0.11 vs. –3.59 ± 0.11 ml/minute/1.73 m^2, respectively), giving a between-group difference of 1.92 ml/minute/1.73 m^2 per year (95% CI, 1.61 to 2.24).[1] Similar results have been consistently demonstrated in the clinical trials of other SGLT2 inhibitors that measured change in eGFR.[1, 11-14] In post-hoc analyses of the EMPA-REG and CREDENCE trials, it has been shown that even in patients experiencing a high initial drop in eGFR (>10%) this does not reduce the SGLT2 inhibitor induced risk reduction for CV and renal outcomes,[15] and has no impact on AE rate.[15, 16] Clinical expert opinion is that conducting an eGFR test in the weeks following SGLT2 inhibitor initiation is not informative and may cause unnecessary concern that could result in termination of a proven renal-protective treatment if the clinician isn't aware of the mechanism of action for this drug class. Furthermore, unlike ACE inhibitor/ARB treatment, SGLT2 inhibitors do not cause increased potassium and therefore do not have the same requirement for monitoring in the weeks following initiation. eGFR monitoring should therefore not be recommended in this context. This is further supported by the draft UK Kidney Association (UKKA) Clinical Practice guideline which recommends that "individuals initiated on an SGLT2 inhibitor **do not routinely require an early assessment of renal function or potassium following initiation of treatment**", because it is important that the early changes in eGFR that occur following initiation of SGLT2 inhibitors do not routinely result in withdrawal of SGLT2 inhibition when people are likely to gain significant benefit from these therapies.[7]	

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				As such, AstraZeneca respectfully request that NICE consider updating both recommendation 1.1.2 and 1.1.3 to reflect this (proposed change in red): Monitor for volume depletion ~~**and eGFR decline**~~	
AstraZeneca	Guideline	General	General	Concern The current draft guideline update does not provide any recommendations for adults with CKD **without T2DM.** AstraZeneca acknowledges that patients with CKD without T2DM are not considered within the scope of this guideline update, and urge NICE to initiate a separate consultation as soon as possible to rectify this clear gap in an otherwise comprehensive and up to date guideline. AstraZeneca believes there to be approximately [redacted] patients with CKD without T2DM in England who could now benefit substantially from treatment with an SGLT2 inhibitor.[4, 5] This is a patient population with a very high unmet need and limited treatment options available, and there is now strong RCT evidence available for the clinical efficacy of dapagliflozin in this population from the DAPA-CKD trial. The use of SGLT2 inhibitors to prevent or delay progression to ESKD and CV events consistently across all CKD populations aligns with the prevention-focussed NHS Long Term Plan,[6] and represents a major opportunity to reduce the clinical and economic burden of kidney disease which has not been possible with current standard care therapies. Not recommending the use of SGLT2 inhibitors in people without T2DM creates a significant challenge in terms of equity of access for all patients with CKD, and this is also expected to be	Thank you for your comment. NICE is currently conducting a technology appraisal to evaluate dapagliflozin for chronic kidney disease. This appraisal is not limited to people with type 2 diabetes, and includes people with CKD without diabetes. This guidance is due to be published in January 2022 (for details see: https://www.nice.org.uk/guidance/indevelopment/gid-ta10808).

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				misaligned with the outcome of the forthcoming NICE single technology appraisal (STA) of dapagliflozin for the treatment of CKD patients with and without T2DM [ID3866]. AstraZeneca also believes inclusion of a link to the recommendation in the technology appraisal guidance would be **insufficient** and there is a clear need for written recommendations of SGLT2 inhibitors in the CKD guidelines and the treatment pathway. This would ensure all recommendations for CKD can be easily found in one place to avoid potential confusion. **Rationale and Evidence** Unmet Need Patients with CKD without T2DM have a very high unmet need, with limited innovative treatment options available to modify the course of disease. Current standard of care for CKD in people without T2DM comprises individually optimised therapy, which may include ACE inhibitors and ARBs to reduce proteinuria.[17, 18] Treatment with ACE inhibitors or ARB therapy alone can leave patients at high risk of disease progression and the risk of mortality remains unacceptably high,[19-21] with some 40–45,000 premature deaths in the UK every year due to CKD.[22] The cost of CKD to the NHS in England was estimated to be £1.44–1.45 billion in 2009–2010, of which over 50% was spent on renal replacement therapy required for just 2% of the CKD population.[23] Every effort should be made to reduce the risk of premature death as well as CV and renal events through evidence-based recommendations. The use of SGLT2 inhibitors to prevent or delay progression to ESKD and CV events such as hospitalisation for heart failure (hHF) consistently across all CKD populations aligns with the prevention-focussed NHS Long Term	

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				Plan,[6] and represents a major opportunity to reduce the clinical and economic burden of kidney disease which has not been possible with current standard care therapies. **Clinical Trial Evidence** Compelling clinical evidence of the efficacy of SGLT2 inhibitors in patients with CKD without T2DM is available from the DAPA-CKD trial (N=4,304), the first clinical trial of an SGLT2 inhibitor to demonstrate efficacy on mortality and renal outcomes in patients with CKD with and without T2DM treated with guideline-based background therapies (ACE inhibitors and ARBs).[1] DAPA-CKD was stopped early upon the recommendation from the IDMC due to overwhelming efficacy, and dapagliflozin met the primary and all secondary endpoints.[1, 24] Compared with placebo, dapagliflozin demonstrated a: • **39%** relative risk reduction (RRR) for the primary endpoint (≥50% sustained decline in eGFR, ESKD, renal and CV death; HR: 0.61; 95% CI: 0.51–0.72; p<0.001) • **44%** RRR in eGFR decline, ESKD or renal death (HR: 0.56; 95% CI: 0.45–0.68; p<0.001) • **29%** RRR in death from CV causes or hHF (HR: 0.51; 95% CI: 0.34–0.76; nominal p=[redacted]) • **31%** RRR in all-cause mortality (HR: 0.69; 95% CI: 0.53–0.88; p=0.004) o Dapagliflozin is the first treatment to demonstrate a treatment benefit on all-cause mortality in patients with CKD in a renal outcomes trial **Critically, a consistent treatment effect was observed across all major pre-specified subgroups including patients with**	

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				and without T2DM.[1, 24] The following results were observed in patients **with** and **without T2DM**:[24] • 36% and 50% RRR for the primary endpoint, respectively (p-value for interaction=0.24) • 43% and 49% RRR in the kidney-specific composite outcome, respectively (p-value for interaction=0.80) • 30% and 21% RRR in the composite of cardiovascular death or hHF (p-value for interaction=0.11) • 26% and 48% RRR for all-cause mortality (p-value for interaction=0.85) At baseline, 32% percent (n=1,398) of the DAPA-CKD cohort did **not** have T2DM at baseline, making DAPA-CKD the largest CKD study in patients without T2DM to date.[1, 24] AstraZeneca estimates that [redacted] of CKD patients in England do not have concomitant T2DM.[4] Dapagliflozin represents a major advancement over current recommended therapies for a large (approximately [redacted] patients), under-studied population with a high unmet clinical need.[4, 5] Consistency of Treatment Effect Across Populations There is strong and consistent evidence across multiple patient populations that the treatment effect of SGLT2 inhibitors on both renal and CV outcomes is independent of diabetes status, and that the mechanism of action of SGLT2 inhibitors is not modified by baseline HbA1c, further supporting the use of SGLT2 inhibitors in non-diabetic patients with CKD. In addition to the DAPA-CKD trial, both the DAPA-HF trial of dapagliflozin and the EMPORER-REDUCED trial of empagliflozin have shown consistent benefit regardless of diabetes status.[11, 25, 26] The DAPA-HF trial, which assessed dapagliflozin treatment for heart failure with reduced	

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				ejection fraction (HFrEF), included 4,744 patients of which 58.2% did not have comorbid T2DM. The results showed that dapagliflozin reduced the rate of worsening HF (hospitalisation or an urgent visit resulting in intravenous therapy for HF) or death from CV causes by 26% (95% CI: 0.65–0.85), with results consistent regardless of diabetes status [redacted][25, 27] The results for the secondary endpoint of worsening kidney failure were also consistent between the non-diabetic (HR 0.67; 95% CI: 0.30–1.49) and diabetic groups (HR 0.73; 95% CI 0.39–1.34; p-value for interaction=0.86).[28] In February 2021 NICE published a recommendation for the use of dapagliflozin to treat symptomatic HFrEF in individuals with and without T2DM based on the strength of evidence from one trial with similar patient numbers to the DAPA-CKD trial.[29] In the EMPOROR-Reduced trial empagliflozin treatment reduced the relative risk of the composite renal endpoint by 58% (HR, 0.42; 95% CI: 0.19–0.97) in patients without diabetes, and by 47% (HR 0.53; 95% CI: 0.31–0.90) in patients with diabetes, with no significant treatment by-diabetes interaction (p-value for interaction=0.65).[30] <u>Cost-Effectiveness of SGLT2 inhibitors in patients with CKD and without T2DM</u> **[This text was identified as confidential and has been removed].** In addition, a modelling approach developed with clinical expert input **from [This text was identified as confidential and has been removed].** uses treatment effect data from the CKD subgroup of DECLARE-TIMI 58 to support the effectiveness of dapagliflozin in subgroups of patients with CKD and without	

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				T2DM across a wider range of ACR categories than was included in DAPA-CKD. *Health economic evidence* AstraZeneca has conducted an economic evaluation to assess the cost effectiveness of dapagliflozin in non-T2DM patients with CKD using the Broad Population Model described above (details of the economic evaluation can be found in the summary modelling report that is submitted alongside this consultation response). The model was applied to compare dapagliflozin vs. standard of care (SoC) in patients with non-T2DM and CKD and ACR <20 mg/mmol or ≥20 mg/mmol [<200 mg/g or ≥200 mg/g]. Dapagliflozin treatment effects in the group of non-T2DM patients were sourced from a combined dataset of DAPA-CKD and DECLARE-TIMI 58 (further details provided in the summary modelling report). Additional modelling inputs (cost inputs, utility values, etc.) were adopted from the economic modelling approach as described in the NICE evidence review. As mentioned above, one adaptation made to the NICE modelling inputs was the cost of dialysis, which the NICE modelling team has set at zero. AstraZeneca feels this is an extremely important cost to include in the model since delays to end-stage renal disease, at which point the costs of dialysis are commonly incurred, is an important outcome for the SGLT2 inhibitor class (see comment 8 below for more details). A summary of outcomes using the Broad Population Model for non-T2DM patients with CKD and low ACR (<20 mg/mmol [<200 mg/g]) is presented in the table below. **[This table was identified as confidential and has been removed].**	

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				A summary of outcomes using the Broad Population Model for patients without T2DM, with CKD and high ACR (≥20 mg/mmol [≥200 mg/g]) is presented in the table below. **[This table was identified as confidential and has been removed].** As with the analysis conducted in patients with T2DM that we present above, this evaluation did not include the beneficial treatment effects on weight and glucose control, suggesting that the presented outcomes can be considered as conservative estimates of the cost effectiveness. Wider Context to the Recommendations Based on the strength of the clinical evidence outlined above and the unmet need in individuals with CKD without diabetes, dapagliflozin received a marketing authorisation for the treatment of CKD in patients with and without comorbid T2DM from the MHRA. The results of the STA for dapagliflozin for the treatment of CKD is due to be published in January 2022, and the reimbursement recommendation for dapagliflozin is expected to include patients with and without comorbid T2DM. Initiation of a separate consultation for patients with CKD without T2DM on the basis of the DAPA-CKD trial results, recent approval of dapagliflozin for the treatment of patients with CKD regardless of diabetes status and pending reimbursement decision for dapagliflozin in CKD is in line with the commitment to "living" guidelines expressed in the NICE five-year strategy and would ensure that the NICE CKD guidelines are outdated for as short a time as possible. **Written recommendations and inclusion in the treatment algorithm of this important patient**	

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				population are crucial to minimise confusion within the clinical community, ensuring treatment recommendations for CKD are not presented across several separate documents which are challenging for healthcare professionals to navigate and align. Summary We respectfully request the NICE Guideline Committee to carefully consider the newly available evidence summarised above and to **initiate a separate consultation on the use of SGLT2 inhibitors in patients with CKD without T2DM, to generate a clear written recommendation for this important patient population.**	
AstraZeneca	Guideline	General	General	Concern The inclusion of the wording "in addition to an ARB or an ACE inhibitor (**titrated to the highest dose that they can tolerate**)" in recommendations 1.1.2 and 1.1.3 risks delaying initiation of SGLT2 inhibitor therapy during ACE inhibitor/ARB up-titration, which typically requires 2–6 appointments over 4–6 weeks.[31] Furthermore, significant clinical benefit of SGLT2 inhibitor treatment was observed in both the DAPA-CKD trial and the DECLARE-TIMI 58 trial, despite 3% and 19.7% of the enrolled trial population not receiving an ACE inhibitor or an ARB at baseline.[1, 2] AstraZeneca also understands from UK clinicians that many patients with CKD are not fully titrated on ACE inhibitor/ARB treatment by the time they are referred to secondary care, whereas SGLT2 inhibitors should be initiated in the primary care setting to gain the maximum possible treatment benefit to prevent deterioration and prolong time to costly dialysis.[31]	Thank you for your comment. As per the NICE guideline on chronic kidney disease, ACE or ARB inhibitors are considered first line treatment for people with an ACR above 3mg/mmol, with the addition of a an SGLT2 inhibitor dependent on ACR levels as outlined in the recommendation. The intention is that ACE/ARB inhibitors should be prescribed first at the maximum tolerated licensed dose and SGLT 2 inhibitors only prescribed if the person still meets the ACR criteria outline in the recommendations. We have reworded the recommendation to make this point clearer. The committee made this recommendation because the majority of participants in the trials considered in the review (including DAPA-CKD and DECLARE-TIMI) were taking ARBs/ACE inhibitors on entry to the trial.

