Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Association of British Clinical Diabetologists	Guideline	General	General	We feel this is a missed opportunity to give guidance on potassium binders, especially if the next iteration of this guideline takes as long to emerge as this one has (six years).	Thank you for your comment. We have added a new recommendation referring to the NICE technology appraisals for treating hyperkalaemia with potassium binders (sodium zirconium cyclosilicate and patiromer).
Association of British Clinical Diabetologists	Guideline	022	023	The draft suggests that SGLT2 inhibitors should be prescribed only when the UACR is 30mg/mmol or more and yet the DAPA-CKD study showed benefit down to an inclusion UACR of 22.6mg/mmol.	Thank you for your comments. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. NICE is also currently undertaking a technology appraisal of dapagliflozin for treating chronic kidney disease which will include the DAPA-CKD trial. Therefore, data from DAPA-CKD has been removed from this update. See https://www.nice.org.uk/guidance/indevelopment/gid-ta10808 for details. The NICE CKD guideline will cross refer to this technology appraisal appraising dapagliflozin when it is published.
Association of British Clinical Diabetologists	Guideline	023	002	It also suggests monitoring for eGFR decline. In our recent ABCD-RA guideline for management of hyperglycaemia in diabetic kidney disease, we advise against "routine assessment of renal function within 6–8 weeks of SGLT-2 initiation since there is likely to be a transient deterioration and this is not a reason to withdraw the drug".	Thank you for your comment. We have included a clarification to the rationale stating that eGFR monitoring should depend on people's circumstances and on the BNF advice of monitoring requirements for people using SGLT2 inhibitors.
Association of British Clinical Diabetologists	Guideline	063	010	The document does not support the use of SGLT2 inhibitors in people who have not been diagnosed with type 2 diabetes, despite evidence of reno-protection	Thank you for your comment. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				irrespective of diabetes status. This is likely to make the guideline out of date very quickly. Note that the recently published scope of the health technology appraisal for dapagliflozin is not limited to reno-protection in diabetes.	recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. NICE is also currently undertaking a technology appraisal of dapagliflozin for treating chronic kidney disease which will include the DAPA-CKD trial. Therefore, data from DAPA-CKD has been removed from this update. See https://www.nice.org.uk/guidance/indevelopment/gid-ta10808 for details. The NICE CKD guideline will cross refer to this technology appraisal appraising dapagliflozin when it is published.
Association of British Clinical Diabetologists	Guideline	081	005 - 010	We feel that the advice to target both systolic and diastolic blood pressure needs to be nuanced. In a scenario where a patient has achieved a systolic target (say, of 125mmHg), we feel that few clinicians would chase a diastolic pressure below 80 mmHg (and hence risk postural hypotension).	Thank you for your comment. We amended the rationale to highlight the importance of individualised blood pressure targets.
Astellas Pharma Limited	Guideline	009 1.1.2 1 019 1.5.5	018	Studies suggest a relationship between anaemia of CKD and poorer patient outcomes, particularly cardiovascular outcomes, progression to end-stage renal disease and increased hospitalisations . We would therefore suggest that presence of anaemia is included as a risk factor in people living with CKD. (Mohanram et al. (2004) Anaemia and end-stage renal disease in patients with type2 diabetes. Kidney International. vol 66, pp1131-113 and Kovesdy et al.(2006) Association of anaemia with outcomes in men with moderate and severe CKD vol 69, issue 3, pp560-564). Cullerton et al. (2006) Impact of anaemia on hospitalisation and mortality in older adults. Blood 15;107(10):	Thank you for your comment. The evidence for adults was not reviewed for the list of factors to test for CKD and for the list of factors for referral for specialist assessment because these areas were out of scope of the current update. The committee agreed that evidence is needed before adding anaemia to these recommendations.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Astellas Pharma Limited	Guideline	033 1.9.1 1	017	A new class of treatment to manage anaemia of CKD is expected to receive marketing authorisation in 2021 (Hypoxia-inducible factor propyl hydroxylase inhibitors (HIF-PHIs)). These treatments have a different mechanism of action to ESAs and will provide an alternative means of managing anaemia in patients with CKD.	Thank you for your comment. We have passed your comment on to the NICE surveillance team who will explore whether this recommendation needs updating in the future.
Astellas Pharma Limited	Research question	009		A new class of treatment to manage anaemia of CKD is expected to receive marketing authorisation in 2021 (Hypoxia-inducible factor propyl hydroxylase inhibitors (HIF-PHIs)). These treatments have a different mechanism of action to ESAs and will provide an alternative means of managing anaemia in patients with CKD.	Thank you for your response. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
AstraZeneca UK Limited	Evidence Review H	043	028 - 029 034 - 035	**Data misrepresentation** The summary of evidence for 'Diabetes medications' attempts to summarise the data for both dapagliflozin and canagliflozin, yet AstraZeneca feels that the approach taken is biased towards canagliflozin in the following places: • the following statement ***"All-cause mortality (RR 0.78 [95% CI 0.68, 0.91], up to 2.4 years follow-up, high quality of evidence)"*** refers to the results of the pair-wise meta-analysis of DAPA-CKD, DELIGHT and CREDENCE trials conducted by the NICE team. However, only dapagliflozin has demonstrated a significant treatment effect on all-cause mortality in the DAPA-CKD trial (HR 0.69; 95% CI, 0.53 to 0.88; P=0.004),[10] whilst the treatment effect with canagliflozin was not statistically significant (HR 0.83; 95% CI, 0.68 to 1.02).[31] This should be	Thank you for your comment. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. NICE is also currently undertaking a technology appraisal of dapagliflozin for treating chronic kidney disease which will include the DAPA-CKD trial. Therefore, data from DAPA-CKD has been removed from this update. See https://www.nice.org.uk/guidance/indevelopment/gid-ta10808 for details. The NICE CKD guideline will cross refer to this technology appraisal appraising dapagliflozin when it is published.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				clearly explained, given that several bullet points make a distinction between data only reported for canagliflozin. The statement also states 'high quality of evidence' whilst the evidence review stated on page 253, in the table summarising outcomes for 'SGLT2 inhibitors vs placebo' that the evidence for all-cause mortality benefit of canagliflozin vs placebo was determined to be of moderate quality. Regarding the following statement: ***"Hospitalisation for heart failure (RR 0.63 [95% CI 0.49, 0.82], 6 months follow-up, moderate quality of evidence, only reported for canagliflozin)"***. In DAPA-CKD, the results for the composite of death from cardiovascular causes or hospitalisation for heart failure indicated a strong treatment effect for dapagliflozin (HR 0.71; 95% CI 0.55–0.92; p=0.009).	
AstraZeneca UK Limited	Evidence Review H	043	021	**Concern** In 'the committee's discussion and interpretation of the evidence' section of Evidence Review H, the Committee summarise the data on relevant SGLT2 inhibitors, dapagliflozin and canagliflozin, under the heading of 'Diabetes medications'. As mentioned above, whilst dapagliflozin is indicated for the treatment of patients with T2DM and T1D, it also has marketing authorisation for treatment of HFrEF.[22] Dapagliflozin has subsequently demonstrated overwhelming efficacy in the DAPA-CKD renal outcomes trial (N=4304), of which 32% of the participants did not have T2DM. The treatment effect of dapagliflozin across	Thank you for your comment. The section has been renamed as 'SGLT2 inhibitors'. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. NICE is also currently undertaking a technology appraisal of dapagliflozin for treating chronic kidney disease which will include the DAPA-CKD trial. Therefore, data from DAPA-CKD has been removed from this update. See https://www.nice.org.uk/guidance/indevelopment/gid-ta10808 for details. The NICE CKD guideline will

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				all endpoints was consistent between the T2DM and non-T2DM populations,[10] and marketing authorisation **[This text was identified as confidential and has been removed].** Categorising dapagliflozin as a 'diabetic medication' is inaccurate and misleading, and AstraZeneca is concerned that this terminology perpetuates misclassification of dapagliflozin and the SGLT2 inhibitor class.	cross refer to this technology appraisal appraising dapagliflozin when it is published.
AstraZeneca UK Limited	Evidence Review H	044	006 - 007	**Concern no. 2** In the Committee's discussion and interpretation of the evidence on interventions to lower proteinuria, the following conclusion is made regarding the decision to restrict the recommendation for SGLT2 inhibitors in patients with T2DM to only patients with an ACR >30 mg/mml: • ***"Overall, the committee agreed that a threshold of ≥30 mg/mmol was a sensible threshold that broadly represented the inclusion criteria of the trials and was consistent with other recommendations in the guideline."*** AstraZeneca disagrees with this conclusion for the following reasons. The DAPA-CKD trial demonstrates significant treatment effect of dapagliflozin across a range of renal and cardiovascular outcome measures in patients with an ACR between 200 and 5000 mg/g (approximately 20 to 500 mg/mmol). A pre-specified	Thank you for your comment. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. NICE is also currently undertaking a technology appraisal of dapagliflozin for treating chronic kidney disease which will include the DAPA-CKD trial. Therefore, data from DAPA-CKD has been removed from this update. See https://www.nice.org.uk/guidance/indevelopment/gid-ta10808 for details. The NICE CKD guideline will cross refer to this technology appraisal appraising dapagliflozin when it is published. Regarding your comment about the risk of dying in adults with macroalbuminuria, we confirm that the risk is reduced with the use of SGLT2 inhibitors. This was reported in the CANVAS trial by Neuen and colleagues in 2019.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
		043	040 - 043	subgroup analysis of the primary endpoint investigated patients with uACR above and below 1000 mg/g (approximately 100mg/mmol) and showed no significant between-group difference, indicating consistency of treatment effect across the ACR spectrum included in the trial. [10] Further evidence to support the consistency of treatment effect with dapagliflozin across the ACR range comes from the DECLARE-TIMI 58 trial (N=17,160) of dapagliflozin in patients with T2DM and established atherosclerotic CVD or multiple cardiovascular risk factors.[26] Dapagliflozin reduced the risk of the secondary renal-specific composite outcome (sustained decline of ≥40% in eGFR to less than 60 mL/min per 1.73m^2, ESRD or death from renal causes) by 47% (95% CI 0·43–0·66; p-value<0.0001), with the treatment effect consistent across all uACR categories including those with normo- and microalbuminurea (<30mg/g, 30-300mg/g, >300mg/g / <3mg/mmol, 3-30mg/mmol, >30mg/mmol) (p-value for interaction=0.3).[27] Based on an analysis using Clinical Practice Research Datalink (CPRD) and QOF data, currently in England there are approximately **[This text was identified as confidential and has been removed]** with CKD and T2DM who have an ACR between 20 and 30 mg/mmol who could potentially benefit from treatment with dapagliflozin.[12, 28] 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	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				NHS,[8] and every effort should be made to achieve this. Recommendations reflecting the full population in which clinical value has been observed in clinical trials would ensure all patients covered by the trial evidence, including those with less severe disease, can benefit from effective therapies. The following statement was also included in the committee's discussion and interpretation of the evidence section of Evidence Review H: • ***"The committee also agreed that this recommendation was for adults with ACR 30 mg/mmol or more because the risk of dying was lowest in adults with macroalbuminuria (ACR >30 mg/mmol)."*** This is not accurate and assumed to be a mistake which is meant to read that the risk of dying was **highest** in adults with macroalbuminuria. However, even when taken as described, this denies access to a therapy that could reduce the risk of mortality until the individuals risk is already unacceptably high, and as such is not a strong rationale for restricting the recommendation for dapagliflozin to a patient population with more severe disease. **AstraZeneca requests the Committee to consider reflecting the full breadth of evidence with the following recommendation (proposed changes in red):**	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				1.6.6: For adults with CKD and diabetes (type 1 and type 2), offer an SGLT2 inhibitor, ~~in addition to an ACE inhibitor or an ARB,~~ if they have: • type 2 diabetes • an ACR of ≥20 mg/mmol for dapagliflozin or ≥30 mg/mmol for canagliflozin meet the criteria in the marketing authorisation (including relevant eGFR thresholds)	
AstraZeneca UK Limited	Guideline	General	General	**SUMMARY** 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, as evidenced by our development of medicines to treat conditions such as CKD, type 2 diabetes mellitus (T2DM) and heart failure (HF). 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 2021 guideline proposed by the NICE Guideline Development Committee. AstraZeneca agrees with many of the recommendations set out by the committee in the draft CKD guideline, particularly the decision to include specific recommendations on pharmacotherapy in patients with proteinuria, including the use of SGLT2 inhibitors for patients with CKD and T2DM.	Thank you for your comments. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. NICE is also currently undertaking a technology appraisal of dapagliflozin for treating chronic kidney disease which will include the DAPA-CKD trial. Therefore, data from DAPA-CKD has been removed from this update. See https://www.nice.org.uk/guidance/indevelopment/gid-ta10808 for details. The NICE CKD guideline will cross refer to this technology appraisal appraising dapagliflozin when it is published. Regarding your comments about the current recommendation to avoid or stop renin-angiotensin-aldosterone system inhibitor (RAASi) therapy in patients with, or at risk of hyperkalaemia, these recommendations are in greyed out areas of the consultation guideline which were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				However, there are areas of the draft guideline which do pose AstraZeneca some concern and/or may represent a significant missed opportunity to improve the lives of patients. These areas include: 1. No recommendation in the 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. Compelling clinical evidence now exists that demonstrates the efficacy and safety of an SGLT2 inhibitor in this important patient population that has very limited alternative treatment options available to it. Given the frequency of NICE guideline updates, it may be several years until the next opportunity arises for SGLT2 inhibitors to be included for the non-diabetic CKD population – we respectfully request the NICE Guideline Committee to carefully consider this newly available evidence and to create a clear recommendation for CKD patients without T2DM. 2. The proposed recommendation for SGLT2 inhibitors in people with T2DM restricts use to those with an ACR of ≥30 mg/mmol, despite strong evidence demonstrating the clinical benefit with dapagliflozin in patients with ACR as low as ~20 mg/mmol. 3. The proposed recommendation for SGLT2 inhibitors in people with T2DM states that	make substantive changes to these recommendations, but we have added a new recommendation referring to the NICE technology appraisals for treating hyperkalaemia with potassium binders (sodium zirconium cyclosilicate and patiromer). We have also passed your issue on to the surveillance team who will explore whether recommendations need updating in the future. Regarding your comment about recommendations on the frequency of monitoring, we have added a note to Table 2 about ACR monitoring which should be individualised based on a person's individual characteristics, risk of progression and whether a change in ACR is likely to lead to a change in management. The rationale has examples about the frequency of ACR monitoring ACR (more frequently monitoring in people with high ACR categories A2 or A3; or where a change in ACR would affect management). The committee agreed to make a research recommendation to identify the optimal frequency of monitoring ACR in adults, children and young people with CKD.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				"eGFR should be monitored following treatment initiation"; it has come to our attention that this recommendation is likely to cause confusion amongst non-specialists that could result in unnecessary termination of SGLT2 inhibitor treatment if the prescriber is unaware that an initial drop in eGFR is expected, due to its direct mechanism of action in the kidney. 4. The current recommendation to avoid or stop renin-angiotensin-aldosterone system inhibitor (RAASi) therapy in patients with, or at risk of hyperkalaemia, are not aligned to NICE's current recommendations for the use of potassium binders. Strong alignment to, or at least clear reference to NICE's guidance on treatments for hyperkalaemia in the CKD guideline, is warranted and would support greater uniformity of care by practitioners. 5. No recommendations are currently provided on the frequency of urine albumin to creatinine ratio (uACR) testing in individuals diagnosed with, or at high-risk of, CKD. We propose that a recommendation is included to test all patients with, or at high risk of CKD, at least annually. 6. Insufficient emphasis is currently placed on communication and electronic data sharing between primary and secondary care, in order to deliver optimised care for patients	