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				Clarity is required for clinicians initiating first-line treatment for patients newly presenting with CKD and T2DM that ACE inhibitor/ARB titration should not delay treatment initiation with SGLT2 inhibitors. As such, AstraZeneca respectfully request that NICE consider updating both recommendation **1.1.2** and **1.1.3** to reflect this (proposed change in red): "in addition to an ARB or an ACE inhibitor ~~(titrated to the highest dose that they can tolerate)~~, if:"	
BAME Health Collaborative (BHC)	Guideline	General	General	We are very supportive of this important recommendation to use SGLT-2 inhibitors for the prevention of progression of CKD and cardiovascular events in people with diabetic and non-diabetic CKD.	Thank you for your comment.
BAME Health Collaborative (BHC)	Guideline	General	General	We acknowledge the recognition of limited evidence in ethnic minority groups and recommend ongoing robust real world data collection to establish efficacy and safety data in these groups, with a clear plan for timely updates communicate to all prescribers and users.	Thank you for your comment. The committee made a research recommendation on the effectiveness of SGLT2 inhibitors in particular ethnic groups as they noted the lack of evidence in this area. The committee recommended that a randomised trial (or subgroup analysis of existing trials) should be conducted to assess the effectiveness of SGLT2 inhibitors in different ethnic groups because they thought that this study design would provide the best evidence on effectiveness.
BAME Health Collaborative (BHC)	Guideline	General	General	However, we strongly recommend that ethnic minority groups should not be excluded from use of these agents whilst these data are collected, as they are very high risk for both CKD and CVD and restriction of use could be very detrimental.	Thank you for your comment. We agree that ethnic minority groups are not excluded from the use of SGLT2 inhibitors and people of all ethnicities are included in the recommendations that have been proposed. The research recommendation does not mean that ethnic minority groups are excluded from the main recommendations in any way.
BAME Health Collaborative (BHC)	Guideline	General	General	Communication about these issues for ethnic minority patients should be transparent and co-written with people from their communities to ensure the language provides appropriate reassurance.	Thank you for your comment. We agree that tailored communication is important and also have published guidance on Community engagement: improving health and wellbeing and reducing health inequalities

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Bayer plc	Evidence review (Appendix I)	226	Table I.5	Bayer would like to clarify that, in the case of those patients with both CKD and T2D, the probability of having a transplant is most likely lower in comparison to the overall CKD population. We are not aware of any data on the number of kidney transplants specific to diabetic patients. During recent clinical consultations conducted by Bayer, UK experts highlighted that patients with T2D are often ineligible for transplantation due to their numerous comorbidities. In contrast, relatively high probabilities of transplantation have been considered in the model used for assessment of SGLT2 inhibitors within this consultation. These probabilities are higher than included originally in the CREDEM-DKD model (Willis 2020). Overestimation of the probability of transplant leads to an underestimation of the treatment benefits resulting from delaying CKD progression and dialysis. This underestimation exists because patients in the model are staying on dialysis shorter than they would in real world clinical practice.	Thank you for your comment. We are also not aware of any data on the number of kidney transplants specific to people with diabetes. We have conducted an additional scenario analysis with lower rates of transplantation (as per the original model) which found that the conclusions of the analysis were unchanged with the application of these alternative rates, and have updated our evidence review to acknowledge this limitation.
Bayer plc	Evidence review (Appendix I)	227	005	Bayer believe that the estimate of mortality included in the cost-effectiveness model is underestimated. Mortality has been modelled based on the extrapolation of data from the CREDENCE study. This study was not designed to provide mortality estimates for this population in the long term. On the other hand, there is a body of data in published literature confirming a significant impact of CKD progression on the increased risk of death. We believe that using this data together with a country specific mortality available for general population is a more appropriate approach. Bayer have performed such an analysis, with the result being a lower number of life years. This approach is more conservative, as the underestimation of	Thank you for your comment. The mortality equations in the economic model were derived from a published analysis of CREDENCE trial data, and provides a framework that is consistent with the other risk equations, most importantly with regards to the patient population. In the absence of access to individual patient data, we were unable to explore and validate alternative extrapolation forms for mortality to be used in the model. We acknowledge the potential validity of the suggested approach, whereby CKD-adjusted UK-specific lifetables could be used. However, the model predicts outcomes on a per-patient basis. Life tables provide mortality estimates on a population level, and it would not be appropriate to include this in the model as it would not capture individual variation in mortality rates and they would not correlate with the predicted risk for other

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				mortality in the model is related to an overestimation of the health benefits related to the life extension.	outcomes (I.e. a patient with slow CKD progression would have the same mortality rate as patients with a faster CKD progression). Since the model's risk equations capture a non-linear relationship between characteristics and outcomes, and between an outcome and other outcomes, it would not be appropriate to use an central estimate of mortality, averaged over all patients generated by the model. The committee were aware of the limitations in the modelling of mortality and that this increased uncertainty in the results and that it made it challenging to conduct additional mortality-related scenario analyses, but that the conclusions of the analysis remained valid.
Bayer plc	Evidence review (Appendix I)	229	General	Bayer considers that not including the cost of dialysis in the cost-effectiveness model is inappropriate, as this is an important component of the management of CKD. Omission may lead to a misleading estimate of cost-effectiveness of interventions for CKD. It is well accepted that NHS investment in a health care technology ought to consider the full stream of future health care costs related to that intervention. This is reflected in the NICE reference case, as follows (see 5.5.7): *"Costs related to the condition of interest and incurred in additional years of life gained as a result of treatment should be included in the reference-case analysis. Costs that are considered to be unrelated to the condition or technology of interest should be excluded."* Rather than aligning the base-case analyses with the above, the decision to exclude downstream dialysis costs was made to align with NICE guidelines including NG107. In NG107 all patients	Thank you for your comment. The base-case analysis has been updated to include dialysis costs. This has not changed the cost-effectiveness of SGLT2 inhibitors in this population.

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				were on dialysis and indeed any additional year of life gained was related to high incremental costs. These incremental costs were mainly due to dialysis itself and not the treatment being assessed. Bayer recognises the issues associated with the exclusion of unrelated dialysis costs in such a population, when as stated, the opportunity cost during these additional years of life are real and associated with an accepted intervention. Whilst Bayer can appreciate the rationale provided in 1.2.6.1 of NG107, the situation is distinctly different to that considered in this consultation. SGLT2 inhibitors are considered as an intervention that address the residual risk of renal deterioration prior to a patient requiring dialysis. Therefore, the argument made in NG107 to exclude unrelated costs only applies to those patients who would initiate SGLT2i whilst receiving dialysis. In contrast, most patients with CKD who are considered suitable within the draft guideline will start treatment with SGLT2 inhibitors at an earlier stage of CKD with the intention to avoid or delay dialysis. The delaying or avoidance of dialysis by SGLT2i use is associated with downstream savings that are related to the intervention. The exclusion of such costs when assessing the cost-effectiveness of a new technology could be considered as inequitable. This is true, insofar as dialysis is associated with significant reductions in both patient and carer quality of life. To underestimate the cost-savings associated with interventions designed to avoid and delay dialysis may bias decision making in CKD towards interventions that extend life on dialysis rather than those that delay the time to dialysis. Should this be true, then the application of this approach to costing may be at variance with NICE guidance principle 9 'aim to reduce health inequalities'.	

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				Assessment of SGLT2 inhibitors and other treatments aiming to delay dialysis should be made according to the NICE reference case.	
Bayer plc	Evidence review (Appendix I)	235	Table I.12	We are surprised by the savings estimated in the economic model for the management of patients in stages CKD 4 and 5. We believe, these savings to be overestimated and unreflective of real-world clinical practice. SGLT2 inhibitors are being evaluated within this consultation to address the residual risk of progression to dialysis. In principle, therefore, the time spent in any earlier CKD stage than dialysis itself should be longer i.e. more expensive. One would, therefore, expect additional expenses, rather than savings related to CKD management before dialysis. Such a result as that observed appears counterintuitive. Moreover, when we have analysed a scenario that includes the cost of dialysis, the model results showed lower savings on dialysis than management of earlier CKD stages. This too is counter intuitive taking into account the aim of using SGLT2 inhibitors and the difference between unit costs of management of patients before and after starting dialysis. The CREDEM-CKD model has been validated against clinical data for its estimates related to starting dialysis, however, we are not aware of any validation performed for this model in terms of its results for earlier stages of CKD which seem to be a key driver of the model results. Therefore, we are concerned that there exists an important degree of uncertainty in the model results.	Thank you for your comment. We believe the cost savings for CKD 4 and 5 and for dialysis to be an artifact of the ten-year time horizon used in the economic model. Since CKD progression is slower in patients on SGLT2 inhibitors, then at ten years there are fewer patients who reached CKD stages 4 and 5 or who received dialysis. To some extent, the expectations of greater CKD management costs before dialysis are captured, as you can see that these are greater CKD 1 and 2 for SGLT2 inhibitors. When the model scenario with a lifetime time horizon is considered, the savings between the two groups are reduced, in line with expectations. As discussed in our evidence review, the committee acknowledged the shorter time horizon as a limitation of the model but felt that results based on the 10-year time horizon were more robust given the challenges in projecting the long-term effectiveness of SGLT2 inhibitors, and that cost-effectiveness of SGLT2 inhibitors was sufficiently represented by this analysis. The conclusion of the analysis with a lifetime horizon was also consistent with that with the 10-year horizon.
Boehringer Ingelheim Ltd	General	General	General	Boehringer Ingelheim welcomes the opportunity to comment on these guidelines. We are pleased to see NICE recognising the latest developments in the treatment of patients with T2DM and	Thank you for your comment.

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				CKD; in particular we support the proposed changes to the treatment pathway and the inclusion of SGLT2s. We feel as though these changes have the potential to benefit both patients and the NHS system. We hope that these additions are recognised in the final NICE guideline	
Boehringer Ingelheim Ltd	Guideline	004	008	We feel that it would be best to add the following: In patients with type 2 diabetes mellitus, the glycaemic efficacy of SGLT2s are dependent on renal function. Glucose lowering efficacy is likely absent with severe renal impairment. Additional glucose lowering agents should be considered in patients with type 2 diabetes and severe renal impairment. For dose adjustment recommendations according to eGFR or CrCL refer to individual SmPCs[1-8]. 1. Jardiance (Empagliflozin) 10mg Summary of product characteristics found at: Jardiance 10 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 2. Jardiance (Empagliflozin) 10mg Summary of product characteristics found at: Jardiance 25 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 3. Forxiga (Dapagliflozin) 5mg Summary of product characteristics found at: Forxiga 5 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 4. Forxiga (Dapagliflozin) 10mg Summary of product characteristics found at: Forxiga 10 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)	Thank you for your comment. We acknowledge that there are many factors to take into account when prescribing SGLT2 inhibitors. All practitioners are expected to refer to the Summary of Product Characteristics and the British National Formulary for when prescribing medicines, which contain information about cautions for use, such as the one outlined here. This update evaluated the benefits of SGLT2 inhibitors for their cardiovascular and renal benefits independent of glycaemic control. We have incorporated the recommendations into the NICE guideline on type 2 diabetes in the section on diabetic kidney disease. We have added the following note to the section on drug treatments for blood glucose lowering: 'See the section on diabetic kidney disease for guidance on SGLT2 inhibitors for people with type 2 diabetes and chronic kidney disease.

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				5. Steglatro (Ertugliflozin) 5mg Summary of product characteristics found at: Steglatro 5 mg Film-Coated Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 6. Steglatro (Ertugliflozin) 15mg Summary of product characteristics found at: Steglatro 15 mg Film-Coated Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 7. Invokana (Canagliflozin) 100mg Summary of product characteristics found at: Invokana 100 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 8. Invokana (Canagliflozin) 300mg Summary of product characteristics found at: Invokana 300 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)	
Boehringer Ingelheim Ltd	Guideline	004	014	For the SGLT2's there are no recommendations to monitor for eGFR decline nor additional renal function monitoring for these agents other than routine renal function testing according to the patients CKD status [1-8] No recommendation to monitor eGFR decline except for those at risk of volume depletion [3, 4, 7, 8] Monitoring of renal function should be: 1) Prior to initiation of SGLT2 (except Dapagliflozin) 2) Periodically during treatment of SGLT2 (at least annually)	Thank you for your comment. In response to comments from stakeholders pointing out that the monitoring requirements may differ between SGLT2 inhibitors, we have removed the sentence about monitoring for eGFR decline and volume depletion from the recommendation. Practitioners should follow advice in the Summary of Product Characteristics and the BNF on monitoring according to the particular SGLT2 inhibitor being prescribed. These resources should always be consulted when prescribing medicines, as set out at the start of the recommendations section in the guideline (see: making decisions using NICE guidelines)

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				3) Also prior to initiation of any concomitant medicinal product that may have a negative impact on renal function [1-4, and 7, 8] Ertugliflozin- additionally has asked for more renal monitoring when eGFR below 60 ml/min/1.73 m^2 or a CrCl below 60 ml/min [5, 6]. Initial increases in creatinine and initial decreases in estimated glomerular filtration rates in patients treated with SGLT2s are generally transient during continuous treatment or reversible after drug discontinuation of treatment. [1-8] If sentence is to be kept, suggest that the guidelines may need to give further clarification as to the time points of when to check the eGFR post initiation of treatment , and demonstrate what is 'expected' and 'acceptable' and what isn't. 1. Jardiance (Empagliflozin) 10mg Summary of product characteristics found at: Jardiance 10 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 2. Jardiance (Empagliflozin) 10mg Summary of product characteristics found at: Jardiance 25 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 3. Forxiga (Dapagliflozin) 5mg Summary of product characteristics found at: Forxiga 5 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 4. Forxiga (Dapagliflozin) 10mg Summary of product characteristics found at: Forxiga 10 mg film-coated	

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Boehringer Ingelheim Ltd	Guideline	005	004	For the SGLT2's there are no recommendations to monitor for eGFR decline nor additional renal function monitoring for these agents other than routine renal function testing according to the patients CKD status. No recommendation to monitor eGFR decline except for those at risk of volume depletion Monitoring of renal function should be: 1) Prior to initiation of SGLT2 (except Dapagliflozin) 2) Periodically during treatment of SGLT2 (at least annually)	Thank you for your comment. In response to comments from stakeholders pointing out that the monitoring requirements may differ between SGLT2 inhibitors, we have removed the sentence about monitoring for eGFR decline and volume depletion from the recommendation. Practitioners should follow advice in the Summary of Product Characteristics and the BNF on monitoring according to the particular SGLT2 inhibitor being prescribed. These resources should always be consulted when prescribing medicines, as set out at the start of the recommendations section in the guideline (see: making decisions using NICE guidelines)

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				3) Also prior to initiation of any concomitant medicinal product that may have a negative impact on renal function Ertugliflozin- additionally has asked for more renal monitoring when eGFR below 60 ml/min/1.73 m^2 or a CrCl below 60 ml/min. Initial increases in creatinine and initial decreases in estimated glomerular filtration rates in patients treated with SGLT2s are generally transient during continuous treatment or reversible after drug discontinuation of treatment. If sentence is to be kept, suggest that the guidelines may need to give further clarification as to the time points of when to check the eGFR post initiation of treatment , and demonstrate what is 'expected' and 'acceptable' and what isn't. 1. Jardiance (Empagliflozin) 10mg Summary of product characteristics found at: Jardiance 10 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 2. Jardiance (Empagliflozin) 10mg Summary of product characteristics found at: Jardiance 25 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 3. Forxiga (Dapagliflozin) 5mg Summary of product characteristics found at: Forxiga 5 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) 4. Forxiga (Dapagliflozin) 10mg Summary of product characteristics found at: Forxiga 10 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)	

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Boehringer Ingelheim Ltd	Guideline	007	009	Regarding the use of SGLT2 for baseline ACR of less than 3 mg/mol, the recommendation would be for NICE to pool or appraise the results of CANVAS[1] (canagliflozin) and DELIGHT[2] studies (Dapagliflozin) that presented ACR < 3 median values for ACR to support an indication for SGLT2 effectiveness. This is whilst there is pending data/ further evidence from studies such as EMPA-KIDNEY [3] References 1. Neuen BL, Ohkuma T, Neal B, Matthews DR, De Zeeuw D, Mahaffey KW, Fulcher G, Desai M, Li Q, Deng H, Rosenthal N. Cardiovascular and renal outcomes with canagliflozin	Thank you for your comment. It is true that the highlighted trials present evidence for people with an ACR of <3 mg/mmol. However, these data were not included in our review because participants may or may not have had CKD. The NICE guideline on CKD indicates that a diagnosis of CKD can be made on the basis of either a lowered eGFR (<60ml/min/1.73m2) or a raised ACR (>3 mg/mmol) or both. The population for the CANVAS and DELIGHT studies were not limited to those with CKD and so its not possible to determine whether those in the ACR<3 mg/mmol subgroup met the criteria for having CKD or not, and so these data were not included.