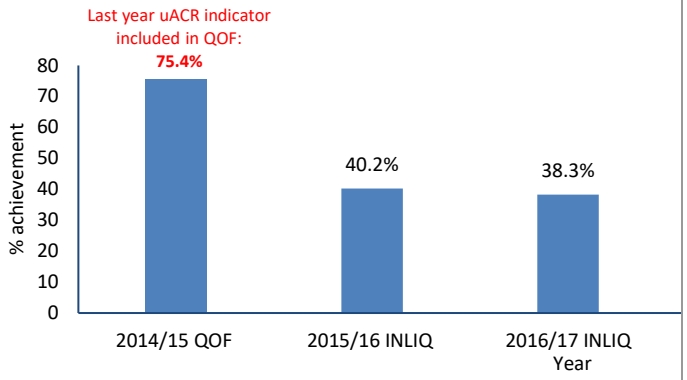
Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				The evidence for these concerns and new recommendations is outlined in detail in the sections below. 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 UK Limited	Guideline	013 014	016 – 029 001 – 008 & Table 2	**<u>Concern no. 5</u>** AstraZeneca is concerned that recommendations 1.3.1 and 1.3.2 on uACR testing in those diagnosed with CKD and those at risk of CKD do not: • provide clear guidance on the frequency of testing • adequately capture the importance and clinical value of considering ACR alongside eGFR uACR testing is of great clinical importance in CKD for two main reasons. 1) Early diagnosis of patients with CKD stages 1 and 2 (when eGFR is >60 ml/min/1.73 m^2) is not possible without ACR testing, making it essential for early intervention and treatment. In order to achieve the maximum risk reduction in ESRD that is possible with new CKD therapies, earlier diagnosis and intervention are essential. 2) Increased ACR correlates directly with increased risk of coronary artery disease (CAD), stroke, HF, CV mortality, all-cause mortality, and risk of reaching ESRD.[47-49] Therefore, uACR testing in those already diagnosed with CKD to identify those at high risk of CV or renal events is a crucial primary prevention step and should	Thank you for your comment. We have added a note to Table 2 about the frequency of ACR monitoring stating that ACR monitoring should be individualised based on a person's individual characteristics, risk of progression and whether a change in ACR is likely to lead to a change in management. ACR monitoring was not recommended alongside to eGFR because eGFR is used to define progression rather than ACR and so more frequent monitoring is needed (see recommendations 1.3.5 to 1.3.8 which define progression in adults with the use of eGFR). No specific evidence on ACR monitoring frequency was found but the committee noted that it is a costly test and should not be used every time eGFR is measured, but on an individual basis. The rationale has examples about the frequency of ACR monitoring ACR (more frequently monitoring in people with high ACR categories A2 or A3; or where a change in ACR would affect management). The committee agreed to make a research recommendation to identify the optimal frequency of monitoring ACR in adults, children and young people with CKD.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				be performed alongside eGFR testing as part of regular monitoring. Since the QOF indicators for uACR testing in people with diabetes or on the CKD register were removed in 2013/2014 and 2014/2015, the proportion of patients receiving an annual uACR test in England has reduced dramatically, particularly for patients without diabetes.[50] In 2018/19, just 39% of patients with CKD received a uACR test in the last 12 months, a drop from 74% in 2014/15, the last year that testing was included in QOF (Figure *1*). [50] This decline in testing rates is likely to be driven by a combination of factors, including a misperception amongst HCPs that uACR testing is less valuable in the diagnosis and management of CKD than eGFR testing due to its removal from QOF,[51] and it's positioning in the NICE CKD guidelines.	

Figure 1: uACR testing rates before and after removal of uACR testing indicator for individuals with CKD (including those with diabetes) from the QOF registry



Source: [50]
Abbreviations: CKD: chronic kidney disease; INLIQ: indicators no longer in QOF; QOF: Quality of Outcomes Framework
Notes: uACR testing indicator was CKD004: percentage of patients on the CKD register whose notes have a record of a urine:creatinine ratio (or protein:creatinine ratio) test in the preceding 12 months.

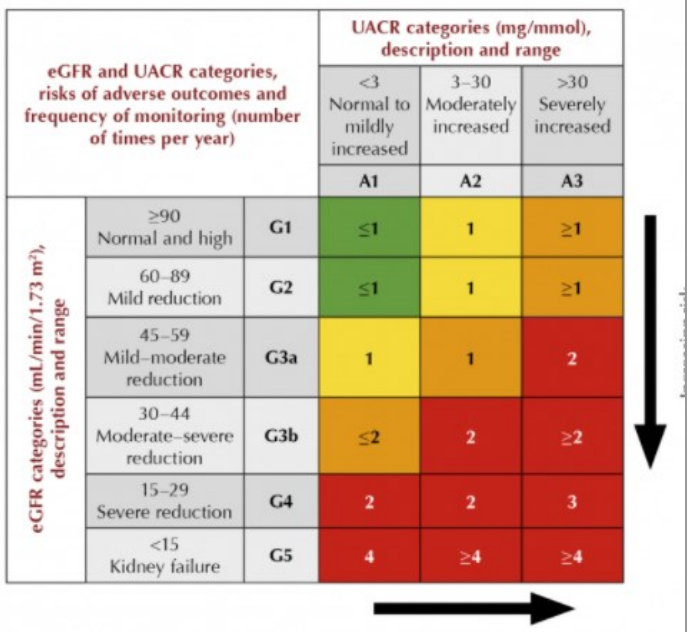
Role of uACR testing in early diagnosis

Based on an analysis of UK CPRD and QOF data, the removal of uACR testing indicators from QOF in 2013/2014 and 2014/2015, resulted in **[This text was identified as confidential and has been removed]** fewer patients being diagnosed in England with Stage 1 and Stage 2 CKD in the following year, respectively.[12, 28] The latest available data for 2018/2019 shows similar

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				patient numbers (**Error! Reference source not found.**). E very individual with CKD that is not detected early, risks disease progression. Currently, the majority of CKD cases in the UK are diagnosed at stage 3, by which time irreversible, yet preventable, kidney damage has occurred and the patients' health-related quality of life has already begun to decline as the disease progresses.[52, 53] **[This text was identified as confidential and has been removed]** ***Importance of regular uACR testing in those with or at-risk of developing CKD to assess prognosis and monitor disease progression*** Recommendation 1.3.2 states that both the uACR rate and the eGFR rate should be used to determine the patients risk category and therefore the number of **eGFR tests** that should be performed annually. The current draft guidelines provides no recommendation on the frequency of uACR testing. Similarly, the role of uACR in assessing the **risk of CKD progression** is currently not included in the guideline, with all recommendations on defining disease progression (1.3.3 – 1.3.6) focused on eGFR, with the powerful prognostic ACR measure omitted. The KDIGO guidelines state that uACR testing should be conducted alongside eGFR testing, since both parameters are required to accurately assess disease progression. They use the same risk categorisation	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				approach as CG182 to inform the frequency that **both eGFR and uACR tests** should be performed, annually (Figure 2).[54] KDIGO recommend that uACR be tested *'at least annually in people with CKD, and more often in those at higher risk of progression, and/or where measurement will impact therapeutic decisions'*.[54] This is reinforced in a recent consensus statement by the Diabetic Kidney Disease Testing Consensus Committee that is endorsed by the Primary Care Diabetes Society (PCDS), Association of Clinical Diabetologists (ABCD), UK Clinical Pharmacy Association, TREND Diabetes, Renal Association, Association of Nephrology Nurses and Diabetes UK (DUK).[51] **uACR testing is a critical aspect of determining CKD progression and risk**, since the development of albuminuria or rising albuminuria correlates directly with increased risk, which cannot be determined by eGFR alone. According to the KDIGO recommendations on CKD risk management (Figure 2), which are also adopted by NICE in CG182, if a patient transitions from G3a A2 to G3a A3, or from G3b A1 to G3b A2 then they become high-risk and should be referred to a nephrologist for specialist review.[54] If uACR testing is not repeated regularly to inform disease management then such disease progression cannot be detected and these high-risk patients would go unoticed.	

Figure 2: KDIGO recommendations on frequency of monitoring of GFR and uACR for people with or at risk of CKD



eGFR and UACR categories, risks of adverse outcomes and frequency of monitoring (number of times per year)			UACR categories (mg/mmol), description and range		
			<3 Normal to mildly increased	3–30 Moderately increased	>30 Severely increased
			A1	A2	A3
eGFR categories (mL/min/1.73 m²), description and range	≥90 Normal and high	G1	≤1	1	≥1
	60–89 Mild reduction	G2	≤1	1	≥1
	45–59 Mild–moderate reduction	G3a	1	1	2
	30–44 Moderate–severe reduction	G3b	≤2	2	≥2
	15–29 Severe reduction	G4	2	2	3
	<15 Kidney failure	G5	4	≥4	≥4

Source: [54]
Abbreviations: ACR: albumin:creatine ratio; CI: confidence interval; ESRD: End-stage renal disease; UACR urine albumin:creatine ratio

Regularly testing of ACR to determine the presence or increase of albuminuria is of equal importance to eGFR in defining risk of accelerated progression and CV risk.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Elevations in ACR can have important implications for clinical management including increased frequency of review (as per KDIGO guidelines)[54], pharmacotherapy changes including optimisation of RAASi, tighter BP control, more intensive lipid control and even referral to a nephrologist. NICE clinical guidelines for CKD management are heavily referenced and influential for clinical practice in the UK, particularly for primary care. In order to optimise patient and population level health outcomes, it's important that this influence be utilised to encourage better uACR testing rates following the decline observed since its removal from QOF. This necessitates recognition from NICE of the equal significance of uACR and eGFR testing and clear recommendations on the frequency of monitoring required. **AstraZeneca requests the Committee to consider reflecting this evidence with the following recommendation (proposed changes in red):** • Page 14, Table 2: Minimum number of monitoring checks (eGFR **and uACR**) per year for adults, children and young people with or at risk of chronic kidney disease Based on clinical input from General Practitioners, AstraZeneca believes this is achievable since for most patients managed in primary care this recommendation would only lead to one uACR test annually per patient with or at risk of CKD. Based on feedback from specialists, for those high-risk patients managed in	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				secondary care this updated recommendation is likely to more closely reflect current clinical practice since their ACR will normally be monitored alongside eGFR as standard.[25]	
AstraZeneca UK Limited	Guideline	021	001 - 003	**Suggestion no. 6** Ensuring the correct management setting for patients with CKD is critical to achieving patient centred care and optimising outcomes. In UK clinical practice, the volume of referrals to specialist care often outweighs the capacity of specialist services for consultations, leading to long waiting times for patients. Referrals for patients with CKD often lack the detail required for effective triage, limiting the ability of specialists to determine the need to see patient or whether advise / guidance to the PCP on management in primary care would be more appropriate. Consequently, patients who should be seen urgently may wait for long periods and those who could be managed in primary care under the advice of a specialist may receive a specialist consultation anyway, unnecessarily prolonging waiting times. Waiting times have also increased dramatically as a result of the COVID-19 pandemic, and there is expected to be a considerable back-log of referrals for some time. Recommendation 1.5.7 on referral set out in CG182 encourages GPs to seek advice/guidance from a specialist in cases where referral may not be required. AstraZeneca supports this recommendation but suggest that NICE plays a role in encouraging best practice with	Thank you for your comment. The committee agreed with your assessment and believed this guideline will enable more appropriate referrals. Regarding your comment about encouraging collaboration between primary and secondary care, the last bullet point of recommendation 1.5.9 suggests specifying criteria for future referral and re-referral if GP follow up is agreed; and for children and young people, these criteria should be agreed between the GP and secondary care services.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				respect to communication between primary and secondary care, and mechanisms through which that can be achieved. Examples of best practice are being observed across the UK, including in East London where virtual CKD clinics allow nephrologists to access general practice patient records and enter management suggestions for the PCP. In this case, just 20% of patients referred to the virtual clinic required a hospital visit and wait time for a specialist opinion reduced from 64 days to 5-10 days.[55] Owing to its considerable success, this management system was quoted in the NHS Long Term Plan,[8] with this and similar approaches being reviewed by the Renal Association to drive innovation and change to CKD pathways nationally. For many patients, the most appropriate management setting is primary care, and with effective advice/guidance systems and virtual clinics in place the capabilities and knowledge of specialists can be utilised in primary care, optimising the management of patients whilst reducing hospital visits. Minimising hospital contact and the need to travel long distances is also of further importance during the COVID-19 pandemic, particularly for clinically vulnerable people. This goal would be supported by additional recommendations in the NICE guideline to further encourage collaboration between primary and secondary care as well within MDTs that should include different but interlinked specialities including nephrology, endocrinology and cardiology.	

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
AstraZeneca UK Limited	Guideline	022 - 023	002	**Concern no. 3** 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 of 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.[29] eGFR subsequently increases again over several months and henceforth the SLT2i treatment slows progressive eGFR decline as compared with individuals not taking SGLT2 inhibitors. In the DAPA-CKD 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).[10] Similar results have been consistently demonstrated in the clinical trials of other SGLT2 inhibitors that measured change in eGFR.[10, 13, 26, 30, 31] 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	Thank you for your comment. We have included a clarification to the rationale stating that eGFR monitoring should depend on people's circumstances and on the BNF advice of monitoring requirements for people using SGLT2 inhibitors.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				induced risk reduction for CV and renal outcomes,[32] and has no impact on AE rate.[32, 33] 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 treatment if the HCP isn't aware of the mechanism of action for this drug class. Furthermore, unlike ACEi/ARB treatment, SGLT2 inhibitors do not cause increased potassium and therefore do not have the same requirement for monitoring in the weeks following initiation. Therefore eGFR monitoring should not be recommended in this context. **AstraZeneca requests the Committee to consider reflecting this with the following recommendation (proposed changes in red):** 1.6.6: For adults with CKD and diabetes (type 1 and type 2), offer an SGLT2 inhibitor~~, in addition to an ACE inhibitor or an ARB,~~ if they have: • type 2 diabetes • an ACR of ≥20 mg/mmol for dapagliflozin or ≥30 mg/mmol for canagliflozin • meet the criteria in the marketing authorisation (including relevant eGFR 1 thresholds) Monitor for volume depletion ~~and eGFR decline~~	
AstraZeneca UK Limited	Guideline	023	007 – 012	**Concern no. 1** For adults with CKD **without diabetes**, the committee has not included a recommendation for the use of SGLT2 inhibitors. This is a patient population with very	Thank you for your comment. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				high unmet need and limited treatment options available to it, having not benefited from any pharmacotherapeutic advances for over 20 years. AstraZeneca believes there to be approximately 1.4 million of these patients in England, who could now benefit substantially from treatment with an SGLT2 inhibitor. On page 63 of the Guideline (lines 9-12) it is stated that ***"The committee agreed that this was a fast moving area and that studies were being done to assess the usefulness of SGLT2 inhibitors in people with CKD who do not have diabetes, but they agreed the evidence was not yet strong enough to make a recommendation, even though it looked promising".*** AstraZeneca disagrees with this conclusion for the following reasons: 1) Patients with CKD without T2DM have a very high unmet need, with limited innovative treatment options available to modify the course of disease 2) Substantial clinical benefit of SGLT2 inhibitors has been demonstrated with dapagliflozin in CKD patients with and **without T2DM** in a large, randomised controlled clinical trial – the Phase 3 DAPA-CKD trial. These benefits include reduced risk of renal function decline and progression to ESRD, hospitalisation for cardiovascular complications and premature mortality – outcomes that together represent one of the greatest burdens in patients with long-term conditions and for the NHS today.	September 2021, and the review will publish in November 2021. NICE is also currently undertaking a technology appraisal of dapagliflozin for treating chronic kidney disease which will include the DAPA-CKD trial. Therefore, data from DAPA-CKD has been removed from this update. See https://www.nice.org.uk/guidance/indevelopment/gid-ta10808 for details. The NICE CKD guideline will cross refer to this technology appraisal appraising dapagliflozin when it is published.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				3) The approach to 'evidence synthesis' that was taken by the NICE guidelines team is not consistent and omits evidence in patients without T2DM from DAPA-CKD – this evidence appears to have not been reviewed thoroughly by the committee. 4) 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. 5) Dapagliflozin is a well-established therapy in the UK; there is already extensive safety data, clinical experience and RWE for dapagliflozin across it's licenced indications for T2DM, T1D and HF. 6) 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. **Further detail on each of these points** 1) There remains a very high unmet need and limited treatment options in patients with **CKD without T2DM**. As recommended in CG182, current standard of care for CKD in people without T2DM comprises individually optimised therapy which may include RAAS inhibitors (angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs)) to reduce proteinuria.[1, 2] Treatment with RAASi therapy alone can leave patients at high risk of disease progression and the risk of mortality	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				remains unacceptably high,[3-5] with some 40-45,000 premature deaths in the UK every year due to CKD.[6] Every effort should be made to reduce the risk of premature death as well as CV and renal events through evidence-based recommendations, especially when there is compelling new clinical evidence available. 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.[7] The use of SGLT2 inhibitors to prevent or delay progression to ESRD and CV events such as hospitalisation for heart failure (hHF) consistently across all CKD populations, aligns with the prevention-focussed NHS Long Term Plan,[8] 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. 2) The DAPA-CKD trial (N=4304) is the first to demonstrate efficacy on mortality & renal outcomes in CKD patients with and without T2DM treated with guideline-based background therapies (ACEi and ARBs).It was stopped early due to overwhelming efficacy. • Dapagliflozin met the primary and all secondary endpoints compared with placebo: [9-11] o 39% relative risk reduction (RRR) for the primary endpoint (≥ 50% sustained	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				decline in estimated glomerular filtration rate (eGFR), end-stage kidney disease (ESRD), renal and cardiovascular (CV) death) o 44% RRR in eGFR decline, ESRD or renal death o 29% RRR in death from CV causes or hHF o 31% RRR in all-cause mortality, making dapagliflozin 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 and without T2DM**.[9-11] The following results were observed In patients **with** and **without T2DM**:[11] o **36%** and **50%** RRR for the primary endpoint, respectively (p-value for interaction=0.98) o **43%** and **49%** RRR in the kidney-specific composite outcome, respectively (p-value for interaction=0.80) o **30%** and **21%** RRR in the composite of cardiovascular death or hHF (p-value for interaction=0.11) o **26%** and **48%** RRR for all-cause mortality (p-value for interaction=0.85)	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Thirty two (32) percent (n=1,398) of the DAPA-CKD cohort did **not** have diabetes at baseline, making DAPA-CKD the largest CKD study in patients without diabetes to date.[10] AstraZeneca estimates that **[This text was identified as confidential and has been removed]** of CKD patients in England do not have concomitant diabetes.[12] Dapagliflozin represents a major advancement over current recommended therapies for a large, under-studied population with a high unmet clinical need. Based on the strength of this evidence and the unmet need in individuals with **CKD without diabetes**, dapagliflozin **[This text was identified as confidential and has been removed]** by the Medicines and Healthcare products Regulatory Agency (MHRA), with marketing authorisation **[This text was identified as confidential and has been removed]** (subject to satisfactory responses to MHRA questions), 2 months before the planned publication date for this guideline update. AstraZeneca is submitting a single technology appraisal for dapagliflozin for the treatment of CKD **[This text was identified as confidential and has been removed]** It's currently anticipated that the base case ICER will be approximately **[This text was identified as confidential and has been removed]**	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Dapagliflozin is therefore expected to be a highly cost-effective use of NHS resources in patients with CKD with and without T2DM. 3) With respect to NICE's assessment of the strength of evidence for SGLT2 inhibitors in CKD patients without T2DM, AstraZeneca refers to Evidence Review H. The DAPA-CKD study was identified and included in the SLR (Evidence Review H, page 47, lines 6-7), but appears to have been excluded from the summary of evidence for patients without T2DM (page 24, Table 17). The study protocol (presented in Appendix A of Evidence Review H) doesn't indicate that DAPA-CKD is not relevant to the review question in the non-diabetic subgroup of patients. Later in the Evidence Review H document, the Committee's discussion and interpretation of the evidence includes no mention of the evidence for dapagliflozin in people without T2DM, and it therefore appears this has not been accounted for in the Committee's decision making. Furthermore, the approach to evidence synthesis and decision making by the Committee appears to be inconsistent. ACEi or ARB therapies are recommended by NICE despite a paucity of clinical trial evidence to support their use in people without T2DM, with the vast majority of trials having been conducted in people with diabetes only, and the few trials that included patients without diabetes recruiting very small numbers (as demonstrated in Evidence Review H). In the Committee's	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				assessment of ARB therapies it was determined that the evidence indicates ARBs **don't** reduce the risk of ESRD in people with **CKD without T2DM** (Guideline, page 61, lines 9-15), but may do in patients **with T2DM**. The committee concluded that: ***"Based on the limitations of the evidence and the evidence available for people with type 2 diabetes, the committee recommended both ACE inhibitors and ARBs"*** for people **without** diabetes. Here, the Committee retains a recommendation for the use of ARBs in non-diabetics despite a lack of robust evidence demonstrating positive treatment effect based on the availability of data showing efficacy in people with T2DM. **4)** The evidence continuing to emerge on SGLT2 inhibitors across divergent patient populations demonstrates consistency of treatment effect in terms of both renal and CV outcomes in patient with and without T2DM. 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.[13-15] The DAPA-HF trial, which assessed dapagliflozin treatment for heart failure with reduced ejection fraction (HFrEF), included 4,744 patients of which 58.2% did not have comorbid diabetes. The results showed that dapagliflozin reduced the rate of worsening heart failure (hospitalisation or an urgent visit resulting in intravenous therapy for heart failure)	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				or death from CV causes by 26% (95% CI 0.65–0.85), with results consistent regardless of diabetes status **[This text was identified as confidential and has been removed]** 5) The results for the secondary endpoint of worsening kidney failure were also consistent between the non-diabetic (HR 0.67; 95% CI 0.30 to 1.49) and diabetic groups (HR 0.73; 95% CI 0.39 to 1.34; p-value for interaction=0.86).[17] 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 patients numbers to the DAPA-CKD trial**.[18] In the EMPORER-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). This growing body of evidence suggests that the mechanism of action of SGLT2 inhibitors is not modified by baseline HbA1c and independent of diabetes status, further supporting the use of SGLT2 inhibitors in non-diabetic patients with CKD. 6) Oral dapagliflozin has been widely used in the NHS, in both primary and secondary care settings, as a treatment for T1DM, T2DMM and HFrEF since the recommendations by NICE in 2019, 2013 and 2020	