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				according to baseline kidney function: data from the CANVAS Program. Circulation. 2018 Oct 9;138(15):1537-50 2. Pollock, Carol; Stefansson, Bergur; Reyner, Daniel; Rossing, Peter; Sjostrom, C David; Wheeler, David C; Langkilde, Anna Maria; Heerspink, Hiddo J L; Albuminuria-lowering effect of dapagliflozin alone and in combination with saxagliptin and effect of dapagliflozin and saxagliptin on glycaemic control in patients with type 2 diabetes and chronic kidney disease (DELIGHT): a randomised, double-blind, placebo-controlled trial.; The lancet. Diabetes & endocrinology; 2019; vol. 7 (no. 6); 429-441 3. EMPA – KIDNEY (The Study of Heart and Kidney Protection With Empagliflozin) (not yet published) found at EMPA-KIDNEY (The Study of Heart and Kidney Protection With Empagliflozin) - Full Text View - ClinicalTrials.gov	
Boehringer Ingelheim Ltd	Guideline	007	028	Please add in after 'number of cardiovascular events' : end stage renal events and reduce risk of death from CV and renal causes 1 1. DAPA-CKD - Dapagliflozin in Patients with Chronic Kidney Disease | NEJM	Thank you for your comment. We have amended the wording to include end stage renal events as suggested. We have not incorporated the additional wording about reducing risk of death as this point was specifically about future cost savings.
Diabetes UK (with clinical input from the ABCD and UKKA)	Guideline	004	001	We strongly support shared decision making and agree that treatment with SGLT2i should be initiated only after ensuring adequate understanding of the patient in the following aspects: • Discuss individualised benefits of taking SGLT2i	Thank you for your comment. We are aware that shared decision making is important. NICE has a guideline on shared decision making which gives information on how shared decision making should be put into practice.

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				• Common side effects • Uncommon side effects • Foot care • Drink plenty of fluids to avoid dehydration unless you have been told to restrict fluids by your healthcare professionals due to heart or kidney problems or some other reason Reference: https://pubmed.ncbi.nlm.nih.gov/33179277/ When initiating someone with type 2 diabetes onto an SGLT2i, other glucose lowering medications that may cause hypoglycaemia, such as insulin and sulphonylureas, should be reviewed and consideration should be given to reduce the dose when SGLT2i is started, particularly if the individual's HbA1c is at target when the treatment is being initiated. If the insulin requirement reduces considerably, one should be cautious of a higher risk of developing DKA. The healthcare professional should review diuretic and anti-hypertensive therapy periodically if hypertension improves or if there is postural hypotension.	We acknowledge that there are many factors to take into account when prescribing SGLT2 inhibitors. All practitioners are expected to refer to the summary of product characteristics and the British National Formulary for when prescribing medicines, which contain information about cautions for use, such as the ones outlined here.
Diabetes UK (with clinical input from the ABCD and UKKA)	Guideline	004	001	It is vital to select the right patient for SGLT2i in order to achieve health benefits without precipitating complications like DKA. We recommend the information in our joint position statement and recommendations with the Association of British Clinical Diabetologists (ABCD) for non-diabetes specialists on the use SGLT2i in people with type 2 diabetes (January 2021) on this matter be included in this guideline.	Thank you for your comment. This update focused on providing recommendations on the use of SGLT2 inhibitors for people with type 2 diabetes and CKD. We recognise that there is other useful information available for practitioners, but this was not the focus of this update. The review protocol for this update, which was agreed with the guideline committee, asked us to review RCT evidence. As the information you suggest including does not fall

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				We do not recommend signposting to this information but including it in the actual guidance. Non-specialist healthcare professionals have a plethora of guidance they need to follow, and to minimise potential harm it is important healthcare professionals can quickly, and easily access this information. Reference: https://www.rcpjournals.org/content/clinmedicine/21/3/204	into this category, we were unable to review it and include in this guideline. We acknowledge that there are many factors to take into account when prescribing SGLT2 inhibitors. All practitioners are expected to refer to the summary of product characteristics and the British National Formulary for when prescribing medicines, which contain information about cautions for use, such as the ones outlined here.
Diabetes UK (with clinical input from the ABCD and UKKA)	Guideline	004	001	The healthcare professional initiating the use of these drugs must have an education session with the person with diabetes and offer advice on who to contact if the person taking the SGLT2i is not feeling well. The need to provide the patient 'sick day guidance' and DKA needs to made explicit in this guidance, and the need for the information to be provided in a language or suitable format (e.g. Easy Read) that fulfils the unique requirements of the individual. Advice on managing illness when you have diabetes can be found on our website, which includes information on SGLT2i. Reference: https://www.diabetes.org.uk/guide-to-diabetes/life-with-diabetes/illness#Illness	Thank you for your comment. We acknowledge that there are many factors to take into account when prescribing SGLT2 inhibitors and that patient education is important to consider. However, this guidance is not intended to be a comprehensive guide to prescribing and patient education was not within the remit of this update. All practitioners are expected to refer to the Summary of Product Characteristics and the British National Formulary for when prescribing medicines, which contain information about cautions for use, such as the one outlined here.
Diabetes UK (with clinical input from the ABCD and UKKA)	Guideline	004	005 - 005	We recommend including a link to the relevant sections for SGLT2i in the British National Formulary here as well as the general prescribing guidance. Reference: https://bnf.nice.org.uk/drug/dapagliflozin.html	Thank you for your comment. We have not made this change as there are many SGLT2 inhibitors, only some of which have a current licensed indication for use in chronic kidney disease. However, the licensing status of other SGLT 2 inhibitors might change in the future so we wish to avoid referring to specific medicines in the guideline.

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Diabetes UK (with clinical input from the ABCD and UKKA)	Guideline	004 - 005	014 - 015/5	We welcome this recommendation about monitoring for volume depletion and eGFR decline. However, the Committee should offer a suggested timescale for this to be included in the guidelines and to provide further clarity on this point. The document states "Monitor for volume depletion and estimated glomerular filtration rate (eGFR) decline". It is widely accepted that eGFR falls after initiation of a SGLT2i but this is followed by eGFR stabilisation and is not a reason to withdraw treatment, as might be the case for an ACE inhibitor or angiotensin receptor blocker. Therefore, we suggest the addition of the following recommendation: "An initial fall in eGFR is to be expected and would not normally lead to withdrawal of the SGLT2i. Furthermore, there is no need for more frequent monitoring of eGFR than that required for the stage or grade of CKD".	Thank you for your comment. In response to comments from stakeholders pointing out that the monitoring requirements may differ between SGLT2 inhibitors, we have removed the sentence about monitoring for eGFR decline and volume depletion from the recommendation. Practitioners should follow advice in the Summary of Product Characteristics and the BNF on monitoring according to the particular SGLT2 inhibitor being prescribed. These resources should always be consulted when prescribing medicines, as set out at the start of the recommendations section in the guideline (see: making decisions using NICE guidelines)
Diabetes UK (with clinical input from the ABCD and UKKA)	Guideline	007	017 - 020	We agree that more research needs to be done to find evidence that shows the increased risk some ethnic groups have of micro and macrovascular complications. We already know that type 2 diabetes is more common in people of South Asian and African and African-Caribbean descent and presents at a younger age, leading to a longer duration of time with the condition and an increased risk of complications. Consideration of this is needed to fully understand the potential benefits of these treatments to people in these ethnic groups and make the most effective case for their wider use.	Thank you for your comment. We agree that further research is needed in this area and the committee had already made a research recommendation which covers this.
Diabetes UK (with clinical input from the ABCD and UKKA)	Guideline	General	General	We welcome the development of new and explicit recommendations on the use of SGLT2i for people with type 2 diabetes and chronic kidney disease.	Thank you for your comment. This update was limited to considering SGLT2 inhibitors for people with type 2 diabetes and CKD. SGLT2 inhibitors were the focus of the review because of recent license extensions to SGLT 2 inhibitors to include chronic kidney disease as a licensed indication – no such licence

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				Diabetes is a relentless condition to live with and the fear of complications including cardiovascular morbidity and mortality, can have a significant impact on the emotional wellbeing of a person living with diabetes. Cardiovascular disease remains the leading cause of loss of life expectancy in type 2 diabetes and we welcome any recommendations that increase the prescribing of drugs with robust evidence of reducing cardiovascular and renal morbidity and mortality in people with the condition. We re-iterate our previous comments highlighting that SGLT2is are already widely prescribed and their effectiveness is well–evidenced. We remain disappointed that updated recommendations on other, newer therapies like GLP-1s are not included in the scope of this guideline update. Therefore, we would strongly recommend that the 'Glucose-lowering medication in Type 2 diabetes: overall approach' on page 6 of the ADA/ EASD Consensus report, including both GLP-1 and SGLT2i, be considered for adoption in these guidelines. References: http://care.diabetesjournals.org/content/diacare/early/2018/09/27/dci18-0033.full.pdf https://onlinelibrary.wiley.com/doi/full/10.1111/dme.13825	extension currently exists for GLP-1 mimetics. These recommendations will be incorporated into the NICE guideline on type 2 diabetes which considers a wider range of treatments, including GLP 1 mimetics. There is a separate ongoing project to update parts of this guideline, including recommendations on GLP 1 mimetics for a broader population. For details of this project, see the guideline development page.
King's College Hospital NHS Foundation Trust	Guideline	004	014	Could there be more specific guidance on monitoring for volume depletion and estimated glomerular filtration rate please? There is an expected fall in eGFR on starting any SGLT2 inhibitor, so it would be important for this to be appreciated to prevent premature withdrawal, but with possible guidance for when a fall in eGFR is of concern.	Thank you for your comment. In response to comments from stakeholders pointing out that the monitoring requirements may differ between SGLT2 inhibitors, we have removed the sentence about monitoring for eGFR decline and volume depletion from the recommendation. Practitioners should follow advice in the Summary of Product Characteristics and the BNF on monitoring

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					according to the particular SGLT2 inhibitor being prescribed. These resources should always be consulted when prescribing medicines, as set out at the start of the recommendations section in the guideline (see: making decisions using NICE guidelines)
King's College Hospital NHS Foundation Trust	Guideline	005	004	Same comment as Comment 1	Thank you for your comment. In response to comments from stakeholders pointing out that the monitoring requirements may differ between SGLT2 inhibitors, we have removed the sentence about monitoring for eGFR decline and volume depletion from the recommendation. Practitioners should follow advice in the Summary of Product Characteristics and the BNF on monitoring according to the particular SGLT2 inhibitor being prescribed. These resources should always be consulted when prescribing medicines, as set out at the start of the recommendations section in the guideline (see: making decisions using NICE guidelines)
King's College Hospital NHS Foundation Trust	Guideline	005	006	In line with the proposed NICE Type 2 diabetes guidance update, we feel there needs to be reference to checking before starting an SGLT2 inhibitor to check the person is not following a very low carbohydrate or ketogenic diet because of the risk of diabetic ketoacidosis, that the patient is not pregnant or planning pregnancy or breastfeeding, to not start a very low carbohydrate or ketogenic diet without discussing it with their healthcare professional, because of the need to suspend SGLT2 inhibitor treatment to avoid DKA and to stop taking the SGLT2 inhibitor if they become ill (for example with fever, diarrhoea or vomiting). In addition, adjustment of existing glucose lowering medications of high hypoglycaemia risk may be required. Reference to sick day rules (e.g. the NHS England guidance) would be helpful.	Thank you for your comment. These recommendations will be incorporated into the type 2 diabetes guideline update. We acknowledge that there are many factors to take into account when prescribing SGLT2 inhibitors. All practitioners are expected to refer to the Summary of Product Characteristics and the British National Formulary for when prescribing medicines, which contain information about cautions for use, such as the one outlined here. In relation to NHS England guidance on sick day rules, as outlined in the NICE guidelines manual we are unable to quote or link to other guidelines unless the organisation's process has been accredited by NICE and the evidence reviews have been critically appraised to verify quality. See here for further information: https://www.nice.org.uk/process/pmg20/chapter/linking-to-other-guidance#guidance-from-other-developers

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Leeds Teaching Hospital Trust and Leeds Clinical Commissioning Group	Evidence Review	007	Population	People with T2DM who are hyperglycaemic and are requiring rescue therapy were excluded from this study. We are concerned that this is not transparent in the recommendations.	Thank you for your comment. Specific recommendations for people who are hyperglycaemic and require rescue therapy are given in NICE guideline on type 2 diabetes which states 'Consider insulin (see the section on insulin-based treatments) or a sulfonylurea, and review treatment when blood glucose control has been achieved'. The new recommendations from this update will be incorporated into this guideline before publication, and we think this will make it clearer that the recommendation on SGLT2 inhibitors should not be read in isolation but in the context of the whole guideline on type 2 diabetes management.
Leeds Teaching Hospital Trust and Leeds Clinical Commissioning Group	Evidence review	008	Outcome	We wonder if the committee could consider referring to albuminuria instead of proteinuria given ACR is being measured.	Thank you for your comment. We have not made this change. While it is true that ACR measures albuminuria specifically, the NICE guideline on chronic kidney disease recommendations that an ACR of 3mg/mmol or more should be regarded as clinically important proteinuria so we think that 'proteinuria' is appropriate.
Leeds Teaching Hospital Trust and Leeds Clinical Commissioning Group	Evidence Review	020	010	Could this have been included as a research recommendation? It appears that there is concern over renal bone disease with SGLT2s although this is still theoretical.	Thank you for your comment. The committee considered that renal bone disease was less important for decision making than other outcomes because it was only a theoretical risk from SGLT2 inhibitors and was unlikely to be a substantial factor when weighing up the risks and benefits of treatment. The committee therefore did not prioritise research on this for a research recommendation.
Leeds Teaching Hospital Trust and Leeds Clinical Commissioning Group	Evidence Review	021	010	We would be grateful if the committee could include findings for AKI if possible, in the main guideline to give reassurance for use	Thank you for your comment. We have not included this finding in the rationale section because although there was no evidence of a difference in AKI between groups, this might have arisen because of an insufficient number of participants to find an effect rather than a true equivalence between groups – we have added this explanation to the evidence review. The rationale and impact section of the main guideline is there as a summary of the key