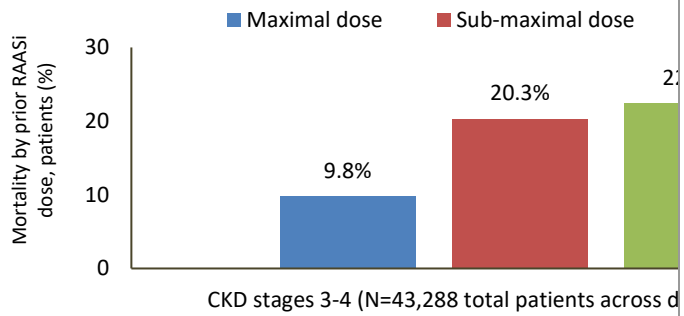
Stakeholder	Document	Page No	Line No	Comments	Developer's response
				respectively.[19-21] As such, both primary and secondary care clinicians have extensive clinical experience in prescribing dapagliflozin. Regulatory approval and NICE recommendation of dapagliflozin for the treatment of HFrEF was based on the DAPA-HF trial which demonstrated consistent treatment effect in HF patients with and without T2DM.[14, 22] A new licence for the treatment of CKD regardless of T2DM status is **[This text was identified as confidential and has been removed].** 7) Dapagliflozin is currently available for patients with T1DM, T2DM and HFrEF. Not recommending SGLT2 inhibitors for patients with CKD without T2DM creates inequality of access depending on diabetes status; this is also expected to be misaligned with the outcome of the forthcoming NICE STA of dapagliflozin for the treatment of CKD patients with and without T2DM. Following the current update of the NICE CKD guidelines, given the typical frequency of NICE guideline updates, it will be several years until the next opportunity for SGLT2 inhibitors to be included in the NICE CKD guidelines for the non-diabetic population. Given the rapidly evolving health environment, we understand that NICE is working towards creating more forward-looking guidelines. This is clearly evidenced by the 'future-proofed' recommendations already set out in this draft for SGLT2 inhibitors in patients with T2DM. The evidence discussed above warrants the same pragmatic approach for patients without T2DM.	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				With respect to the positioning of SGLT2 inhibitors for the treatment of individuals with CKD without diabetes, in the DAPA-CKD trial patients with an ACR down to ~20 mg/mmol achieved significant treatment benefit with dapagliflozin in addition to standard care which may include ACEi/ARB. However, the evidence suggests that the treatment effect of SGLT2 inhibitors is consistent regardless of the presence or absence of ACEi/ARB treatment. In the DECLARE-TIMI 58 trial which included 17,160 patients with T2D across a wide range of eGFR and uACR measurements**[This text was identified as confidential and has been removed].** Real-world evidence from the CVD-REAL-3 study which investigated a large cohort of patients with diabetes demonstrated consistency of treatment effect on a composite renal endpoint (50% eGFR decline or ESRD) with SGLT2 inhibitors regardless of the presence or absence of ACEi/ARB (p-value for interaction=0.72).[24] Given the strong evidence that the treatment effect of SGLT2 inhibitors is not modified by diabetes status, it is reasonable to assume that a treatment benefit with SGLT2 inhibitors would be observed regardless of ACEi/ARB therapy in non-diabetic patients too. AstraZeneca has heard from clinical experts that some patients with CKD cannot tolerate RAASi therapy due to issues such as hyperkalaemia, and who consequently have extremely limited treatment options therefore, it is even more crucial for these patients to have access to SGLT2 inhibitors.[25] Taken together, AstraZeneca believes that treatment with SGLT2 inhibitors should be	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				recommended in patients without diabetes independent of recommendations for the initiation of ACEi/ARBs. **AstraZeneca respectfully requests the Committee to include this important evidence in its evidence summary and consider amending its recommendation to include CKD patients without T2DM (AstraZeneca's proposed changes are below in red):** 1.6.8. For adults with CKD but without diabetes: • refer for nephrology assessment and offer an ACE inhibitor or ARB if they have an ACR of 70 mg/mmol or more, and/or • offer an SGLT2 inhibitor if they meet the criteria in the marketing authorisation. 1.6.9. For adults with CKD **and hypertension** but without diabetes, offer: • an ACE inhibitor or an ARB if they have an ACR of 30 mg/mmol or more, and/or • an SGLT2 inhibitor In July 2021, not all SGLT2 inhibitors were licensed for this indication.	
AstraZeneca UK Limited	Guideline	024 – 025	015 - 017 003 - 005	**Concern no. 4** The following recommendations contradict the NICE guidance on potassium binders (TA599 and TA623) and have not been amended in this update of the guideline:	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations, but we have added a new recommendation referring to the NICE technology

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				• ***"1.6.14: Do not routinely offer a renin–angiotensin system antagonist to adults with CKD if their pretreatment serum potassium concentration is greater than 5.0 mmol/litre."*** • ***"1.6.17: Stop renin–angiotensin system antagonists in adults if the serum 3 potassium concentration increases to 6.0 mmol/litre or more and other 4 drugs known to promote hyperkalaemia have been discontinued."*** RAASi therapy is a cornerstone of CKD treatment; it has been shown to reduce blood pressure and proteinuria,[34] delay glomerular filtration rate (eGFR) decline,[35] and reduce the risks of progressing to ESRD, CV morbidity and all-cause mortality in the CKD population.[36] Down-titration or discontinuation of RAASi therapy are associated with a loss of these cardio-renal benefits; data from a retrospective database analysis indicate that **CKD patients on a suboptimal dose of RAASi therapy have a similar 5-year mortality risk to those that cease RAASi therapy entirely** (Figure 3).[37] In the UK, it is estimated that 50% of patients down-titrate their RAASi therapy following their first hyperkalaemia (HK) event.[38] Furthermore, despite guideline recommendations, RAASi therapy is unfortunately seldom re-instated following an episode of HK at, or after, discharge even if a clear precipitating cause of HK was detected and eliminated. This may further exacerbate the loss of cardio-renal protection from RAASi therapy.[39, 40]	appraisals for treating hyperkalaemia with potassium binders (sodium zirconium cyclosilicate and patiromer). We have also passed your issue on to the NICE surveillance team who will explore whether recommendations 1.6.12, 1.6.14 and 1.6.17 (these numbers have been updated to 1.6.13, 1.6.15 and 1.6.18 after consultation) need updating in the future.

Figure 3: Mortality by prior dose of RAASi amongst patients with hyperkalaemia in a US retrospective database study over a 5-year period



Source: [37]
Abbreviations: RAASi: renin-angiotensin-aldosterone system inhibitor; US: United States
Notes: data included any services in hospitals as well as office and outpatient setting; descriptive statistics only, no statistical analysis performed

Two potassium binders, sodium zirconium cyclosilicate (SZC) and patiromer calcium sorbitex, have recently been recommended by NICE for the treatment of hyperkalaemia in adults with CKD. NICE TA599 and TA623 recommend the use of SZC and patiromer, respectively, for **treating hyperkalaemia in adults with CKD stage 3b to 5 if they have confirmed serum potassium levels ≥6mmol/litre, are not taking optimised dosage of RAASi because of the HK, and are not on dialysis.**[41, 42] Potassium binders are a step-change in the management of HK; offering an alternative to down-titration/discontinuation of RAASi therapy whilst maintaining normokalaemia.[39, 43] This allows patients to

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				continue to accrue the cardio-renal benefits of RAASi therapy whilst reducing the risks associated with hyperkalaemia. SZC and patiromer are recommended for patients with CKD in both the 2020 Renal Association Guidelines and the 2018 ESC consensus statement in order to allow continued RAASi therapy.[39, 44] KDIGO also recommended the use of potassium binders to manage hyperkalaemia in those with diabetic kidney disease to avoid down titrating or stopping RAASi therapy.[45] In February 2021, KDIGO also published a clinical practice guideline for the management of blood pressure which recommends that RAASi therapy is administered at the highest approved tolerated dose. In people with CKD who develop chronic or acute hyperkalaemia due to RAASi treatment, the guideline recommends that potassium binders can be used to reduce the serum potassium levels rather than down-titrating or stopping RAASi.[46] Recommendations 1.6.14 and 1.6.17 of this draft guideline contradict the recommendations set out in NICE TA599 and TA623 and the aforementioned guidelines. Furthermore, whilst the importance of achieving an optimal RAASi dose is included in recommendation 1.6.12, the NICE recommended potassium binders which can help to achieve this are not mentioned. AstraZeneca notes that that this was raised by several stakeholders during the scoping phase for this guideline	

Stakeholder	Document	Page No	Line No	Comments	Developer's response

				update, and the response from NICE stated: ***"The updated guideline on the assessment and management of chronic kidney disease will have the opportunity to cross-refer to these technology appraisals as appropriate. The scope has been amended to include the two in development technology appraisals."*** So far this has not been actioned.
				
				The clinical benefit of potassium binders in allowing continuation of RAASi therapy has been accepted by NICE and embraced by the clinical community. Failure to reflect this appropriately in the recommendation wording itself risks patients having their RAASi treatment discontinued or down-titrated unnecessarily, with the potential for major health consequences.
				
				AstraZeneca requests the Committee to consider amending the recommendations to reflect the guidance published by NICE on potassium binders (proposed changes in red):
				• 1.6.12: Explain to adults with CKD (and their family members or carers, as appropriate) who are prescribed renin–angiotensin system antagonists about the importance of:
				  • achieving the ~~optimal~~ maximal tolerated dose of renin–angiotensin system antagonists in order to reduce the risk of CV events and mortality **and**
				  • monitoring eGFR and serum potassium in achieving this safely.	

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				• 1.6.14: Do not routinely offer a renin–angiotensin system antagonist to adults with CKD if their pretreatment serum potassium concentration is greater than 5.0 mmol/litre and they are not suitable for a potassium binder. • 1.6.17: ~~Stop~~ In adults taking renin–angiotensin system antagonists, ~~in adults~~ if the serum potassium concentration increases to 6.0 mmol/litre or more and other drugs known to promote hyperkalaemia have been discontinued offer a potassium binder to reduce serum potassium instead of discontinuing or down titrating the renin–angiotensin system antagonist See NICE recommendations for potassium binders SZC and patiromer in TA599 and TA623	
At the 4 Front	Algorithm			**Adults with Diabetes -> ACR 3 mg/mmol or more -> Offer an ACE inhibitor or ARB -> Add an SGLT2 inhibitor if type 2 diabetes and ACR 30mg/mmol or more and criteria in licence met** - with the evidence around SGLT2 inh should we be adding in at the same time as an ACE/ARB or earlier rather than waiting	Thank you for your comment. The algorithm has been amended to be in line with recommendations 1.6.6 and 1.6.7. These recommendations have been amended to include the importance of optimising the dose of an ARB or an ACE inhibitor before offering an SGLT2 inhibitor.
At the 4 Front	Guideline	007	020	**Do not use reagent strips to identify proteinuria. [2021]** This should possibly state that reagent strips can be used to diagnose or quantify proteinuria.	Thank you for your comment. The committee agreed that evidence was not reviewed for the use of reagent strips in adults. Therefore, we have reinstated (recommendation removed before this consultation in January 2021) the recommendation for adults that was made in 2008 to specify that the use of reagent strips to identify proteinuria in adults should be limited to tests being capable of measuring albumin at low concentrations and expressing the result as an ACR.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
At the 4 Front	Rationale and impact	062	014	**The committee noted the high costs of these drugs and the lack of any cost effectiveness evidence**. This rationale states that these drugs are high cost. These drugs are not high cost, they may be of a higher cost than Metformin or SU's but the term "High Cost" is normally used to describe medicines that along with their associated costs of care are disproportionately high cost compared to the other expected costs of care within the HRG, which would affect fair reimbursement. The trem high cost here could potentially effect the delivery of effective medicines to certain groups of patients	Thank you for your comment. We have changed the wording and removed the term "High Cost"
Bayer plc	Guideline	General	General	Notwithstanding the concerns about implementation of a KFRE in clinical practice, Bayer recognise the value in determining referral criteria to reduce unnecessary referrals, and lead to earlier referrals in those who go on to develop ESRD. Bayer recognises that the guideline identifies risk factors associated with CKD progression in adults (1.3.5; 1.3.7) and also other factors that can guide referral (1.5.5). However, the guideline is missing the opportunity to identify patients at risk of progression, and quantify this risk, where interventions could be offered to delay progression and reduce the risk of adverse clinical events. Prognosis of CKD can be predicted based on GFR and albuminuria as well as other risk factors and comorbid conditions (1). Understanding prognosis and risk can guide management to delay or prevent complications associated with adverse health outcomes. Considering the high mortality and morbidity in patients with CKD,	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations. (recommendations 1.3.5 and 1.3.7). These recommendations were not added to the update because the NICE surveillance team did not find evidence that would impact on these 2 recommendations during the surveillance review of the guideline. Regarding your comment about the risk prediction model reported by Nelson and colleagues, this study was not included in review F because the risk prediction model reported by Nelson and colleagues was about the primary prevention of kidney disease (incident kidney disease) and review F was limited to studies recruiting adults, children and young people who already had chronic kidney disease.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				primary prevention of its development would seem prudent. As identified in Major et al. (2) many individuals with CKD will be at low risk for progression to ESRD but will have raised risk of cardiovascular disease events. Indeed, the leading cause of death in patients with CKD is cardiovascular disease (3). Sullivan et al report on the associations between multimorbidity and adverse clinical outcomes in CKD. Important opportunities therefore exist for improving care, maintaining function, reducing progression and minimising and managing complications. ACE and ARB have been the mainstay treatment for retarding the progression toward end-stage renal disease for decades (4). Whilst there have been limited treatment options since the introduction of ACE/ ARB in patients with CKD, recent studies have shown positive results in reducing the risk of both CV and renal events in patients with CKD (5-7) and further study outcomes in patients considered to be at lower risk according to the KGIGO grid are upcoming (8). As more treatments become available, guidelines which inform treatment decisions according to risk of CV and renal outcomes and stage in the treatment pathway would be valuable. In the meantime, a tool to predict progression of disease, not solely to inform referral should be developed. The KDIGO guidelines (1) report on the work by Levey et al (9) which presents the relative risk of (i) all-cause mortality, (ii) CV mortality, (iii) kidney failure, (iv) AKI and (v) progressive CKD, all plotted onto the	

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				KDIGO grid. Clinically usable methods for risk stratification for each outcome are important for informing treatment decisions (10). A risk prediction model and evaluation of performance has been reported in JAMA (11). Nelson and colleagues used data from more than 4 million adults without diabetes and nearly 800 000 adults with diabetes from 34 multinational cohorts to develop equations that predict the 5-year risk of developing reduced estimated glomerular filtration rate (eGFR), using the standard definition of less than 60 mL/min/1.73 m^2. During a mean follow-up period of 4 years, 15% of individuals without diabetes and 40% of individuals with diabetes developed reduced eGFR. The models included characteristics that could be abstracted from health records: sociodemographic factors, smoking status, cardiovascular disease, hypertension, body mass index, eGFR, and albuminuria. For those with diabetes, the model also included presence and type of diabetes medications and haemoglobin A1c levels. This risk prediction model shifts the focus from secondary to primary prevention of kidney disease. The editorial notes that while the well-validated Kidney Failure Risk Equation (KFRE) accurately risk-stratifies patients with moderate-to-severe CKD for progression to kidney failure, identifying individuals before the onset of kidney disease would present a much larger opportunity to influence disease trajectory (12).	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				If not included in this guideline, then Bayer consider this could be an important area of research to determine whether use of such a risk equation could improve clinical outcomes. However, Bayer consider that such a risk tool was within scope of this guideline update (Section 3.3 of the final scope, point number 2): Classification of CKD in adults, children and young people − classification of CKD − ***determining the risk of adverse outcomes*** (1) Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease .Kidney inter., Suppl.2013;3: 1–150. (2) Major RW, Shepherd D, Medcalf JF, Xu G, Gray LJ, Brunskill NJ (2019) The Kidney Failure Risk Equation for prediction of end stage renal disease in UK primary care: An external validation and clinical impact projection cohort study. PLoS Med 16(11): e1002955. (3) Sullivan MK, Rankin AJ, Jani BD, et al. Associations between multimorbidity and adverse clinical outcomes in patients with chronic kidney disease: a systematic review and meta-analysis. BMJ Open 2020;10:e038401. doi:10.1136/bmjopen-2020-038401 (4) Viazzi et al. Renin–angiotensin–aldosterone system blockade in chronic kidney disease:	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				current strategies and a look ahead. Intern Emerg Med (2016) 11:627–635 (5) Perkovic et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. The New England Journal of Medicine (2019) 380(24): 2295-2306. (6) Heerspink et al. Dapagliflozin in Patients with Chronic Kidney Disease. New England Journal of Medicine (2020); 383:1436-1446 (7) Bakris et al. Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes. New England Journal of Medicine 2020; 383:2219-2229 (8) Ruilope et al. Design and Baseline Characteristics of the Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease Trial. Am J Nephrol 2019;50:345–356 (9) Levey et al. The definition, classification, and prognosis ofchronic kidney disease: a KDIGO Controversies Conference report. Kidney International (2011) 80, 17–28; doi:10.1038/ki.2010.483 (10) Tangri et al. Risk Prediction Models for Patients With Chronic Kidney Disease. A Systematic Review. Ann Intern Med.2013;158:596-603. (11) Nelson et al for the CKD Prognosis Consortium. Development of Risk Prediction Equations for Incident Chronic Kidney Disease. JAMA. 2019;322(21):2104-2114 (12) Tummalapalli, Estrella. Predicting Risk of Kidney Disease – Is Risk-Based Kidney Care on the	

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Horizon? JAMA December 3 2019. Vol 322, Number 21, pages 2079-2081	
Bayer plc	Guideline	007	020	In respect of reagent strips, CG182 (1.1.17) recommends their use in adults provided they are capable of specifically measuring albumin at low concentrations and expressing the result as an ACR. However, draft recommendation (1.1.11) has changed to now state that reagent strips should not be used to identify proteinuria. In "Why the committee made the recommendations" (presented on page 56 lines 14-18) it is stated, incorrectly, that reagent strips are not currently recommended in adults whereas they are in fact currently recommended (CG182 1.1.17). The committee then considers that not recommending reagent strips is also applicable to children and young people. The literature available for children and young people may support not recommending reagent strips in this group, however the evidence for reagent strips in adults was not reassessed - as such there is no basis to change the recommendation as previously applied to adults which should remain as in CG182. Bayer notes that the draft guideline is in conflict with the conclusions of NHSx who is currently partnering with Healthy.io in support of testing a potential 500,000 adults over the next three years with semi-quantitative reagent strips that express results as an ACR (1).	Thank you for your comment. The committee agreed that evidence was not reviewed for the use of reagent strips in adults. Therefore, we have reinstated (recommendation removed before this consultation in January 2021) the recommendation for adults that was made in 2008 to specify that the use of reagent strips to identify proteinuria in adults should be limited to tests being capable of measuring albumin at low concentrations and expressing the result as an ACR.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				(1) https://htn.co.uk/2021/02/08/nhsx-supports-smartphone-tech-for-detecting-early-kidney-disease/	
Bayer plc	Guideline	014	Table 2	Bayer believes that Table 2 might have been mis-labelled and therefore in addition, the wording of 1.3.2 on the previous page is also misleading. The table is titled *"minimum number of monitoring checks (eGFR) per year for adults, children and young people with or at risk of chronic kidney disease."* The reason why we believe this is mislabelled/ mis-worded is two-fold. Firstly, 1.3.1 on page 13 refers to frequency of monitoring of eGFRcreatinine **and** ACR. Also, Evidence review F (6), Table 13 and the text below on page 95, indicate that eGFR and ACR should **both** be measured at each monitoring appointment. ACR is a powerful independent marker of the risk of adverse outcomes in CKD, and the use of ACR and GFR in combination will allow better risk stratification and we believe this is the intention of the guideline (as per section 1.2 of the guideline – classification of CKD). Bayer suggest that the wording in 1.3.2 on page 13 and the title of Table 2 on page 14 be reviewed and amended to include reference to monitoring of ACR. In our response to the scope consultation, Bayer highlighted the low uptake of ACR testing and remain concerned about the lack of prominence given to ACR. • The National Chronic Kidney Disease Audit - National Report (Part 1) January 2017, reported that: whilst over	Thank you for your comment. We have added a note to Table 2 about ACR monitoring which should be individualised based on a person's individual characteristics, risk of progression and whether a change in ACR is likely to lead to a change in management. ACR monitoring was not recommended alongside to eGFR because eGFR is used to define progression rather than ACR and so more frequent monitoring is needed (see recommendations 1.3.5 to 1.3.8 which define progression in adults with the use of eGFR). No specific evidence on ACR monitoring frequency was found but the committee noted that it is a costly test and should not be used every time eGFR is measured, but on an individual basis. The rationale has examples about the frequency of ACR monitoring ACR (more frequently monitoring in people with high ACR categories A2 or A3; or where a change in ACR would affect management). The committee agreed to make a research recommendation to identify the optimal frequency of monitoring ACR in adults, children and young people with CKD.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				80% of those with CKD had had an eGFR test in the previous year, only 31% had a repeat ACR test (1) • The National Diabetes Audit 2018-19. Report 1: Care Processes and Treatment Targets. England and Wales, reports on the uptake of NICE recommended care processes and found that in 2018/19, for those with type 2 diabetes, 94% of patients had an annual check of serum creatinine, but only 61% had an annual check of urine albumin. The low level of urine albumin checking is highlighted in the key findings of the report and has declined from 84.4% in 2013/14, with marked variation between CCGs and LHBs. The audit recommends the need to increase rates of Urine Albumin care process checks. It is of interest and perhaps surprising that ACR testing is no longer included in QOF (3,4). (1) https://www.lshtm.ac.uk/research/centres-projects-groups/ckdaudit#report-downloads (2) https://files.digital.nhs.uk/B2/24D150/REF161%20National%20Diabetes%20Audit%202018-19%20Full%20Report%201%2C%20Care%20Processes%20and%20Treatment%20Targets.pdf (3) Molokhia et al. Br J Gen Pract 2020; DOI: https://doi.org/10.3399/bjgp20X713105 (4) NHS Digital. Quality and Outcomes Framework (QOF) business rulesv45.0 2020–2021 baseline release. 2020. https://digital.nhs.uk/data-andinformation/data-collections-and-data-sets/data-collections/quality-andoutcomes-	