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					findings and not intended to be as comprehensive as the discussion section in the evidence review.
Leeds Teaching Hospital Trust and Leeds Clinical Commissioning Group	Evidence Review	021	019 - 020	We would be grateful if the committee could include findings for amputation and fracture if possible, in the main guideline to give reassurance for use. We also feel that it is important to highlight groups of patients in whom these drugs should either not be used or only initiated by specialist teams (e.g. T1, T3C, chronic alcoholism etc due to potential DKA risk). We are also concerned that potential hypoglycaemia on adding into insulin/SUs in people who still have eGFR>45ml/min has not been highlighted.	Thank you for your comment. We have not added a sentence to the rationale section in the short guideline regarding amputation and fracture because although the evidence identified in our evidence review did not show a statistically significant difference between groups for people with CKD and diabetes this might have been because the trials were too small to identify an effect, rather than because and effect was not present. We have added this explanation to the evidence review. The rationale and impact section of the main guideline is there as a summary of the key findings and not intended to be as comprehensive as the discussion section in the evidence review Information about specific precautions and contraindications for use are given in the summary of product characteristics and British National Formulary entries for SGLT2 inhibitors. Prescribers are expected to refer to these resources when prescribing medicines (see: Making decisions using NICE guidelines)
Leeds Teaching Hospital Trust and Leeds Clinical Commissioning Group	Evidence Review	022	017 - 018	We are concerned that this more detailed recommendation has not been reflected in the recommendations included. Is 6 monthly monitoring what is being suggested? We are concerned that this is not likely to be useful and is not in line with the BNF or SPCs.	Thank you for your comment. In response to comments from stakeholders pointing out that the monitoring requirements may differ between SGLT2 inhibitors, we have removed the sentence about monitoring for eGFR decline and volume depletion from the recommendation. Practitioners should follow advice in the summary of product characteristics and the BNF on monitoring according to the particular SGLT2 inhibitor being prescribed. These resources should always be consulted when prescribing medicines, as set out at the start of the recommendations section in the guideline (see: making decisions using NICE guidelines)

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Leeds Teaching Hospital Trust and Leeds Clinical Commissioning Group	Evidence Review	030	Section 12	We wonder if the committee could consider referring to albuminuria instead of proteinuria given ACR is being measured.	Thank you for your comment. We have not made this change. While it is true that ACR measures albuminuria specifically, the NICE guideline on chronic kidney disease recommendations that an ACR of 3mg/mmol or more should be regarded as clinically important proteinuria so we think that 'proteinuria' is appropriate.
Leeds Teaching Hospital Trust and Leeds Clinical Commissioning Group	Evidence Review	031	Section 12	We have concern that DKA is not listed here in the primary outcomes under drug effects. In your initial table on p 8 it was included so may just be an omission. If not, was this not a pre-specified outcome of this review?	Thank you for your comment. We can confirm that diabetic ketoacidosis was included as an outcome in the review. This has now been corrected.
Leeds Teaching Hospital Trust and Leeds Clinical Commissioning Group	Evidence Review	033	Section 16	We are concerned that the updated Cochrane Handbook was not used given the reference is for the 2011 Cochrane Handbook	Thank you for your comment. We can confirm that the latest version of the Cochrane Handbook was referred to when carrying out this review and this reference has been updated
Leeds Teaching Hospital Trust and Leeds Clinical Commissioning Group	Evidence Review	224	Baseline characteristics	We have concern over the use of 'maximum dose' – we think this might be maximum tolerated dose as per trial protocol.	Thank you for your comment. We have amended to maximum tolerated dose.
Leeds Teaching Hospital Trust and Leeds Clinical Commissioning Group	Guideline	004	007	Rec 1.1.1 We are concerned about the cross referencing to the CKD guideline. This is a large onerous document to navigate in addition to the T2DM guidelines. The group feel that all information to manage a person living with diabetes in a holistic way should be consolidated into one document. We appreciate that avoidance of duplication is why this is being done but this is impractical for use.	Thank you for your comment. We recognise there is a lot of information to manage and that both guidelines need to be read. Most of the recommendations in both the diabetes and CKD guidelines would be relevant when management a person with both diabetes and CKD. As well as cross referring to the CKD guideline we have now reproduced the information about prescribing ARBs and ACE inhibitors to people with CKD and

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					type 2 diabetes in the type 2 diabetes guideline, to reduce the need to consult both guidelines simultaneously. The NICE strategy outlines how we are planning to integrate guidelines into a more usable format, please see link for details: https://www.nice.org.uk/about/who-we-are/corporate-publications/the-nice-strategy-2021-to-2026
Leeds Teaching Hospital Trust and Leeds Clinical Commissioning Group	Guideline	004	009	Rec 1.1.2 consider amending to 'titrated to the highest licensed dose they can tolerate' rather than the current statement ('titrated to the highest dose they can tolerate'	Thank you for your comment. This has been amended to 'highest licensed dose' as suggested.
Leeds Teaching Hospital Trust and Leeds Clinical Commissioning Group	Guideline	004	011	Rec 1.1.2 We would appreciate your consideration to use both mg/mmol and mg/g for ACR as licences etc. vary in units used. It is easier if you can quickly see the criteria in both units rather than having to calculate and there is less chance for error. Also not doing so many add unconscious bias to one agent over another.	Thank you for your comment. The NICE style guide advises that SI units should be used in NICE guidance, and so the units mg/mmol have been used for this guideline update. This is also consistent with the units used throughout the NICE guideline on chronic kidney disease.
Leeds Teaching Hospital Trust and Leeds Clinical Commissioning Group	Guideline	004	011	Rec 1.1.2 We would ask that the committee considers making it clear that the ACR needs to be confirmed and not just a one-off sample. No need to repeat where ACR > 30mg/mmol/ The need to repeat is to confirm microalbuminuria 3-30 mg/mmol	Thank you for your comment. Guidance on measuring ACR is given in the NICE guideline on chronic kidney disease, which is cross referred to from this guideline.
Leeds Teaching Hospital Trust and Leeds Clinical Commissioning Group	Guideline	004	014	Rec 1.1.2 We would appreciate your consideration to add monitoring intervals and what eGFR rate of decline would be acceptable?	Thank you for your comment. In response to comments from stakeholders pointing out that the monitoring requirements may differ between SGLT2 inhibitors, we have removed the sentence about monitoring for eGFR decline and volume depletion from the recommendation. Practitioners should follow advice in the Summary of Product Characteristics and the BNF on monitoring

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					according to the particular SGLT2 inhibitor being prescribed. These resources should always be consulted when prescribing medicines, as set out at the start of the recommendations section in the guideline (see: making decisions using NICE guidelines)
Leeds Teaching Hospital Trust and Leeds Clinical Commissioning Group	Guideline	004	014	Rec 1.1.2 We would like the committee to consider adding a research recommendation relating to eGFR. Considerations given to monitoring intervals, is there any advice on how long after getting to stable dose on ACEi/ARB is it then reasonable to add in SGLT21, any additional precautions when adding into loop diuretics/thiazide diuretics. Committee to also consider other monitoring requirements e.g. Lying/Standing blood pressure specifically in higher risk patients e.g. heart failure	Thank you for your comment. In response to comments from stakeholders pointing out that the monitoring requirements may differ between SGLT2 inhibitors, we have removed the sentence about monitoring for eGFR decline and volume depletion from the recommendation. Practitioners should follow advice in the Summary of Product Characteristics and the BNF on monitoring according to the particular SGLT2 inhibitor being prescribed. These resources should always be consulted when prescribing medicines, as set out at the start of the recommendations section in the guideline (see: making decisions using NICE guidelines). As eGFR monitoring was not within the scope of this update, an initial evidence search in this area was not carried out. Research recommendations are developed when a systematic assessment of gaps in the current evidence base has been carried out, and the committee identify this as a priority for research. Further information on research recommendations can be found here: https://www.nice.org.uk/process/pmg20/chapter/writing-the-guideline#formulating-research-recommendations
Leeds Teaching Hospital Trust and Leeds Clinical Commissioning Group	Guideline	004	014	Rec 1.1.2 we are concerned that it is not made clear that GFR cut offs for use vary from those used when treating hyperglycaemia in a person living with T2DM. You included a table on p221 that may be useful to include in the recommendations.	Thank you for your comment. In response to comments from stakeholders pointing out that the monitoring requirements may differ between SGLT2 inhibitors, we have removed the sentence about monitoring for eGFR decline and volume depletion from the recommendation. Practitioners should follow advice in the Summary of Product Characteristics and the BNF on monitoring according to the particular SGLT2 inhibitor being prescribed. These documents should always be consulted when prescribing

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					medicines, as set out at the start of the recommendations section in the guideline (see: making decisions using NICE guidelines)
Leeds Teaching Hospital Trust and Leeds Clinical Commissioning Group	Guideline	004	014 - 015	Rec 1.1.2 We are concerned this statement is too diffuse and it would be helpful to have some parameters around this e.g. when to stop, when to continue and a note added when to check eGFR	Thank you for your comment. In response to comments from stakeholders pointing out that the monitoring requirements may differ between SGLT2 inhibitors, we have removed the sentence about monitoring for eGFR decline and volume depletion from the recommendation. Practitioners should follow advice in the Summary of Product Characteristics and the BNF on monitoring according to the particular SGLT2 inhibitor being prescribed. These resources should always be consulted when prescribing medicines, as set out at the start of the recommendations section in the guideline (see: making decisions using NICE guidelines).
Leeds Teaching Hospital Trust and Leeds Clinical Commissioning Group	Guideline	004	018	Rec 1.1.3 Offer vs. consider – a subtle difference that is likely to be confusing without expansion on what the additional considerations might be. We ask that the committee looks to reference patients here who are highest risk to give some focus areas.	Thank you for your comment. It is NICE style to use 'offer' and 'consider' to reflect the relative strength or quality of the underpinning evidence and the trade-off between benefits and harms. The box above section 1.1 contains a link to Making decisions using NICE guidelines which explains this. Clinical judgement should always be exercised in the care of each patient with individual risk factors taken into account The recommendation for the A2 population was to consider SGLT2 inhibitors because of uncertainty in the evidence and economic modelling in this area. There were no particular subpopulations within this group where the evidence was stronger and so a more prescriptive recommendation could not be made. All practitioners are expected to refer to the Summary of Product Characteristics and the British National Formulary for when prescribing medicines, which contain information about cautions for use.

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Leeds Teaching Hospital Trust and Leeds Clinical Commissioning Group	Guideline	004	019	Rec 1.1.3 consider amending to 'titrated to the highest licensed dose they can tolerate' rather than the current statement ('titrated to the highest dose they can tolerate'	Thank you for your comment. This has been amended to 'highest licensed dose' as suggested.
Leeds Teaching Hospital Trust and Leeds Clinical Commissioning Group	Guideline	005	001	Rec 1.13 We would appreciate your consideration to use both mg/mmol and mg/g for ACR as licences etc. vary in units used. It is easier if you can quickly see the criteria in both units rather than having to calculate and there is less chance for error. Also we would ask that the committee considers making it clear that the ACR needs to be confirmed and not just a one off sample.	Thank you for your comment. The NICE style guide advises that SI units should be used in NICE guidance, and so the units mg/mmol have been used for this guideline update. This is also consistent with the units used throughout the NICE guideline on chronic kidney disease.
Leeds Teaching Hospital Trust and Leeds Clinical Commissioning Group	Guideline	005	004	Rec 1.1.3 We would appreciate your consideration to add monitoring intervals and what eGFR rate of decline would be acceptable	Thank you for your comment. In response to comments from stakeholders pointing out that the monitoring requirements may differ between SGLT2 inhibitors, we have removed the sentence about monitoring for eGFR decline and volume depletion from the recommendation. Practitioners should follow advice in the Summary of Product Characteristics and the BNF on monitoring according to the particular SGLT2 inhibitor being prescribed. These resources should always be consulted when prescribing medicines, as set out at the start of the recommendations section in the guideline (see: making decisions using NICE guidelines)
Leeds Teaching Hospital Trust and Leeds Clinical Commissioning Group	Guideline	007	004	The committee has noted clinical and cost efficacy uncertainty in the ACR 3-30mg/mmol. Were there any populations that were noted as having shown better clinical and cost efficacy?	Thank you for your comment. There were no sub-populations identified within the A2 category that had better clinical or cost effectiveness. There was more certainty around the clinical and cost effectiveness for the A3 (>30mg/mmol) group.
Leeds Teaching Hospital Trust and Leeds	Guideline	007	014	We have concern over the reference to the BNF. Dapagliflozin in the BNF states that If eGFR <60ml/min/1.73m2 then monitor renal function 2-4 times a year' and no mention in the SPC of this.	Thank you for your comment. We noticed the discrepancy between the SPC and BNF for dapagliflozin before consultation on this draft guidance, and we alerted the BNF to this. We have

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Clinical Commissioning Group				BNF must be kept up to date if you are going to refer to this. Empagliflozin and Canagliflozin say annual. Ertugliflozin says 'frequent' – a standardised recommendation for this would be useful.	checked the BNF entry for dapagliflozin and noted no mention of eGFR monitoring, consistent with the SPC for dapagliflozin and so we think that the BNF entry has now been updated to be consistent with the SPC. In response to comments from stakeholders pointing out that the monitoring requirements may differ between SGLT2 inhibitors, we have removed the sentence about monitoring for eGFR decline and volume depletion from the recommendation. Practitioners should follow advice in the Summary of Product Characteristics and the BNF on monitoring according to the particular SGLT2 inhibitor being prescribed. These resources should always be consulted when prescribing medicines, as set out at the start of the recommendations section in the guideline (see: making decisions using NICE guidelines)
Leeds Teaching Hospital Trust and Leeds Clinical Commissioning Group	Guideline	007	025	We have concern over the cost impact in a primary care setting. Recognition of the initial cost impact is appreciated however is there any consensus/modelling that could be included on how long costs will need to be floated before savings on outcomes are made?	Thank you for your comment. Due to the potential high resource impact of recommendations an economic analysis was conducted which suggested that SGLT2 inhibitors were cost saving compared to standard of care over 10 years. A resource impact report and local resource impact template have been developed to support implementation of these recommendations.
Leeds Teaching Hospital Trust and Leeds Clinical Commissioning Group	Questions	Comment form	Q1	Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why We believe the biggest impact on practice will be cohort of people living with microalbuminuria. This is likely to be large numbers and there is less clarity from the recommendations on any risk stratification. This population has traditionally been under recognised and identification (both testing and acting on that testing) has been challenging.	Thank you for your comment. The recommendation for the A2 population was to consider SGLT2 inhibitors because of uncertainty in the evidence and economic modelling in this area. There were no particular subpopulations within this group where the evidence was stronger and so a more prescriptive recommendation could not be made.
Leeds Teaching Hospital Trust	Questions	Comment form	Q2	Would implementation of any of the draft recommendations have significant cost implications?	Thank you for your comment. Due to the potential high resource impact of recommendations an economic analysis was conducted

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and Leeds Clinical Commissioning Group				Yes. Both in the costs of the agents and in the screening and processes needed to get them appropriately on these agents.	which suggested that SGLT2 inhibitors were cost saving compared to standard of care over 10 years. A resource impact report and local resource impact template have been developed to support implementation of these recommendations.
Leeds Teaching Hospital Trust and Leeds Clinical Commissioning Group	Questions	Comment form	Q3	What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or examples of good practice.) We thought this guidance would benefit from having recommendations for use and also recommendations for implementation. A lot of useful information about safety is included in the evidence review and is lost in the recommendations. Information could also be included then about sick day rules. An algorithm would be useful, or this being added into the algorithm in the T2DM Management guideline. A kidney risk tool may help the decision process regarding the need for SGLT2 in those with an ACR 3-30 mg/mmol We would like to highlight the importance of QoF indicators for this being added.	Thank you for your comment. When we publish guidance, we also have a tools and resources tab which lists implementation tools and other useful resources. An example of this can be found here alongside the CKD guideline. NICE routinely produce baseline assessment and resource impact tools. To encourage the development of other practical support tools, we run an endorsement scheme aimed at encouraging our partners to develop these in alignment with NICE recommendations. Eligible tools are assessed and if successful, will be endorsed by NICE and featured on the NICE website alongside the relevant guideline. Indicators for the QOF are reviewed and updated on an annual basis, the process for this can be found here These recommendations will be incorporated into the NICE guideline on the management of type 2 diabetes in adults. There is another update to this guideline in development (see the guideline development page for details). As part of this work a visual summary of the recommendations on choosing medicines for type 2 diabetes has been produced. It is the intention that these recommendations will be included in the final version of visual summary when it is published (expected publication date February 2022).

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Napp Pharmaceuticals Ltd	Equality impact assessment	General	General	No comments	Thank you for your comment.
Napp Pharmaceuticals Ltd	Evidence review	General	General	No comments	Thank you.
Napp Pharmaceuticals Ltd	Guideline	001	004	The title used for this draft document is somewhat confusing, as it uses the same title as GID-NG10160 (NG28 update), which is running as a parallel but separate consultation. It's Napp's understanding that the guidance being consulted on in this document will be incorporated into both NG203 and GID-NG10160, but will not be published as an independent final guideline. We assume that this is the reason why the GID-NG10160 title has also been used for this consultation document. Napp would like to request that NICE pay particular attention to adding clear explanations, titles, and cross-references to the final published documents, in order to ensure readers clearly understand the relationship between them.	Thank you for your comment. As correctly noted, there is another ongoing consultation on a more substantial update of this guideline. The results of both consultations will ultimately be incorporated into the NICE guideline on Type 2 diabetes in Adults.
Napp Pharmaceuticals Ltd	Guideline	002	Text box titled "Related Guidance"	The statement "*We are developing a technology appraisal on canagliflozin for treating chronic kidney disease in people with type 2 diabetes"* is incorrect and should be removed. This STA was discontinued in mid 2020: https://www.nice.org.uk/guidance/indevelopment/gid-ta10555	Thank you for your comment. This has now been corrected to refer to the ongoing technology appraisal of dapagliflozin for the treatment of CKD. https://www.nice.org.uk/guidance/indevelopment/gid-ta10808
Napp Pharmaceuticals Ltd	Guideline	004 + 005	014 + 004	Napp are concerned by inclusion of the advice that patients *"should be monitored for eGFR decline",* without any context or qualification as to what level of eGFR decline should constitute cause for concern. The unqualified statement is likely to be interpreted by many readers as implying that "SGLT2i therapy should be discontinued if eGFR acutely declines after initiation". This would constitute inappropriate clinical advice, as rapid decline in eGFR after SGLT2i initiation is believed to be representative of a reversal of pathological glomerular	Thank you for your comment. In response to comments from stakeholders pointing out that the monitoring requirements may differ between SGLT2 inhibitors, we have removed the sentence about monitoring for eGFR decline and volume depletion from the recommendation. Practitioners should follow advice in the Summary of Product Characteristics and the BNF on monitoring according to the particular SGLT2 inhibitor being prescribed. These documents should always be consulted when prescribing

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				hyperfiltration rather than loss of filtration capacity. There are no data to suggest that a large (but <30%) decrease in eGFR on SGLT2i initiation is associated with any acute or chronic adverse effect. On the contrary, there are now data suggesting that a larger initial decrease in eGFR on initiation of SGLT2i therapy is correlated with a lower subsequent long-term decrease in eGFR. A very good summary of these considerations can be found in this recently published article: https://cjasn.asnjournals.org/content/16/8/1278 Napp strongly suggest that either the recommendation to monitor eGFR after SGLT2i initiation is simply removed (which is in line with both current clinical opinion and SGLT2i product licences), or if NICE wish to retain this statement, then an explanation should be added as to what variance in eGFR can be considered normal *vs.* abnormal, and what clinical actions are appropriate in either scenario. Napp suggest a suitable starting point for drafting this guidance could be the section of this NICE CKS that describes management of serum creatinine and eGFR on initiation/titration of ACE inhibitors. Though this CKS refers to a different class of agents, the fundamental principles are highly analogous to the SGLT2i class: ACEi are well-known to cause an acute, reversible decline in eGFR on initiation/titration via direct intrarenal efferent vasodilation, which leads to reduced intraglomerular filtration pressure and a long-term renoprotective effect: https://pubmed.ncbi.nlm.nih.gov/8879974/. This is directly comparable to the acute, reversible, decline in eGFR; decrease in glomerular filtration pressure, and renoprotective effect seen with use of SGLT2i in T2DM & CKD (albeit that this effect occurs via afferent arteriole constriction): care.diabetesjournals.org/content/39/Supplement_2/S165.	medicines, as set out at the start of the recommendations section in the guideline (see: making decisions using NICE guidelines)

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				The recommendations made with respect to threshold creatinine and eGFR levels in the above mentioned CKS are specifically intended to aid the healthcare professional in distinguishing clinically between beneficial alterations in glomerular haemodynamics *vs* other distinct pathological processes, both of which manifest as acutely decreased eGFR. This guidance could therefore be useful in developing similar guidance for SGLT2i initiation in this population, or may even be considered to be broadly applicable across both drug classes in its current form.	
Napp Pharmaceuticals Ltd	Guideline	General	General	Napp are very much in support of the position taken by NICE in this proposed update. Specifically, Napp support the suggestion that an SGLT2i should be *offered* to T2DM patients with ACR >30mg/mmol and *considered* in patients with ACR 3-30mg/mmol. This represents a fair and balanced interpretation of the available trial data – insofar as there is a high degree of certainty of a large effect size in severe albuminuria, and a reasonable degree of certainty of a significant effect size in moderate albuminuria.	Thank you for your comment.
NHS County Durham CCG	Guideline	006 + 007	009 + 016	Please clarify whether the addition of an SGLT2 drug for raised ACR and CKD is independent of glycaemic control.	Thank you for your comment. We confirm that this update evaluated the benefits of SGLT2 inhibitors for their cardiovascular and renal benefits independent of glycaemic control. We have incorporated the recommendations into the NICE guideline on type 2 diabetes in the section on diabetic kidney disease. We have added the following note to the section on drug treatments for blood glucose lowering: 'See the section on diabetic kidney disease for guidance on SGLT2 inhibitors for people with type 2 diabetes and chronic kidney disease. Note that, for this group, SGLT2 inhibitors should not be counted when making decisions to intensify drug treatment for type 2 diabetes (in recommendations 1.6.27, 1.6.28 and 1.6.30).'
NHS South Sefton CCG	Guideline	General	General	Agree recommendations which could be a bit of a challenge for primary care, initially, as not all SGLT2 inhibitors are licensed for	Thank you for your comment. We acknowledge that not all SGLT2 inhibitors are currently licensed for people with CKD, as

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				the indications proposed at the time of reviewing the guidelines, as stated.	stated in the recommendations. Prescribers are expected to consult the Summary of Product Characteristics and British National Formulary when prescribing medicines as set out in this document on making decisions using NICE guidelines. The committee thought that making a class recommendation for SGLT-2 inhibitors was appropriate because the benefits and harms of these medicines were likely to be class effects.
NHS South Sefton CCG	Guideline	General	General	Reference is made to the medication's marketing authorisation but in addition does there need to be a caution regarding diet i.e avoiding very low calorie or ketogenic diet for people living with type 2 diabetes as well as advice regarding what to do if unwell and at risk of becoming volume depleted especially when patients are also taking an ACE or ARB medication?	Thank you for your comment. We acknowledge that there are many factors to take into account when prescribing SGLT2 inhibitors. All practitioners are expected to refer to the Summary of Product Characteristics and the British National Formulary for when prescribing medicines, which contain information about cautions for use, such as the one outlined here.
North Wood Group Practice	Guideline	004	009	We welcome the guideline stressing the importance of titrating ACE inhibitors/ARBs to maximum tolerated dose. Our recommendation would be to add 'titrated to the highest licensed dose they can tolerate' rather than the current statement ('titrated to the highest dose they can tolerate') which may suggest continuing to titrate over and above the maximum licensed dose	Thank you for your comment. We have amended this wording as suggested.
North Wood Group Practice	Guideline	004	014 - 015	We would welcome clarity on 'monitoring volume depletion and eGFR decline', specifically in regards to (1)frequency and timing of monitoring given known early dip in renal function and recovery (2) parameters to work within e.g. advice on managing on any associated renal drop identified through monitoring	Thank you for your comment. In response to comments from stakeholders pointing out that the monitoring requirements may differ between SGLT2 inhibitors, we have removed the sentence about monitoring for eGFR decline and volume depletion from the recommendation. Practitioners should follow advice in the Summary of Product Characteristics and the BNF on monitoring according to the particular SGLT2 inhibitor being prescribed. These resources should always be consulted when prescribing medicines, as set out at the start of the recommendations section in the guideline (see: making decisions using NICE guidelines)
North Wood Group Practice	Guideline	004	019	We welcome the guideline stressing the importance of titrating ACE inhibitors/ARBs to maximum tolerated dose. Our	Thank you for your comment. This has been amended to 'highest licensed dose' as suggested.

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				recommendation would be to add 'titrated to the highest licensed dose they can tolerate' rather than the current statement ('titrated to the highest dose they can tolerate') which may suggest continuing to titrate over and above the maximum licensed dose	
North Wood Group Practice	Guideline	005	004	We would welcome clarity on 'monitoring volume depletion and eGFR decline', specifically in regards to (1)frequency and timing of monitoring given known early dip in renal function and recovery (2) parameters to work within e.g. advice on managing on any associated renal drop identified through monitoring	Thank you for your comment. In response to comments from stakeholders pointing out that the monitoring requirements may differ between SGLT2 inhibitors, we have removed the sentence about monitoring for eGFR decline and volume depletion from the recommendation. Practitioners should follow advice in the Summary of Product Characteristics and the BNF on monitoring according to the particular SGLT2 inhibitor being prescribed. These resources should always be consulted when prescribing medicines, as set out at the start of the recommendations section in the guideline (see: making decisions using NICE guidelines)
Novartis Pharmaceuticals UK Limited	Guideline	004 - 005	008 – 020 001 - 003	The draft guideline states "offer an SGLT2 inhibitor, in addition to an ARB or an ACE inhibitor" (section 1.1.2) and "consider an SGLT2 inhibitor, in addition to an ARB or an ACE inhibitor" (section 1.1.3), for adults with type 2 diabetes and CKD if their ACR level meets certain thresholds. From the proposed wording it is not entirely clear whether SGLT2 inhibitor treatment may be initiated concurrently with ARB or ACE inhibitor treatment, or only if a person's ACR still meets the specified threshold despite the person already being treated with an ARB or an ACE inhibitor titrated to the highest (licensed) dose that they can tolerate (i.e. whether an SGLT2 inhibitor could be used as part of a combination therapy from the outset or only as an add-on therapy if an ARB or an ACE inhibitor alone proves not to be sufficient in lowering ACR).	Thank you for your comment. As per the NICE guideline on chronic kidney disease, ACE or ARB inhibitors are considered first line treatment for people with an ACR above 3mg/mmol, with the addition of a an SGLT2 inhibitor dependent on ACR levels as outlined in the recommendation. The intention is that ACE/ARB inhibitors should be prescribed first at the maximum tolerated licensed dose and SGLT 2 inhibitors only prescribed if the person still meets the ACR criteria outline in the recommendations. We have reworded the recommendation to make this point clearer. The committee made this recommendation because the majority of participants in the trials considered in the review were taking ARBs/ACE inhibitors on entry to the trial.

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Novartis Pharmaceuticals UK Limited	Guideline	004 – 005	008 – 020 001 - 003	In relation to the dosing of an ARB or an ACE inhibitor, the draft guideline (sections 1.1.2 and 1.1.3) states "titrated to the highest dose that they can tolerate". The guideline Chronic kidney disease: assessment and management (NG203) uses a wording of "titrated to the highest licensed dose that they can tolerate" (refer to sections 1.6.5, 1.6.6, 1.6.8-10 in NG203). The word "licensed" should be included in the proposed guideline update.	Thank you for your comment. We have changed the wording of the recommendation to 'highest licensed dose' for consistency with the NICE guideline on chronic kidney disease.
Novo Nordisk UK	Guideline	004	008 - 013	While limiting the progression of CKD remains an important facet in the clinical management of people with type 2 diabetes, these recommendations do not consider any alternative therapeutic options for patients with chronic kidney disease who cannot tolerate SGLT-2 inhibitor therapy or for whom SGLT-2 inhibitors might be contraindicated. Specific GLP-1RAs have established cardiovascular (CV) protection for which many patients with CKD are at high risk and clinical benefits of GLP1RAs on CKD are recognised within data from cardiovascular outcome trials.[1,2] In type 2 diabetes patients with CVD or at high CV risk, Liraglutide reduced new or worsening nephropathy in the LEADER trial.[1] In the SUSTAIN-6 trial (patients with T2DM and established CVD or CV risk factors), new or worsening nephropathy occurred less often in patients treated with semaglutide.[2] As was seen in LEADER, this renal outcome was also driven by a reduction in new onset macroalbuminuria.[1-3] Although there is less evidence in terms of hard renal endpoints, albuminuria is a strong predictor of renal outcomes and this places the GLP-1RAs as an option when SGLT-2 inhibitors cannot be used.[3] The combination of the glycaemic control offered by GLP 1RAs alongside their reno-protective effects would place them to be considered as the alternative in the treatment pathway here.[1-4]	Thank you for your comment. Our scope in this instance was to review the evidence for SGLT-2 inhibitors in people with CKD and type 2 diabetes. These recommendations will be included in the update of the type 2 diabetes in adults guideline which considers different treatment options.