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				framework-qof/quality-and-outcome-framework-qof-businessrules/quality-and-outcomes-framework-qof-business-rules-v45.0-2020-2021-baseline-release	
Bayer plc	Guideline	019	025 - 028	Bayer have concern regarding the potential over-reliance on the 4-variable Kidney Failure Risk Equation for referral. Bayer are concerned about the applicability in practice when there is evidence for low levels of ACR testing and poor coding in CKD. In addition to the references supporting comment 2, a Scottish study investigated the development of a renal replacement therapy risk prediction tool and compared this to the 3- and 4-variable KFRE. It was found that **the KFRE 4-variable model could only be applied to 12% of the validation cohort** because of a lack of baseline urinary albumin creatinine ratio data, thus limiting its use in routine clinical practice (1). This underscores the importance of efforts to improve testing of ACR which is essential for risk stratification. A recently published study conducted in South London (2) reported that > 50% of CKD was uncoded and, for those patients the quality of care was lower compared with coded CKD. Bayer would like to see greater prominence given to the recommendations for UACR testing and appropriate primary care coding to ensure that patients are appropriately monitored, treated and followed up. Indeed, if UACR is not being recorded, then it is difficult to envisage the KFRE being implemented in clinical practice.	Thank you for your comment. The KFRE is designed to be used in patients with stages 3, 4 and 5 CKD and therefore the other referral criteria should capture patients with stages 1 and 2 who need referring to secondary care. Regarding your comment about the lack of ACR testing, we have added a note to Table 2 about ACR monitoring which should be individualised based on a person's individual characteristics, risk of progression and whether a change in ACR is likely to lead to a change in management. ACR monitoring was not recommended alongside to eGFR because eGFR is used to define progression rather than ACR and so more frequent monitoring is needed (see recommendations 1.3.5 to 1.3.8 which define progression in adults with the use of eGFR). No specific evidence on ACR monitoring frequency was found but the committee noted that it is a costly test and should not be used every time eGFR is measured, but on an individual basis. The rationale has examples about the frequency of ACR monitoring ACR (more frequently monitoring in people with high ACR categories A2 or A3; or where a change in ACR would affect management). The committee agreed to make a research recommendation to identify the optimal frequency of