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				We recommend that the guideline is reviewed to consider alternatives to SGLT-2 inhibitors when they are unsuitable in the population of patients with type 2 diabetes and CKD. **References:** 1. Marso SP, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2016; 375:311-322. DOI: 10.1056/NEJMoa1603827 2. Marso SP, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med*. 2016; 375(19):1834-1844. DOI: 10.1056/NEJMoa1607141. 3. Persson F, et al. Changes in Albuminuria Predict Cardiovascular and Renal Outcomes in Type 2 Diabetes − A Post Hoc Analysis of the LEADER Trial. *Diabetes Care*. 2021; 44(4): 1020-1026. DOI: https://doi.org/10.2337/dc20-1622 4. Sattar N, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol*. 2021; 9: 653–62. https://doi.org/10.1016/S2213-8587(21)00203-5	
Novo Nordisk UK	Guideline	004	008 - 013	The guideline does not make it clear that whilst a SGLT-2 inhibitors may be used for the treatment of the CKD in patients with type 2 diabetes, the glycaemic lowering efficacy of SGLT-2 inhibitors may be impaired when used in these patients. This is highlighted in the relevant SmPCs of the SGLT-2 inhibitors.[1-4] We recommend that the guideline makes this point clear and provides suggestions of which anti-diabetes treatments can be used to address glycaemic lowering in those patients with reduced renal	Thank you for your comment. We acknowledge that there are many factors to take into account when prescribing SGLT2 inhibitors. All practitioners are expected to refer to the Summary of Product Characteristics and the British National Formulary for when prescribing medicines, which contain information about cautions for use, such as the one outlined here.

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				function as seen in the 2020 KDIGO Diabetes Management in CKD Guideline.[5] Liraglutide and semaglutide (oral and subcutaneous) are licensed to be used in patients with mild, moderate or severe renal impairment without dose adjustment, an important consideration for clinicians in this situation.[6-8] Additionally, the glucose lowering efficacy (HbA_{1c}) of liraglutide and semaglutide (oral and subcutaneous) are maintained in patients with different degrees of renal impairment, with a consistency of benefit seen independent of baseline eGFR status.[9,10] We propose that additional recommendations are added to reflect the need to consider glycaemic lowering in addition to SGLT-2is in this context. **References:** 1. Janssen-Cilag International NV; Invokana® Summary of Product Characteristics: 26-June-2020; Available from: https://www.medicines.org.uk/emc/product/8855/smpc#NUMBER [Accessed: 23-Sept-2021] 2. AstraZeneca UK Limited; Forxiga® Summary of Product Characteristics: 5-August-2021; Available from: https://www.medicines.org.uk/emc/product/7607/smpc [Accessed: 23-Sept-2021] 3. Merck Sharp & Dohme (UK) Limited; Steglatro® Summary of Product Characteristics: 01-Jan-2021; Available from: https://www.medicines.org.uk/emc/product/10099/smpc [Accessed: 23-Sept-2021] 4. Boehringer Ingelheim International GmbH; Jardiance® Summary of Product Characteristics: 04 Aug 2021; Available from:	SGLT2s were shown to be cost-effective for renal protection, not cardiovascular protection, and therefore their effect or lack of on glycaemic control wouldn't have changed the committee's conclusion.

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				https://www.medicines.org.uk/emc/product/5441/smpc#INDICATIONS; [Accessed: 23-Sept-2021] 5. Ian H. de Boer; Executive summary of the 2020 KDIGO Diabetes Management in CKD Guideline: evidence-based advances in monitoring and treatment; *Kidney International*. 2020; 98: 839–848; https://doi.org/10.1016/j.kint.2020.06.024 6. Novo Nordisk Limited; Ozempic® Summary of Product Characteristics 7. Novo Nordisk Limited; Rybelsus® Summary of Product Characteristics 8. Novo Nordisk Limited; Victoza® Summary of Product Characteristics 9. Cherney D, et al. HbA1c reduction with the GLP-1 receptor agonist semaglutide is independent of baseline eGFR - post hoc analysis of SUSTAIN and PIONEER program. *American Society of Nephrology - Kidney Week 2020*. Abstract and Presentation 10. Davies MJ, et al. Efficacy and Safety of Liraglutide Versus Placebo as Add-on to Glucose-Lowering Therapy in Patients With Type 2 Diabetes and Moderate Renal Impairment (LIRA-RENAL): A Randomized Clinical Trial. *Diabetes Care*. 2016; 39(2): 222-230. https://doi.org/10.2337/dc14-2883	
Novo Nordisk UK	Guideline	General	General	We are concerned that this set of recommendations, being separate from the NG28 guideline, may result in confusion or potentially being missed by clinicians when making treatment decisions for their patients with type 2 diabetes. Given that this renal guidance is specifically for adult patients with type 2 diabetes it would seem logical for it to be incorporated within the NG28 guideline. This would also make it easier to link and	Thank you for your comment. These recommendations will be incorporated into the NICE guideline on type 2 diabetes which considers a wider range of treatments. There is a separate ongoing project to update parts of this guideline. For details of this project, see the guideline development page.

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				recommend which medications should be considered for glycaemic lowering in patients with renal impairment. We recommend that this guideline is incorporated fully into the NG28 guideline.	
Novo Nordisk UK	Guideline	General	General	It is unclear why the review question is focused solely on sodium-glucose co-transporter-2 (SGLT-2) inhibitors in the context of managing patients with type 2 diabetes and chronic kidney disease (CKD) rather than considering all the evidence for medicines such as glucagon-like-peptide-1 receptor agonists (GLP-1RAs) that may be used to treat people with type 2 diabetes who also have CKD.[1-4] Similarly, understanding the benefits and choices of therapeutic options is not based on CKD, glucose management, or the treatment of cardiovascular risk in isolation but instead takes a combined approach and at an individual level for each person with type 2 diabetes, according to their personal circumstances. We recommend that the scope of this piece of guidance is broadened to include assessment of all medicines used to treat type 2 diabetes and CKD and that the results are incorporated into NG28 in a patient-centred set of recommendations reflecting the multi-factorial nature of type 2 diabetes, similar to the ADA-EASD Consensus statement.[5,6] **References** 1. Marso SP, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2016; 375:311-322. DOI: 10.1056/NEJMoa1603827	Thank you for your comment. This update was limited to considering SGLT2 inhibitors for people with type 2 diabetes and CKD. SGLT2 inhibitors were the focus of the review because of recent license extensions to SGLT 2 inhibitors to include chronic kidney disease as a licensed indication – no such licence extension currently exists for GLP-1 mimetics. These recommendations will be incorporated into the NICE guideline on type 2 diabetes which considers a wider range of treatments, including GLP 1 mimetics. There is a separate ongoing project to update parts of this guideline, including recommendations on GLP 1 mimetics in a broader population. For details of this project, see the guideline development page. We have also recently published and updated of the CKD guideline which explores different treatment options for this population.

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				2. Marso SP, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med*. 2016; 375(19):1834-1844. DOI: 10.1056/NEJMoa1607141. 3. Persson F, et al. Changes in Albuminuria Predict Cardiovascular and Renal Outcomes in Type 2 Diabetes − A Post Hoc Analysis of the LEADER Trial. *Diabetes Care*. 2021; 44(4): 1020-1026. DOI: https://doi.org/10.2337/dc20-1622 4. Sattar N, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol*. 2021; 9: 653–62. https://doi.org/10.1016/S2213-8587(21)00203-5 5. Buse, JB, et al. 2019 update to: Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia*. 2020; 43(2): p221–228. doi: 10.2337/dci19-0066. 6. Davies, MJ, et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2018. 41(12):2669-2701. doi: 10.2337/dci18-0033.	
Perspectum Diagnostics Ltd	Guideline	General	General	The use of Magnetic Resonance Imaging (MRI) techniques to monitor renal function or comorbidities in other organs is not mentioned within these guidelines.	Thank you for your comment. In response to comments from stakeholders pointing out that the monitoring requirements may differ between SGLT2 inhibitors, we have removed the sentence about monitoring for eGFR decline and volume depletion from the

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				Recommendation 1.1.2. and 1.1.3. state that volume depletion and eGFR should be monitored in patients with type 2 diabetes and chronic kidney disease on SGLT2 inhibitors in addition to an ARB or an ACR inhibitor. We propose that the use of **multi-organ MRI techniques** to monitor kidney function, including volume depletion, and monitor beneficial effects of SGLT2 inhibitors on other comorbidities, including progression of co-prevalent **non-alcoholic fatty liver disease (NAFLD),** is added to **Recommendations 1.1.2.** and **1.1.3.** Total kidney volume (TKV) is associated with the rate of kidney growth and the development of advanced stages of chronic kidney disease (CKD) and when measured by MRI is an FDA-approved measure to predict disease progression in polycystic kidney disease[1]. Using MRI, low TKV has been observed with increased age, albuminuria and cardiovascular disease, whilst high TKV is associated with increased prevalence of hypertension, diabetes, lower HDL cholesterol, higher triglycerides and higher BSA[2]. MRI has been shown to accurately quantify TVK[1,3,4] and correlates with eGFR[1,5] in patients with kidney disease. Furthermore, in type 2 diabetes (T2D) changes in kidney volume are associated with change in fasting glucose[6]. Therefore, we recommend the use of MRI technology to provide accurate values of TKV to monitor kidney volume depletion and CKD progression in patients with type 2 diabetes and chronic kidney disease on SGLT2 inhibitors. There is high prevalence of co-morbidities in patients with T2D. For example, there is a 60% prevalence of non-alcoholic fatty liver	recommendation. Practitioners should follow advice in the Summary of Product Characteristics and the BNF on monitoring according to the particular SGLT2 inhibitor being prescribed. These resources should always be consulted when prescribing medicines, as set out at the start of the recommendations section in the guideline (see: making decisions using NICE guidelines). Information on monitoring renal function is included in the NICE guideline on chronic kidney disease and methods for monitoring kidney function were outside of the scope of this update, which was focused on evaluating the effectiveness of SGLT2 inhibitors for people with type 2 diabetes and CKD.

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				disease (NAFLD)[7,8], 34-51% prevalence of CKD[9] and a 32% prevalence of cardiovascular disease[10] in patients with T2D. This is supported in the non-alcoholic fatty liver disease (NAFLD): assessment and management NICE guideline; **Recommendation 1.1.1.** states that non-alcoholic fatty liver disease (NAFLD) is more common in people who have T2D or metabolic syndrome. As argued by the Chief Medical Officer for England, the high prevalence of comorbidities in patients type 2 diabetes highlights the need for a multi-specialty approach to the monitoring of the disease[11] and these should include multi-organ MRI technologies. Multi-organ MRI provides quantitative tissue characterisation of multiple organs as well as functional and structural information[12,13]. Multi-organ MRI techniques have the potential to complement existing diagnostics by allowing clinicians to diagnose, monitor and stratify co-prevalent diseases in patients with T2D and CKD. The use of multi-organ MRI on patients with T2D has demonstrated a high prevalence of multi-organ abnormality including fatty infiltration and/or fibroinflammatory changes in the liver (75% of patients), pancreas (66%), spleen (58%), kidney (17%), aorta (67%) in type 2 diabetes patients[14]. Data from the UK BioBank indicate that body muscle and fat composition and liver steatosis and fibroinflammation differ between T2D patients with and without obesity[14,15]. Furthermore, separate studies by multi-organ MRI in T2D patients show that changes in kidney volume are associated with change in fasting glucose and abdominal visceral adipose tissue[6,16].	

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				Meta-analysis indicates that SGLT2i can have a beneficial effect on reducing progression of NAFLD in patients with type 2 diabetes[16]. This has been monitored as a change in the MRI biomarker liver PDFF (proton density fat fraction), which has shown to have superior accuracy in diagnosing and stratifying grades of liver steatosis in NAFLD[17,18,19], even compared to histology[20]. Diagnosing and/or monitoring NAFLD or the progressive form non-alcoholic steatohepatitis (NASH) also requires evaluation of other liver tissue characteristics, inflammation, hepatocellular injury (ballooning) and fibrosis, which strongly correlate with MRI biomarker cT1 (corrected T1)[21]. cT1 can predict clinical outcomes[12,22,23] and has shown diagnostic accuracy in identifying NASH in type 2 diabetes[24,25,26]. cT1 shows low measurement failure rates, and high repeatability and reproducibility that are best in class for imaging[27-31] in NAFLD. The evidence for support of cT1 and PDFF in diagnosis of NASH is currently under consideration by the NICE Diagnostic Assessment Programme, for adoption in the NICE guidelines for fatty liver disease as a replacement for biopsy. Evidence on the applicability of multi-organ MRI techniques to examine multi-organ abnormality is provided by studies on post-COVID syndrome (PCS), another disease area that exhibits multi-organ involvement and for which diabetes is a risk factor[32]. A prospective cohort study of 201 PCS individuals from two UK centres applied quantitative MRI techniques to assess injury the heart, kidneys, liver, pancreas, and spleen, which revealed multi-	

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				organ injury in 29% of patients with recovering from COVID-19[33]. Organ impairment was associated with hospitalisation during acute COVID-19, with liver volume, fat accumulation in the liver and pancreas and pancreatic inflammation displaying a positive association with hospitalisation, whilst severe PCS was associated with evidence of myocarditis. In support, a separate study also revealed multi-organ impairment in the lungs, brain, heart liver and kidneys in 58 PCS patients in the UK by use of multi-organ MRI technology[34]. Earlier detection of complications and co-prevalent disease provides opportunity to prevent or slow disease progression, reverse disease, and improve outcomes. Therefore, we recommend using multi-organ MRI to monitor co-morbidities and changes to kidney volume depletion resulting from effects of SGLT2 inhibitors in persons with T2D and CKD. *References* (1) Yu, A.S.L. et al. (2017). Baseline Total Kidney Volume and the Rate of Kidney Growth Are Associated with Chronic Kidney Disease Progression in Autosomal Dominant Polycystic Kidney Disease. *Kidney international,* 93(3), 691–99. (2) Roseman, D.A. et al. (2017). Clinical Associations of Total Kidney Volume: The Framingham Heart Study. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association,* 32(8), 1344–50.	

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				a systematic literature review of scientific evidence from across the world in 2007–2017. *Cardiovascular Diabetology*, 17(1), 83. (11) Whitty, C.J. et al. (2020). Rising to the challenge of multimorbidity. *BMJ*, 368, l6964 (12) Bradley, C.R. et al. (2018). Multi-organ assessment of compensated cirrhosis patients using quantitative magnetic resonance imaging. *Journal of hepatology*, 69(5), 1015-1024. (13) Chouhan, M.D. Taylor, S.A. and Mookerjee, R.P. (2018). Multi-organ quantitative MRI for the assessment of liver disease–A whole much more than the sum of its parts. *Journal of hepatology*, 69(5), 996-998. (14) Telford A. et al. (2021). High prevalence of multi-organ steatosis and fibroinflammation, identified by multi-parametric MRI, in people with type 2 diabetes. *American Association Study of Liver Disease Liver Meeting*; accepted. (15) Waddell T. et al. (2021). Multi-organ multiparametric magnetic resonance imaging reveals distinct ectopic fat distribution in type-2 diabetics with and without co-existing obesity. *Eur Assoc Study Diabetes Conf*.; accepted. (16) Notohamiprodjo, M. et al. (2020). Renal and renal sinus fat volumes as quantified by magnetic resonance imaging in subjects with prediabetes, diabetes, and normal glucose tolerance. *PloS one*, 15(2), e0216635. (17) Beyer, C. et al. (2021). Comparison between magnetic	

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				(32) Ayoubkhani D. et al. (2021). Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study. *BMJ*, 372, n693 (33) Dennis, A. et al. (2021). Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: a prospective, community-based study. *BMJ open*, 11(3), e048391. Raman, B. et al. (2021). Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge. *EClinicalMedicine*, 31, 100683.	
Primary Care Diabetes Society	Guideline	004	014	RECOMMENDATION 1.1 Monitor for volume depletion and estimated glomerular filtration rate 15 (eGFR) decline We are concerned that this recommendation will add unnecessary work load to primary care. Even though there is a transient drop in the Egfr and rise in serum creatinine after initiating SGLT2-Is, these changes revert to baseline within 2-3 weeks. There have not be an increase in the occurrence of acute kidney injuries in both the CREDENCE AND DAPA-CKD trials.	Thank you for your comment. In response to comments from stakeholders pointing out that the monitoring requirements may differ between SGLT2 inhibitors, we have removed the sentence about monitoring for eGFR decline and volume depletion from the recommendation. Practitioners should follow advice in the Summary of Product Characteristics and the BNF on monitoring according to the particular SGLT2 inhibitor being prescribed. These documents should always be consulted when prescribing medicines, as set out at the start of the recommendations section in the guideline (see: making decisions using NICE guidelines)
Renal Pharmacy Group and UK Kidney Association	Guideline	004	011	Could ACR cut-off be lowered to 25mg/mmol given cohort of Dapa-CKD that included patients from 200mg/g (22.6mg/mmol) and provided good data for this population	Thank you for your comment. The committee considered data stratified into A1, A2 and A3 categories. The threshold categories were chosen a priori and specified in the review protocol. They are aligned with the international KDIGO A1, A2 and A3 categories. The CKD guideline recommends that people with CKD should be classified according to these categories, and the categorisation used to indicate the risk of them experiencing an adverse outcome. The NICE CKD guideline also recommends management according to these categories, for example

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					recommending different monitoring frequencies according to ACR and eGFR categorisations. Categorisation into the A3 category (ACR more than 30mg/mmol) also partly determines whether someone is cared for in primary or secondary care. The evidence review contains a justification for the chosen of eGFR and ACR categories for subgroup analysis. As noted in the evidence review, The DAPA-CKD study recruited participants with an ACR of greater than 20 mg/mmol which was between the A2 and A3 categories. However, the median ACR for the group with type 2 diabetes (that met the inclusion criteria for this review) was 116 mg/mmol (IQR 53 to 23), and so most participants in this trial would have fallen into the A3 category.
Renal Pharmacy Group and UK Kidney Association	Guideline	004	014 - 015	An acute dip in GFR is expected within the context of the mechanism of action (constriction of afferent arteriole thereby dropping intraglomerular pressure) – Advising to monitor for GFR decline when listed alongside volume depletion implies this is an adverse or unwanted effect and is highly likely to lead to inappropriate discontinuation – especially when these GFR dips have the potential to trigger AKI alerts on electronic systems when it is not a true AKI but an intended/expected effect of the medication A recommendation that routine monitoring of renal function is NOT required upon initiation of an SGLT-2 inhibitor would be more useful - or a statement that if renal function is monitored that this GFR dip is taken into consideration when interpreting the GFR result.	Thank you for your comment. In response to comments from stakeholders pointing out that the monitoring requirements may differ between SGLT2 inhibitors, we have removed the sentence about monitoring for eGFR decline and volume depletion from the recommendation. Practitioners should follow advice in the Summary of Product Characteristics and the BNF on monitoring according to the particular SGLT2 inhibitor being prescribed. These resources should always be consulted when prescribing medicines, as set out at the start of the recommendations section in the guideline (see: making decisions using NICE guidelines)
Renal Pharmacy Group and UK	Guideline	005	004	As above in comment 2	Thank you for your comment. In response to comments from stakeholders pointing out that the monitoring requirements may differ between SGLT2 inhibitors, we have removed the sentence

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Kidney Association					about monitoring for eGFR decline and volume depletion from the recommendation. Practitioners should follow advice in the Summary of Product Characteristics and the BNF on monitoring according to the particular SGLT2 inhibitor being prescribed. These resources should always be consulted when prescribing medicines, as set out at the start of the recommendations section in the guideline (see: making decisions using NICE guidelines)
Royal College of Nursing	General	General	General	Thank you for the opportunity to contribute to this guideline. We do not have any comments on this occasion.	Thank you for your comment.
Royal College of Physicians and Surgeons of Glasgow	Guideline	General	General	The Royal College of Physicians and Surgeons of Glasgow although based in Glasgow has a membership of 15,000 and represents Fellows and Members throughout the United Kingdom. While NICE has a remit for England, many of the recommendations are applicable to all devolved nations including Scotland. They should be considered by the relevant Ministers of the devolved governments. The College welcomes this guidance update and endorse its principles.	Thank you for your comment.
Royal College of Physicians and Surgeons of Glasgow	Guideline	General	General	Our Expert reviewer considered there were no issues with this guideline. There were clear and concise recommendation concerning the use of SGLT-2 inhibitors in CKD.	Thank you for your comment.
St George's University Hospitals NHS Foundation Trust – London Kidney Network	Guideline	004	014 - 015	We strongly urge the removal of any instruction to monitor eGFR post initiation of SGLT2-inhibitors. All trial data supports that these medications are protective to the kidney, and decrease rates of AKI. We suggest that the following recommendation is made in place of the existing point in line 14-15.	Thank you for your comment. In response to comments from stakeholders pointing out that the monitoring requirements may differ between SGLT2 inhibitors, we have removed the sentence about monitoring for eGFR decline and volume depletion from the recommendation. Practitioners should follow advice in the Summary of Product Characteristics and the BNF on monitoring according to the particular SGLT2 inhibitor being prescribed. These documents should always be consulted when prescribing

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				Following commencement of an SGLT2I there will be a physiological dip in GFR in a proportion of patients. This does not have any adverse implications. Therefore, kidney function should be monitored only at the next routine planned assessment. If the change in kidney function is a concern (>20%) we would advise investigating other causes of a deterioration in kidney function (NSAIDS, concurrent illness etc). If no cause found, consider raising this with your local nephrologist. The London Kidney Network consists of colleagues from primary and secondary care and they are unanimous that this will improve GP confidence in prescribing as well as optimising outcomes in this cohort.	medicines, as set out at the start of the recommendations section in the guideline (see: making decisions using NICE guidelines)
St George's University Hospitals NHS Foundation Trust – London Kidney Network	Guideline	004 + 005	018-020 + 001-003	The extension of the guideline to 'consider' SGLT2-inhibitor initiation in ACR 3-30 mg/mmol is a positive one (in line with UK Kidney Association draft guidance out to consultation). We are concerned that this will be confusing to primary care, who are the main target audience for this guideline. Can we give recommendations as to which patients in this group would benefit the most from the economic modelling to guide GP's? For example, in patients with suboptimal glycaemic control and eGFR > 45 we would expect a benefit in HbA1c - use in these patients would be more cost-effective.	Thank you for your comment. We use ' 'offer' and 'consider' to reflect the relative strength or quality of the underpinning evidence and the trade-off between benefits and harms in this population. This allows for clinical judgement which should always be exercised in the care of each patient. (see Making decisions using NICE guidelines). The clinical evidence considered by the committee did not Identify any particular sub-population that might particularly benefit within the A2 group.
St George's University Hospitals NHS Foundation Trust – London Kidney Network	Guideline	005	004	We strongly urge the removal of any instruction to monitor eGFR post initiation of SGLT2-inhibitors. All trial data supports that these medications are protective to the kidney, and decrease rates of AKI. We suggest that the following recommendation is made in place of the existing point in line 14-15.	Thank you for your comment. In response to comments from stakeholders pointing out that the monitoring requirements may differ between SGLT2 inhibitors, we have removed the sentence about monitoring for eGFR decline and volume depletion from the recommendation. Practitioners should follow advice in the Summary of Product Characteristics and the BNF on monitoring according to the particular SGLT2 inhibitor being prescribed. These documents should always be consulted when prescribing

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				Following commencement of an SGLT2I there will be a physiological dip in GFR in a proportion of patients. This does not have any adverse implications. Therefore, kidney function should be monitored only at the next routine planned assessment. If the change in kidney function is a concern (>20%) we would advise investigating other causes of a deterioration in kidney function (NSAIDS, concurrent illness etc). If no cause found, consider raising this with your local nephrologist. The London Kidney Network consists of colleagues from primary and secondary care and they are unanimous that this will improve GP confidence in prescribing as well as optimising outcomes in this cohort.	medicines, as set out at the start of the recommendations section in the guideline (see: making decisions using NICE guidelines)
The Dirac Foundation	Evidence Review	General	General	I am concerned that the work in this evidence mostly predates experience with COVID-19 in mid-2020 and there is insufficient impact of the interactions of SGLT2 inhibition with COVID infection, severe COVID infection and Long COVID, which can have impact, sometimes sudden impact, on renal function. Even the 2021 report by Willis et al. appears to be a 10-year study. Increased eGFR monitoring is required in cases of potential COVID infection and after infection. While SGLT2 may be best action in the absence of clear information except constant eGFR monitoring, urgent study is required. It may be that the effects are beneficial in COVID (Chatterjee S. SGLT-2 inhibitors for COVID-19 - A miracle waiting to happen or just another beat around the bush?. *Prim Care Diabetes*. 2020;14(5):564-565. doi:10.1016/j.pcd.2020.05.013), but NHS Leeds advised caution Diabetes and COVID-19 - NHS Leeds Clinical Commissioning Group (leedsccg.nhs.uk). "Despite several putative benefits with the use of SGLT2i in COVID-19, there are certain attendant risks. Firstly, cytokine storm characterised by elevations in IL-6 and TNF-α can cause peripheral lipolysis, leading to ketosis. This,	Thank you for your comment. The NICE COVID-19 guideline team has considered this comment in relation to the COVID-19 rapid guideline on CKD (NG176). NG176 includes a recommendation (3.4) to: 'Advise patients to continue taking their medicines (including ACE inhibitors, angiotensin receptor blockers, immunosuppressants and diuretics) as normal, unless advised to stop by their healthcare professional. This includes patients who have symptoms of COVID-19.' We note the potential need to temporarily stop taking SGLT2 inhibitors in the event of being acutely unwell and that the summary of products characteristics (SPC) for these drugs contains the following advice: *Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses.* We consider that this issue relates to general acute illness rather than being specific to people with COVID-19. Healthcare professionals should make sure that people who are receiving

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				coupled with a dehydration inherent to any febrile state, could lead to increased risk of euglycaemic DKA. Though potentially fatal, DKA with the use of SGLT2i is underwhelmingly low in patients with T2DM (0.5 per 1000 person years in CANVAS and 0.1% in DECLARE). Increased predisposition to euglycaemic DKA is seen in T1DM" (Das, L, Dutta, P. SGLT2 inhibition and COVID-19: The road not taken. Eur J Clin Invest. 2020; 50:e13339. https://doi.org/10.1111/eci.13339). The issue is complex. Sex, Age group, ethnic group, BMI, and eGFR already imply circa 512 combinations for which log risk may not be independently additive (i.e., there may be strong interdependency/cross terms) especially in considering COVID impact. Clearly an extensive study is required.	SGLT2 inhibitors are aware of what action to take if they become seriously unwell with any illness. We also note that NG176 includes a recommendation (3.5) to review the use of medicines for patients with CKD and suspected or confirmed COVID-19. Therefore, we consider that no specific action is required in relation to the COVID-19 rapid guideline on CKD (NG176). We will continue to monitor this issue through our COVID-19 guideline surveillance activities.
UK Clinical Pharmacy Association (UKCPA)	Evidence Review	007	Population	People with T2DM who are hyperglycaemic and are requiring rescue therapy were excluded from this study. We are concerned that this is not transparent in the recommendations.	Thank you for your comment. Specific recommendations for people who are hyperglycaemic and require rescue therapy are given in NICE guideline on type 2 diabetes which states 'Consider insulin (see the section on insulin-based treatments) or a sulfonylurea, and review treatment when blood glucose control has been achieved'. The new recommendations from this update will be incorporated into this guideline before publication, and we think this will make it clearer that the recommendation on SGLT2 inhibitors should not be read in isolation but in the context of the whole guideline on type 2 diabetes management.
UK Clinical Pharmacy Association (UKCPA)	Evidence review	008	Outcome	We wonder if the committee could consider referring to albuminuria instead of proteinuria given ACR is being measured.	Thank you for your comment. We have not made this change. While it is true that ACR measures albuminuria specifically, the NICE guideline on chronic kidney disease recommendations that an ACR of 3mg/mmol or more should be regarded as clinically important proteinuria so we think that 'proteinuria' is appropriate.
UK Clinical Pharmacy Association (UKCPA)	Evidence Review	020	010	Could this have been included as a research recommendation? It appears that there is concern over renal bone disease with SGLT2s although this is still theoretical.	Thank you for your comment. The committee considered that renal bone disease was less important for decision making than other outcomes because it was only a theoretical risk from SGLT2 inhibitors and was unlikely to be a substantial factor when

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					weighing up the risks and benefits of treatment. The committee therefore did not prioritise research on this for a research recommendation.
UK Clinical Pharmacy Association (UKCPA)	Evidence Review	021	010	We would be grateful if the committee could include findings for AKI if possible, in the main guideline to give reassurance for use	Thank you for your comment. We have not included this finding in the rationale section because although there was no evidence of a difference in AKI between groups, this might have arisen because of an insufficient number of participants to find an effect rather than a true equivalence between groups. – We have added this explanation to the evidence review**.** The rationale and impact section of the main guideline is there as a summary of the key findings and not intended to be as comprehensive as the discussion section in the evidence review.
UK Clinical Pharmacy Association (UKCPA)	Evidence Review	021	019 - 020	We would be grateful if the committee could include findings for amputation and fracture if possible, in the main guideline to give reassurance for use. We also feel that it is important to highlight groups of patients in whom these drugs should either not be used or only initiated by specialist teams (e.g. T1, T3C, chronic alcoholism etc due to potential DKA risk). We are also concerned that potential hypoglycaemia on adding into insulin/SUs in people who still have eGFR>45ml/min has not been highlighted.	Thank you for your comment. We have not added a sentence to the rationale section in the short guideline regarding amputation and fracture because although the evidence identified in our evidence review did not show a statistically significant difference between groups for people with CKD and diabetes this might have been because the trials were too small to identify an effect, rather than because and effect was not present. We have added this explanation to the evidence review. The rationale and impact section of the main guideline is there as a summary of the key findings and not intended to be as comprehensive as the discussion section in the evidence review Information about specific precautions and contraindications for use are given in the summary of product characteristics and British National Formulary entries for SGLT2 inhibitors. Prescribers are expected to refer to these resources when prescribing medicines (see: Making decisions using NICE guidelines)
UK Clinical Pharmacy	Evidence Review	022	017 - 018	We are concerned that this more detailed recommendation has not been reflected in the recommendations included. Is 6 monthly	Thank you for your comment. In response to comments from stakeholders pointing out that the monitoring requirements may

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Association (UKCPA)				monitoring what is being suggested? We are concerned that this is not likely to be useful and is not in line with the BNF or SPCs.	differ between SGLT2 inhibitors, we have removed the sentence about monitoring for eGFR decline and volume depletion from the recommendation. Practitioners should follow advice in the summary of product characteristics and the BNF on monitoring according to the particular SGLT2 inhibitor being prescribed. These resources should always be consulted when prescribing medicines, as set out at the start of the recommendations section in the guideline (see: making decisions using NICE guidelines)
UK Clinical Pharmacy Association (UKCPA)	Evidence Review	030	Section 12	We wonder if the committee could consider referring to albuminuria instead of proteinuria given ACR is being measured.	Thank you for your comment. We have not made this change. While it is true that ACR measures albuminuria specifically, the NICE guideline on chronic kidney disease recommendations that an ACR of 3mg/mmol or more should be regarded as clinically important proteinuria so we think that 'proteinuria' is appropriate.
UK Clinical Pharmacy Association (UKCPA)	Guideline	004	007	Rec 1.1.1 We are concerned about the cross referencing to the CKD guideline. This is a large onerous document to navigate in addition to the T2DM guidelines. The group feel that all information to manage a person living with diabetes in a holistic way should be consolidated into one document. We appreciate that avoidance of duplication is why this is being done but this is impractical for use.	Thank you for your comment. We recognise there is a lot of information to manage and that both guidelines need to be read. Most of the recommendations in both the diabetes and CKD guidelines would be relevant when management a person with both diabetes and CKD. As well as cross referring to the CKD guideline we have now reproduced the information about prescribing ARBs and ACE inhibitors to people with CKD and type 2 diabetes in the type 2 diabetes guideline, to reduce the need to consult both guidelines simultaneously. The NICE strategy outlines how we are planning to integrate guidelines into a more usable format, please see link for details: https://www.nice.org.uk/about/who-we-are/corporate-publications/the-nice-strategy-2021-to-2026
UK Clinical Pharmacy Association (UKCPA)	Guideline	004	009	Rec 1.1.2 consider amending to 'titrated to the highest licensed dose they can tolerate' rather than the current statement ('titrated to the highest dose they can tolerate'	Thank you for your comment. This has been amended to 'highest licensed dose' as suggested.