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Bayer are also concerned about a major limitation of the KFRE. The KFRE does not assess kidney failure risk in patients with CKD stages G1(GFR ≥90 mL/min/1.73m^2) and G2 (GFR 60-89 mL/min/1.73m^2). Previous studies have shown that patients with stages G1 to G2 and high levels of albuminuria should be considered as high risk (3). (1) Marks et al. Looking to the future: predicting renal replacement outcomes in a large community cohort with chronic kidney disease. Nephrol Dial Transplant (2015) 30: 1507–1517 (2) Molokhia et al. Br J Gen Pract 2020; DOI: https://doi.org/10.3399/bjgp20X713105 Tangri et al. for the KD Prognosis Consortium. Multinational Assessment of Accuracy of Equations for Predicting Risk of Kidney Failure. A Meta-analysis. JAMA. 2016;315(2):164-174.	monitoring ACR in adults, children and young people with CKD. Regarding the studies you cited: Molokhia (2020) would not be included in our review of the evidence because it is a cross-sectional study and we limited the inclusion to cohort studies. Marks (2015) has been included now in evidence review F. Evidence from this study strengthens overall evidence on the KFRE 4-variable model, which is recommended, and also provides data on another model, which was only reported in this study. This evidence is presented in the evidence review and was considered by the committee, but did not have an impact on the recommendations that were made. Tangri (2016) was included and relevant outcomes were reported in evidence review F: The best combination of measures to identify increased risk of progression in adults, children and young people.
Boehringer Ingelheim	Algorithm 1	General	General	We therefore recommend that the effects of empagliflozin on kidney function and cardiorenal outcomes, in patients with and without albuminuria at baseline, are considered beyond the impact on the progression of albuminuria. This would also reflect the most recent Kidney Disease: Improving Global Outcomes (KDIGO) guidelines where SGLT2i are recommended in adult, eligible patients with CKD and type 2 diabetes irrespective of albuminuria status (KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease)	Thank you for your comment. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Available at: https://kdigo.org/wp-content/uploads/2020/10/KDIGO-2020-Diabetes-in-CKD-GL.pdf (Accessed March 2021)	
Boehringer Ingelheim	Algorithm 1	General	General	Albuminuria is a marker of kidney damage and can be viewed as an independent risk factor for CKD progression. Both the NICE CG182 CKD and KDIGO guidelines recommend that glycemic control, blood pressure control, lipid management, exercise, smoking cessation and nutrition advice are managed to reduce cardiorenal risk.	Thank you for your comment. The section on 'Risk factors associated with CKD progression in adults' includes recommendation 1.3.9 which is about optimising people's health to reduce the risk of CKD progression and includes managing some of the factors that you mention in your comment.
Boehringer Ingelheim	Evidence review H	043, 045, 046	General General General	Proteinuria is a marker of structural kidney damage and Urine albumin creatinine ratio (UACR) is independently associated with kidney function decline and increased risk for clinically relevant outcomes such as end stage kidney disease (Hoefield R *et al* 2010). To detect and identify proteinuria, UACR is commonly used in the UK and is the recommended screening method for people living with diabetes (NICE CKD guidelines 2014). We recommend to consider data for treatment effects on proteinuria in the context of both kidney functional decline (estimate glomerular function) and clinical kidney endpoints such as end stage kidney disease for a holistic view of the impact of treatment on the kidney. Proteinuria as a surrogate parameter enables the physician to evaluate kidney protective effects on the short term which translate into long-term kidney benefits and the cost savings to the NHS. However, Empagliflozin has also demonstrated stabilization of eGFR and reductions in clinical kidney endpoints in patients with type 2 diabetes and established	Thank you for your comment. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. The EMPA-REG OUTCOME trial published by Wanner and colleagues will be considered as part of this work.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				cardiovascular disease, which were consistent across proteinuria classes at baseline (Wanner C *et al* 2016. Furthermore, empagliflozin has been shown to reduce major cardiovascular outcomes, particularly cardiovascular death in this population. This is in a consistent manner irrespective of albuminuria status at baseline on top of the current standard of care (Wanner C *et al* 2018). Wanner C, *et al. New Engl J Med* 2016;375:323–334 Hoefield R. *et al*. *Nephrol Dial Transplant (2011) 26: 887–892* Wanner C. *et al.* Circulation 2018;137:119–129.	
Boehringer Ingelheim	Evidence review H	043	General	A meta-analysis of renal outcomes from SGLT2i CVOT and dedicated cardiorenal trials in patients with type 2 diabetes demonstrated a consistent benefit for the class across differing renal composite endpoints in the trials, with a HR of 0.62 (0.56-0.70). There was no significant interaction on the pooled renal composite outcomes with the presence or absence of ASCVD, baseline albuminuria or history of heart failure (McGuire DK *et* al 2020). McGuire DK. *et al JAMA Cardiology*. 2020. doi:10.1001/jamacardio.2020.4511	Thank you for your comment. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. The publication by McGuire and colleagues will be considered as part of this work.
Boehringer Ingelheim	Evidence review H	043	General	Patients with metabolic and cardiovascular disease are at increased risk of developing chronic kidney disease, as Cardio-Renal-Metabolic system are closely connected. Any acute or chronic dysfunction in the heart, kidneys or metabolic system may induce a dysfunction in another (Song MK *et al.* 2014).	Thank you for your comment.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Through a variety of haemodynamic, neurohormonal or biochemical mechanisms, each organ has the ability to initiate and perpetuate disease in other organs. This can lead to a dysfunction of the Cardio-Renal-Metabolic system and may lead to an increased risk of CV death and all cause mortality. Albuminuria as an independent risk factor for heart failure and CV disease (Rangaswami J *et al*. 2019). Song MK *et al.* J diabetes Res 2014;2014:e313718;2 Rangaswami J *et al.* Circulation 2019;139:e840;3	
Boehringer Ingelheim	Evidence review H	043	021	Empagliflozin has demonstrated a reduction in existing and new onset macroalbuminuria in patients with type 2 diabetes (T2D) and established cardiovascular disease on top of standard of care for diabetes and cardiovascular disease (Wanner C *et al* 2016). This data is in line with other agents within the SGLT2 inhibitor class that have demonstrated a reduction in kidney outcomes in broader T2D patient populations without established cardiovascular disease (McGuire K *et al* 2021). Note this was not seen with the SGLT2 inhibitor ertugliflozin (Cannon C *et al* 2020). We therefore recommend that SGLT2 inhibitors with kidney benefit, such as empagliflozin, are used in adult patients with T2D to reduce proteinuria in patients with moderately or severely increased proteinuria on top of SOC (i.e. RAASi), and to prevent the new onset of proteinuria in patients with T2D Wanner C, *et al. New Engl J Med* 2016;375:323–334	Thank you for your comment. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				McGuire DK. *et al JAMA Cardiology*. 2020. doi:10.1001/jamacardio.2020.4511 Cannon C *et al*. *N Engl J Med.* 2020; 383:1425-1435	
Boehringer Ingelheim	Evidence review H	043 228 253	021, Figure 7 General	EMPA-REG OUTCOME also explored a kidney composite of progression to macroalbuminuria, doubling of the serum creatinine level, initiation of kidney-replacement therapy, or death from kidney disease. This composite demonstrated a HR of 0.61 (95% CI 0.53-0.70), p<0.001 in the pooled empagliflozin treated arms against placebo, with an absolute risk reduction of 6.1%. A post hoc kidney composite outcome (a doubling of the serum creatinine level, the initiation of kidney-replacement therapy, or death from kidney disease) showed a HR of 0.54 (95% CI, 0.4 – 075) p<0.001 with the use of empagliflozin. Within these endpoints, all components contributed towards the overall composite outcome (Wanner C *et al* 2016). Wanner C, *et al. New Engl J Med* 2016;375:323–334	Thank you for your comment. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. The EMPA-REG OUTCOME trial published by Wanner and colleagues will be considered as part of this work.
Boehringer Ingelheim	Evidence review H	043 229 230	032, General, General	In the EMPA-REG OUTCOME trial, patients with chronic kidney disease at baseline, defined as an eGFR <60ml/min per 1.73m^2 or the presence of macroalbuminuria, demonstrated comparable cardiovascular outcomes to those without CKD at baseline. The stratification of cardiovascular events by baseline UACR (normo, micro and macro albuminuria) also demonstrated a consistent effect of empagliflozin on cardiovascular outcomes between stages of UACR progression (Wanner C *et al* 2016). Therefore, our recommendations would be to use SGLT2 inhibitors such as empagliflozin in individuals	Thank you for your comment. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. The EMPA-REG OUTCOME trial published by Wanner and colleagues will be considered as part of this work.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				with T2D, CKD and albuminuria as this can provide additional CV benefits with respect to CV death and all-cause mortality on top of standard of care. Wanner C. *et al.* Circulation 2018;137:119–129.	
Boehringer Ingelheim	Evidence review H	043	038	An exploratory analysis of EMPA-REG OUTCOME, investigated the effects of empagliflozin vs placebo on UACR. Empagliflozin demonstrated in normoalbuminuric patients, there was a delay progression of albuminuria onset. There were similar patterns of UACR reductions in patients with micro and macroalbuminuria at baseline, with significant reductions in UACR in patients with micro and macroalbuminuria at baseline after week 12, which were sustained through to week 164 of follow up with a 30% and 32% reduction in UACR at week 164 in the respective groups (Cherney D *et al* 2017). Cherney DZI, *et al*. Lancet Diabetes Endocrinol 2017;5:610–621	Thank you for your comment. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. The EMPA-REG OUTCOME trial published by Cherney and colleagues will be considered as part of this work.
Boehringer Ingelheim	Evidence review H	043	038	The data underlying the recommendations for the SGLT2i class in KDIGO guidelines originates in the cardiovascular outcome trials (CVOTs), trials designed to demonstrate cardiovascular safety of glucose lowering agents in people with T2D and at high cardiovascular risk. Beyond cardiovascular outcomes, these trials also had pre-specified secondary kidney composite endpoints, with the EMPA-REG OUTCOME, CANVAS and DECLARE TIMI 58 demonstrating reductions in the respective trial outcomes (Zinman B *et al* 2015; Neal B *et al* 2017, Wiviott S *et al* 2019). Zinman B *et al*. N Engl J Med. 2015;373:2117–2128 Neal B *et al. N Engl J Med* 2017;377:644	Thank you for your comment. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. The EMPA-REG OUTCOME, CANVAS and DECLARE TIMI 58 trials will be considered as part of this work.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Wiviott SD *et al.* N Engl J Med 2019;380:347	
Boehringer Ingelheim	Evidence review H	045	General	Beyond EMPA-REG OUTCOME various trials evaluating glucose-lowering drugs in patients with T2D with or without CKD demonstrated strong kidney benefits, particularly SGLT2i. Due to this, KDIGO recommend the use of metformin + a SGLT2i with demonstrated cardiovascular and kidney risk reduction in patients with T2D and CKD as first line therapy in eligible adult patients. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Available at: https://kdigo.org/wp-content/uploads/2020/10/KDIGO-2020-Diabetes-in-CKD-GL.pdf (Accessed March 2021)	Thank you for your comment. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. The EMPA-REG OUTCOME trial and other evidence will be considered as part of this work.
Boehringer Ingelheim	Evidence review H	045	General	Beyond the CVOTs, data for the impact of SGLT2i on kidney outcomes in within the CRM environment, such as reduced ejection heart failure (HFrEF), with and without T2D is emerging. Both the DAPA-HF and EMPEROR reduced trials have published outcomes, with the latter investigating the effects empagliflozin compared to placebo in patients with symptomatic heart failure with reduced ejection fraction, with or without diabetes, on top of appropriate standard of care (McMurray J *et al* 2019, Packer M *et al* 2020). Further inclusion criteria for the trial applied, however patients with an eGFR down to 20ml/min per 1.73 m^2 were eligible for the EMPEROR reduced trial. The trial primary outcome was a composite of cardiovascular death and hospitalisation for heart failure, however one of the two pre-specified secondary	Thank you for your comment. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. NICE is also currently undertaking a technology appraisal of dapagliflozin for treating chronic kidney disease which will include the DAPA-CKD trial. Therefore, data from DAPA-CKD has been removed from this update. See https://www.nice.org.uk/guidance/indevelopment/gid-ta10808 for details. The NICE CKD guideline will cross refer to this technology appraisal appraising dapagliflozin when it is published.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				endpoints explored the annualised rate of eGFR from placebo, which was 0.55 ml / minute per 1.73 m^2 per year in the empagliflozin arm vs. –2.28 ml / minute per 1.73 m^2 per year in the placebo, for a between-group difference of 1.73 ml per minute per 1.73 m^2 per year (95% CI, 1.10 to 2.37; P<0.001). The trial also reported an exploratory composite kidney outcome of chronic dialysis or kidney transplantation or a profound, sustained reduction in the estimated GFR. The composite kidney outcome occurred in 30 patients (1.6%) in the empagliflozin group and in 58 patients (3.1%) in the placebo group (hazard ratio, 0.50; 95% CI, 0.32 to 0.77) (Packer M *et al* 2020). Packer M *et al.* NEJM 2020 Aug 29. doi: 10.1056/NEJMoa2022190. Online ahead of print. McMurray J *et al* N Engl J Med 2019; 381:1995-2008	
Boehringer Ingelheim	Evidence review H	046	008	Empagliflozin is currently being evaluated in clinical trials for heart failure (preserved ejection fraction) and CKD in patients with and without type 2 diabetes.	Thank you for your comment. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021.
Boehringer Ingelheim	Evidence review H	046	008	Further data in a chronic kidney disease population will be available as the EMPA-Kidney trial. The ongoing EMPA-KIDNEY trial of empagliflozin versus placebo in adults with established CKD with or without diabetes will investigate the effects of empagliflozin on the progression of kidney disease in a broad CKD population with an eGFR ≥20 to <45 ml/min/1.73 m^2, or	Thank you for your comment. We will pass the information about the ongoing trial to the NICE surveillance team which monitors guidelines to ensure that they are up to date.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				eGFR ≥45 to <90 ml/min/1.73 m^2 with UACR ≥200 mg/g (Herrington W *et al* 2018). This trial is expected to complete in 2022. Herrington W *et al* Clin Kidney J. 2020 August; 13(4): 722.	
Boehringer Ingelheim	Evidence review H	228, 229, 043	Figure 7, figure 8, 022 respecti vely	Empagliflozin has reported a cardiovascular outcome trial (CVOT), EMPA-REG OUTCOME, where empagliflozin was compared to placebo, on top of standard of care for type 2 diabetes (T2D) and cardiovascular disease (CVD), to demonstrate non-inferiority for major cardiovascular outcomes (Zinman B *et al* 2015). The trial had a pre-specified composite secondary endpoint of incident or worsening nephropathy, which included the progression to macroalbuminuria (Wanner C *et al* 2016). Wanner C, *et al. New Engl J Med* 2016;375:323–334 Zinman B *et al*. N Engl J Med. 2015;373:2117–2128	Thank you for your comment. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. The EMPA-REG OUTCOME trial and other evidence will be considered as part of this work.
Boehringer Ingelheim	Evidence review H	228 & 045	General & 038	A recent clinical trial investigated the effects of empagliflozin on heart failure outcomes in patients with reduced ejection fraction heart failure, in patients with or without type 2 diabetes. Whilst there is currently no data available around the impact of empagliflozin on albuminuria in this trial, empagliflozin was demonstrated to reduce a kidney composite outcome and the eGFR slope decline (Packer M *et al* 2020). As data and licensing evolves we hope that SGLT2 inhibitors with proven kidney benefits such as empagliflozin are considered for the for slowing down kidney function decline and reduce the risk for hard	Thank you for your comment. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. Additional evidence is being considered as part of this work.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				kidney outcomes such as end-stage kidney disease in non-diabetic patient populations. Packer M *et al.* NEJM 2020 Aug 29. doi: 10.1056/NEJMoa2022190. Online ahead of print.	
Boehringer Ingelheim	Evidence review H	253 - 254, 043	General, General	In the EMPA-REG OUTCOME, the baseline population consisted of patients with T2D and established CVD. At baseline, 25.9% of participants has CKD stage 3a or higher, 28.7% had microalbuminuria and 11% had macroalbuminuria (Wanner C *et al* 2016). The pre-specified secondary kidney outcome in the trial was the composite of the progression to macroalbuminuria, doubling of the serum creatinine level, initiation of kidney-replacement therapy, or death from kidney disease. This composite demonstrated a hazard ratio (HR) of 0.61 (95% CI 0.53- 0.70), p<0.001 in the pooled empagliflozin treated arms (10 and 25 mg doses) against placebo, with an absolute risk reduction of 6.1%. The specific component of progression to macroalbuminuria (specified as urinary albumin-to-creatinine ratio, >300 mg of albumin per gram of creatinine) demonstrated a 38% relative risk and 5% absolute risk reduction (Wanner C *et al* 2016). • Wanner C, *et al. New Engl J Med* 2016;375:323–334	Thank you for your comment. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. The EMPA-REG OUTCOME trial published by Wanner and colleagues will be considered as part of this work.
British Association for Paediatric Nephrology	Guideline	005		Paediatrics should use the Schwartz bedside 2009 formula (or even better the new 2021 formula). A research question we should validate the paediatric formula using a UK based cohort	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations. We will pass your comment

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
British Association for Paediatric Nephrology	Guideline	006		Point 1.1.4 should include children	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.
British Association for Paediatric Nephrology	Guideline	007		Point 1.1.9 should include children	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.
British Association for Paediatric Nephrology	Guideline	008		Point 1.1.14 why are some of these groups restricted to adults? Should all these groups not be adults and children? We should not use age-appropriate creatinine reference ranges but convert them to Pediatric eGFR	Thank you for your comment. This update reviewed evidence in children and young people. The review of evidence in adults was outside the scope of this update. Therefore, recommendation 1.1.14 was amended to incorporate evidence from children and young people keeping the recommendation already made for adults.
British Association for Paediatric Nephrology	Guideline	009		Point 1.1.18 these appropriate age groups should be specified rather than just referring to somewhere else to make guideline usable by clinicians	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline are not part of this update and therefore we cannot change them. The NICE guideline on suspected cancer: recognition and referral is referred to because the appropriate age groups differ depending on the site of cancer.
British Association for Paediatric Nephrology	Guideline	011		Point 1.1.25 this should specify what staging of AKI, does that also includes stage 1? Seems excessive for stage I for children, on 1.1.6 of evidence D the studies do not divide to AKI 1 and are all of v low quality . Also	Thank you for your comment. Most of the studies did not report data on each AKI stage but there was evidence from one study about the risk of developing CKD at 5 years post-hospital discharge in children

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				seems to be at odds with: (Acute kidney injury: prevention, detection and management NICE guideline [NG148] Published date: 18 December 2019 https://www.nice.org.uk/guidance/ng148/chapter/Recommendations#managing-acute-kidney-injury point 1.5.12 Do not refer adults, children or young people to a nephrologist or paediatric nephrologist when there is a clear cause for acute kidney injury and the condition is responding promptly to medical management, unless they have a renal transplant. [2013])	and young people who had AKI stage 1 during hospitalisation (HR 2.2; 95% CI 1.1 to 4.5; Hessey 2019). Therefore, no changes were made to recommendations on specific AKI staging to monitor for the risk of CKD.
British Association for Paediatric Nephrology	Guideline	017		Point 1.4.2 surely it should just say involve 'patients and families' rather than adults	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.
British Association for Paediatric Nephrology	Guideline	018		Point 1.4.6 again it should be patients with CKD rather than adults - we do not want to be excluding children and young people	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.
British Association for Paediatric Nephrology	Guideline	018		Point 1.4.9 please consult paediatric dietitian, in children should say they should receive sufficient protein for growth	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.
British Association for Paediatric Nephrology	Guideline	018		Point 1.4.10 & 1.4.11 again another strange adult thing excluding children, YP and families of CYP.	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					Therefore, we cannot make substantive changes to these recommendations.
British Association for Paediatric Nephrology	Guideline	020		Point 1.5.6 could specify what the specialist is, could be a general paediatrician for the most basic sieve, then general paediatrician with nephrology interest or paediatric nephrology specialist for some of them	Thank you for your comment. The specialist was not specified because the exact referral pathway may differ locally.
British Association for Paediatric Nephrology	Guideline	021		Point 1.5.9 it can be with a general paediatrician as well as GP	Thank you for your comment. Paediatrician has been added to recommendation 1.5.9.
British Association for Paediatric Nephrology	Guideline	024		Point 1.6.12 and 1.6.14 surely this should applied to all patients.	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.
British Association for Paediatric Nephrology	Guideline	025		Point 1.6.18 should apply in children also. Points 1.6.18 & 19 & 20 is confusing as all seem to be saying the same thing. Can be simplified	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.
British Association for Paediatric Nephrology	Guideline	033		Point 1.9.11 – I am not aware of any evidence that suggests adverse outcomes in children where normal haemoglobin levels are targeted. Therefore what is the rationale for targeting lower levels? Is this based on adult evidence? Children (particularly younger ones) are unique and we need to be careful about advising sub-normal Hb levels, as they can lose a lot of blood and drop Hb quickly (e.g. lost HD circuit) and then require transfusion, with the adverse effects this gives including sensitisation.	Thank you for your comment. The committee was aware that while the current recommendations are in line with MHRA guidance, which was based on two studies which did not include findings from a paediatric population or from young people. This information has been passed to the MHRA, and we would update the guideline in the future should the MHRA advice change. Furthermore, current NICE recommendations on optimal Hb levels for children and young people were based on the view that this