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UK Clinical Pharmacy Association (UKCPA)	Guideline	004	011	Rec 1.1.2 We would appreciate your consideration to use both mg/mmol and mg/g for ACR as licences etc. vary in units used. It is easier if you can quickly see the criteria in both units rather than having to calculate and there is less chance for error. Also not doing so many add unconscious bias to one agent over another.	Thank you for your comment. The NICE style guide advises that SI units should be used in NICE guidance, and so the units mg/mmol have been used for this guideline update. This is also consistent with the units used throughout the NICE guideline on chronic kidney disease.
UK Clinical Pharmacy Association (UKCPA)	Guideline	004	011	Rec 1.1.2 We would ask that the committee considers making it clear that the ACR needs to be confirmed and not just a one-off sample. No need to repeat where ACR > 30mg/mmol/ The need to repeat is to confirm microalbuminuria 3-30 mg/mmol	Thank you for your comment. Guidance on measuring ACR is given in the NICE guideline on chronic kidney disease, which is cross referred to from this guideline.
UK Clinical Pharmacy Association (UKCPA)	Guideline	004	014	Rec 1.1.2 We would appreciate your consideration to add monitoring intervals and what eGFR rate of decline would be acceptable?	Thank you for your comment. In response to comments from stakeholders pointing out that the monitoring requirements may differ between SGLT2 inhibitors, we have removed the sentence about monitoring for eGFR decline and volume depletion from the recommendation. Practitioners should follow advice in the Summary of Product Characteristics and the BNF on monitoring according to the particular SGLT2 inhibitor being prescribed. These resources should always be consulted when prescribing medicines, as set out at the start of the recommendations section in the guideline (see: making decisions using NICE guidelines)
UK Clinical Pharmacy Association (UKCPA)	Guideline	004	014	Rec 1.1.2 We would like the committee to consider adding a research recommendation relating to eGFR. Considerations given to monitoring intervals, is there any advice on how long after getting to stable dose on ACEi/ARB is it then reasonable to add in SGLT21, any additional precautions when adding into loop diuretics/thiazide diuretics. Committee to also consider other monitoring requirements e.g. Lying/Standing blood pressure specifically in higher risk patients e.g. heart failure	Thank you for your comment. In response to comments from stakeholders pointing out that the monitoring requirements may differ between SGLT2 inhibitors, we have removed the sentence about monitoring for eGFR decline and volume depletion from the recommendation. As eGFR monitoring was not within the scope of this update, an initial evidence search in this area was not carried out. Research recommendations are developed when a systematic assessment of gaps in the current evidence base has been carried out, and the committee identify this as a priority for research. Further information on research recommendations can be found here:

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					https://www.nice.org.uk/process/pmg20/chapter/writing-the-guideline#formulating-research-recommendations Practitioners should follow advice in the Summary of Product Characteristics and the BNF on monitoring according to the particular SGLT2 inhibitor being prescribed. These resources should always be consulted when prescribing medicines, as set out at the start of the recommendations section in the guideline (see: making decisions using NICE guidelines)
UK Clinical Pharmacy Association (UKCPA)	Guideline	004	014	Rec 1.1.2 we are concerned that it is not made clear that GFR cut offs for use vary from those used when treating hyperglycaemia in a person living with T2DM. You included a table on p221 that may be useful to include in the recommendations.	Thank you for your comment. In response to comments from stakeholders pointing out that the monitoring requirements may differ between SGLT2 inhibitors, we have removed the sentence about monitoring for eGFR decline and volume depletion from the recommendation. Practitioners should follow advice in the Summary of Product Characteristics and the BNF on monitoring according to the particular SGLT2 inhibitor being prescribed. These resources should always be consulted when prescribing medicines, as set out at the start of the recommendations section in the guideline (see: making decisions using NICE guidelines)
UK Clinical Pharmacy Association (UKCPA)	Guideline	004	018	Rec 1.1.3 Offer vs. consider – a subtle difference that is likely to be confusing without expansion on what the additional considerations might be. We ask that the committee looks to reference patients here who are highest risk to give some focus areas.	Thank you for your comment. It is NICE style to use 'offer' and 'consider' to reflect the relative strength or quality of the underpinning evidence and the trade-off between benefits and harms. The box above section 1.1 contains a link to Making decisions using NICE guidelines which explains this. Clinical judgement should always be exercised in the care of each patient with individual risk factors taken into account The recommendation for the A2 population was to consider SGLT2 inhibitors because of uncertainty in the evidence and economic modelling in this area. There were no particular subpopulations within this group where the evidence was

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					stronger and so a more prescriptive recommendation could not be made. All practitioners are expected to refer to the Summary of Product Characteristics and the British National Formulary for when prescribing medicines, which contain information about cautions for use.
UK Clinical Pharmacy Association (UKCPA)	Guideline	004	019	Rec 1.1.3 consider amending to 'titrated to the highest licensed dose they can tolerate' rather than the current statement ('titrated to the highest dose they can tolerate'	Thank you for your comment. This has been amended to 'highest licensed dose' as suggested.
UK Clinical Pharmacy Association (UKCPA)	Guideline	005	001	Rec 1.13 We would appreciate your consideration to use both mg/mmol and mg/g for ACR as licences etc. vary in units used. It is easier if you can quickly see the criteria in both units rather than having to calculate and there is less chance for error. Also we would ask that the committee considers making it clear that the ACR needs to be confirmed and not just a one off sample.	Thank you for your comment. The NICE style guide advises that SI units should be used in NICE guidance, and so the units mg/mmol have been used for this guideline update. This is also consistent with the units used throughout the NICE guideline on chronic kidney disease.
UK Clinical Pharmacy Association (UKCPA)	Guideline	005	004	Rec 1.1.3 We would appreciate your consideration to add monitoring intervals and what eGFR rate of decline would be acceptable	Thank you for your comment. In response to comments from stakeholders pointing out that the monitoring requirements may differ between SGLT2 inhibitors, we have removed the sentence about monitoring for eGFR decline and volume depletion from the recommendation. Practitioners should follow advice in the Summary of Product Characteristics and the BNF on monitoring according to the particular SGLT2 inhibitor being prescribed. These documents should always be consulted when prescribing medicines, as set out at the start of the recommendations section in the guideline (see: making decisions using NICE guidelines)
UK Clinical Pharmacy	Guideline	007	004	The committee has noted clinical and cost efficacy uncertainty in the ACR 3-30mg/mmol. Were there any populations that were noted as having shown better clinical and cost efficacy?	Thank you for your comment. There were no sub-populations identified within the A2 category that had better clinical or cost

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Association (UKCPA)					effectiveness. There was more certainty around the clinical and cost effectiveness for the A3 (>30mg/mmol) group.
UK Clinical Pharmacy Association (UKCPA)	Guideline	007	014	We have concern over the reference to the BNF. Dapagliflozin in the BNF states that If eGFR <60ml/min/1.73m2 then monitor renal function 2-4 times a year' and no mention in the SPC of this. BNF must be kept up to date if you are going to refer to this. Empagliflozin and Canagliflozin say annual. Ertugliflozin says 'frequent' – a standardised recommendation for this would be useful.	Thank you for your comment. We noticed the discrepancy between the SPC and BNF for dapagliflozin before consultation on this draft guidance, and we alerted the BNF to this. We have checked the BNF entry for dapagliflozin and noted no mention of eGFR monitoring, consistent with the SPC for dapagliflozin and so we think that the BNF entry has now been updated to be consistent with the SPC. In response to comments from stakeholders pointing out that the monitoring requirements may differ between SGLT2 inhibitors, we have removed the sentence about monitoring for eGFR decline and volume depletion from the recommendation. Practitioners should follow advice in the Summary of Product Characteristics and the BNF on monitoring according to the particular SGLT2 inhibitor being prescribed. These resources should always be consulted when prescribing medicines, as set out at the start of the recommendations section in the guideline (see: making decisions using NICE guidelines)
UK Clinical Pharmacy Association (UKCPA)	Guideline	007	025	We have concern over the cost impact in a primary care setting. Recognition of the initial cost impact is appreciated however is there any consensus/modelling that could be included on how long costs will need to be floated before savings on outcomes are made?	Thank you for your comment. Due to the potential high resource impact of recommendations an economic analysis was conducted which suggested that SGLT2 inhibitors were cost saving compared to standard of care over 10 years. A resource impact report and local resource impact template have been developed to support implementation of these recommendations.
UK Clinical Pharmacy Association (UKCPA)	Guideline	04	014 - 015	Rec 1.1.2 We are concerned this statement is too diffuse and it would be helpful to have some parameters around this e.g. when to stop, when to continue and a note added when to check eGFR	Thank you for your comment. In response to comments from stakeholders pointing out that the monitoring requirements may differ between SGLT2 inhibitors, we have removed the sentence about monitoring for eGFR decline and volume depletion from the recommendation. Practitioners should follow advice in the Summary of Product Characteristics and the BNF on monitoring

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					according to the particular SGLT2 inhibitor being prescribed. These resources should always be consulted when prescribing medicines, as set out at the start of the recommendations section in the guideline (see: making decisions using NICE guidelines)
UK Clinical Pharmacy Association (UKCPA)	Questions	Comment form	Q1	Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why We believe the biggest impact on practice will be cohort of people living with microalbuminuria. This is likely to be large numbers and there is less clarity from the recommendations on any risk stratification. This population has traditionally been under recognised and identification (both testing and acting on that testing) has been challenging.	Thank you for your comment. The recommendation for the A2 population was to consider SGLT2 inhibitors because of uncertainty in the evidence and economic modelling in this area. There were no particular subpopulations within this group where the evidence was stronger and so a more prescriptive recommendation could not be made.
UK Clinical Pharmacy Association (UKCPA)	Questions	Comment form	Q2	Would implementation of any of the draft recommendations have significant cost implications? Yes. Both in the costs of the agents and in the screening and processes needed to get them appropriately on these agents.	Thank you for your comment. Due to the potential high resource impact of recommendations an economic analysis was conducted which suggested that SGLT2 inhibitors were cost saving compared to standard of care over 10 years. A resource impact report and local resource impact template have been developed to support implementation of these recommendations.
UK Clinical Pharmacy Association (UKCPA)	Questions	Comment form	Q3	What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or examples of good practice.) We thought this guidance would benefit from having recommendations for use and also recommendations for implementation. A lot of useful information about safety is included in the evidence review and is lost in the recommendations. Information could also be included then about sick day rules.	Thank you for your comment. When we publish guidance, we also have a tools and resources tab which lists implementation tools and other useful resources. An example of this can be found here alongside the CKD guideline. NICE routinely produce baseline assessment and resource impact tools. To encourage the development of other practical support tools, we run an endorsement scheme aimed at encouraging our partners to develop these in alignment with NICE recommendations. Eligible tools are assessed and if

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				An algorithm would be useful, or this being added into the algorithm in the T2DM Management guideline. A kidney risk tool may help the decision process regarding the need for SGLT2 in those with an ACR 3-30 mg/mmol We would like to highlight the importance of QoF indicators for this being added.	successful, will be endorsed by NICE and featured on the NICE website alongside the relevant guideline. Indicators for the QOF are reviewed and updated on an annual basis, the process for this can be found here These recommendations will be incorporated into the NICE guideline on the management of type 2 diabetes in adults. There is another update to this guideline in development (see the guideline development page for details). As part of this work a visual summary of the recommendations on choosing medicines for type 2 diabetes has been produced. It is the intention that these recommendations will be included in the final version of visual summary when it is published (expected publication date February 2022).

Organisation name – Stakeholder or respondent	Disclosure on tobacco funding / links	Comments
Novartis Pharmaceuticals UK Limited	Since April 2005 Novartis has exclusively licensed glycopyrronium bromide and certain intellectual property relating to its use and formulation from Vectura and its co-development partner, Sosei Heptares. The following inhaled medications are comprised of, or contain glycopyrronium bromide: • Seebri® Beezhaler® (glycopyrronium bromide) (used as a maintenance treatment for Chronic Obstructive Pulmonary Disease (COPD)) • Ultibro® Breezhaler® (indacaterol/glycopyrronium bromide) is used as a maintenance treatment for COPD • Enerzair® Breezhaler® (indacaterol/glycopyrronium bromide/mometasone furoate) is used as a maintenance treatment for asthma uncontrolled with LABA/ICS. Phillip Morris International (a tobacco company) is currently in the process of acquiring Vectura Group plc.	No further action required

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Bayer plc	**Current Situation** • Bayer does not have direct or indirect links with, or funding from, manufacturers, distributors or sellers of smoking products but Bayer provides pesticides for crops, which would therefore include tobacco crops. • Bayer is a member of the Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA) (http://www.coresta.org/) within the scope of recommendations of pesticides used for protection of tobacco plants. • It is also a member of country and EU business federations such as the Confederation of British Industry (CBI) and 'Business Europe', which include tobacco companies. **Past Situation** In 2006, Bayer and its subsidiary Icon Genetics piloted a new process for producing biotech drugs in tobacco plants. Icon Genetics was acquired by Nomad Bioscience GmbH from Bayer in 2012.	No further action required