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				It is therefore difficult to understand the rationale for targeting sub-normal Hb levels. In addition the comment about avoiding levels of Hb >120g/L is based on adult evidence – to my knowledge there is no evidence for adverse events in children, therefore this statement should be changed to reflect the fact that it can only be applied to adults (in an evidence based way).	population could in general be expected to benefit from similar Hb levels to adults. However, the committee highlighted that coagulation risks in children and young people are very different to those in adults. The committee noted that the current recommendation of Hb levels may be too low for children as in practice higher targets of between 110 -130 g/litre are being used but was unable to draft new recommendations about higher Hb levels because there was no new evidence. The committee agreed that further research in this area was important and highlighted that audit or registry data may also be useful as this would allow data on safety and efficacy to be captured for different Hb targets currently being used in practice. It made a research recommendation to support further research in this area.
British Association for Paediatric Nephrology	Guideline	044		Point 1.11.9 – In infants with CKD – care should be taken to ensure that the higher than normal reference ranges for calcium and phosphate are applied. Also that phosphate levels are not allowed to drop below the normal range as this risks the development of rickets.	Thank you for your comment. Based on clinical experience, the committee said that in growing children and young people, calcium is often maintained close to, but not above the upper limit of the age-related reference range. This have been added to the rationale.
British Association for Paediatric Nephrology	Guideline	046		Point 1.11.17 – also include assessment of alkaline phosphatase in assessment when considering phosphate levels.	Thank you for your comment. Assessment of alkaline phosphatase has been added to recommendation 1.11.17 (this number has been updated to 1.11.8 after consultation).
British Society for Rheumatology	Guideline	009 - 010	018 – 009	In recommendation 1.1.21, Gout should be added to the list of conditions that should prompt testing for CKD. CKD is an important risk factor for gout. 25% of people with gout have CKD stage 3, 4 or 5. Furthermore, CKD has important implications for the management of gout	Thank you for your comment. Gout has been added to the list of risk factors to test for CKD in adults.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				including avoidance of NSAIDs and lower doses of colchicine and allopurinol to avoid serious complications such as rhabdomyolysis and allopurinol hypersensitivity syndrome.	
Daiichi Sankyo UK Limited	Guideline	026	009 - 011	Daiichi Sankyo welcomes the opportunity to comment on the guideline update for Chronic kidney disease: assessment and management [GID-NG10118]. We understand that there are no plans to update section 1.6.23 of guideline CG182 regarding oral antiplatelets and anticoagulants. However, based on the evidence which was available at the time of draft scoping for this guideline update, Daiichi Sankyo believe the following should be taken into consideration: In relation to section 1.6.23 of the draft guideline, we consider that the singular recommendation for only one NOAC, apixaban, in preference to warfarin in patients with NVAF and a confirmed eGFR of 30-50ml/min, taking into account the intended meaning of 'consider' as defined by NICE, is inappropriate and potentially misleading based on the available evidence. The recommendation deviates from the position of other major European guidance, is contrary to the respective positive technology appraisals which recommend other NOACs as options for prevention of stroke and systemic embolism within their respective licensed indications, including patients with moderate renal impairment and also fails to take into account very important clinical (including new published data after 2014 and before the scoping for this guideline update) and practical considerations of the respective NOACs.	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations. We have passed your issue on to the NICE surveillance team who will explore whether this recommendation needs updating in the future.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Edoxaban did not have a technology appraisal document (NICE TA355 published 23rd Sep 2015) at the time of the last NICE CG182 guideline publication (23rd July 2014). The following clinical data for edoxaban, not considered within the 2014 publication should be to be considered given the relevance to the best patient care within this patient group: In the ENGAGE AF-TIMI 48 trial[1], 14071 patients were randomised in a double-blind, dummy-dummy event-driven trial to either high-dose edoxaban-regimen (HDER) (60mg OD with dose reduction to 30mg OD in patients with certain clinical characteristics, one being patients with Cockcroft-Gault creatinine clearance between 30-50ml/min). The primary efficacy endpoint was time to first adjudicated stroke/systemic embolic event and the principal safety endpoint was adjudicated major bleeding (as defined by the ISTH), during treatment. Median duration of follow-up was 2.8 years and mean $CHADS_2$ score was 2.8. 19.6% (n=1379) of patients randomised to HDER underwent protocol mandated dose reduction to 30mg OD due to creatine clearance <50ml/min, along with 19.3% (n=1361) of those in the warfarin arm, who received dose-reduced placebo-matched edoxaban 30mg OD. High-dose edoxaban regimen was non-inferior to well-controlled warfarin (median time-in-therapeutic range 68.4%) for the prevention of stroke and systemic embolism (hazard ratio, 0.79; 97.5% confidence interval CI, 0.63 to 0.99; P<0.001 for noninferiority) and showed significantly lower rates of bleeding (hazard ratio for major bleeding, 0.80; 95% CI,	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				0.71 to 0.91; P<0.001) and death from cardiovascular causes (hazard ratio, 0.86; 95% CI, 0.77 to 0.97; P = 0.01). In a prespecified subgroup analysis of the ENGAGE AF-TIMI 48 trial[2], the relative efficacy, safety, and net clinical benefit of HDER compared with warfarin were consistent with the overall trial findings when evaluated by the prespecified renal subgroups defined by moderate renal dysfunction (CrCl 30–50 mL/min), in which most patients underwent edoxaban dose reduction, and mild or no renal dysfunction (CrCl >50 mL/min) at baseline. The efficacy of HDER was similar to that of warfarin for the prevention of S/SE in the prespecified renal subgroups, with no modification of the treatment effect by renal function (CrCl of 30–50 mL/min: hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.65–1.18; CrCl >50 mL/min: HR, 0.87; 95% CI, 0.72–1.04; P for interaction=0.94). The rate of ISTH major bleeding was higher in those with moderate renal dysfunction at baseline (4.0%/y for HDER and 5.3%/y for warfarin) compared with those with mild or no renal dysfunction (2.5%/y for HDER and 3.1%/y for warfarin). HDER was superior to warfarin for the primary safety end point in both renal subgroups with no modification of the treatment effect by renal function (CrCl of 30–50 mL/min: HR, 0.76; 95% CI, 0.58–0.98; CrCl >50 mL/min: HR, 0.82; 95% CI, 0.71–0.95; P for interaction=0.62). Finally, those with moderate renal dysfunction at baseline were at higher risk for the primary net clinical outcome of S/SE, major bleeding, or death (CrCl of 30–50 mL/min: 11.4%/y for HDER and 13.4%/y for warfarin; CrCl >50 mL/min: 6.3%/y for HDER and	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				7.0%/y for warfarin), and HDER resulted in a more favourable net clinical outcome compared with warfarin regardless of renal function (CrCl of 30–50 mL/min: HR, 0.86; 95% CI, 0.75–0.98; CrCl >50 mL/min: HR, 0.91; 95% CI, 0.83–0.99; P for interaction=0.49). Moreover, per the SmPC dosing recommendations for edoxaban[3], a 50% dose reduction from 60mg OD to 30mg OD is applied for patients with Cockcroft-Gault creatinine clearance in the 15-50ml/min range. The dose reduction strategy was extensively examined in the ENGAGE AF-TIMI 48 trial[1], with 25.4% (n=1787) of patients randomised to HDER receiving protocol mandated dose reduction to 30mg, the vast majority of which (n=1361) was due to creatinine clearance ≤50ml/min. The dose reduction strategy was designed to reduce exposure in patients at increased risk of bleeding and resulted in significantly lower drug concentration and anti-FXa activity in patients on edoxaban who had dose reductions compared with those who did not[4]. In a sub analysis that examined the association of edoxaban dose, concentration, anti FXa activity and outcomes from the ENGAGE AF-TIMI 48 trial[4], reducing the dose from 60mg OD to 30mg OD in the HDER arm resulted in mean 29% decrease in exposure (as measured using trough edoxaban concentration) and a 25% decrease in anti-FXa activity. The efficacy compared with warfarin was preserved (Stroke/SEE HDER no dose reduction HR 0.78 [95% CI 0.61-0.99] vs HDER dose-reduced HR 0.81 [95% CI 0.58-1.13] Pint = 0.85), with an even greater reduction in the incidence of major bleeding (Major bleeding HDER	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				no dose reduction HR 0.88 [95% CI 0.76-1.03] vs HDER dose-reduced HR 0.63 [95% 0.50-0.92] Pint = 0.023). Edoxaban is the only once-daily NOAC licensed in the UK that demonstrates non-inferior efficacy to warfarin as well as a significant reduction in major bleeding in patients with mild-moderate renal dysfunction. Once daily dosing regimens generally results in greater adherence vs. BID regimens in cardiovascular patients[5-7]. In the Edoxaban Treatment in Routine Clinical Practice for Patients With Non Valvular Atrial Fibrillation (ETNA-AF-Europe) registry, there was good overall adherence of 83% to the SmPC dosing recommendations, suggesting that the dose reduction criteria of edoxaban are generally followed in routine clinical care[8]. The 2018 European Heart Rhythm Association practical guide on NOACs in patients with atrial fibrillation[9], considers all FXa inhibitors (apixaban/edoxaban/rivaroxaban) equally as treatment options for patients with mild or moderate CKD (CrCl≥30ml/min). Section 6 states: *"With the availability of three FXa inhibitors with less pronounced renal clearance [than dabigatran], the use of the latter [FXa inhibitors] may be preferred in this patient population"*. Thus, the current NICE CG182 recommendation differs significantly from that of this frequently cited, expert-review of evidence for NOAC use in these CKD patients. We note and agree with the comments made by other stakeholders in 2018 at the scoping stage, that no prospective, comparative, randomised clinical trials	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				between NOACs have been conducted and that NICE appear to have considered the respective phase III studies comparing each NOAC to warfarin and then made their recommendation on the basis of which NOAC appears to have the most favourable data in patients with renal impairment. Yet, important differences exist between the phase III NOAC studies, including differences in patient demographics and baseline characteristics, stroke and bleeding risks, endpoints assessed and endpoint definitions. A review by *Camm et al*[10] (2018) highlights the considerable challenges in making these indirect comparisons across the pivotal phase III NOAC trials. Indeed, the authors conclude that, without taking the key issues they highlight into account, direct comparisons of summary results across trials are potentially misleading, and although pooled analyses may superficially be attractive, they do not obviate the need to study individual trial characteristics to interpret reported benefits and hazards in their respective trials. Taking the conclusions of *Camm et al* into consideration and exercising due caution in interpretation of indirect comparisons, a systematic review and network meta-analysis by *Andò et al*[12] on the use NOACs in Chronic kidney disease was published in 2017. Whilst apixaban ranks as having the highest probability of being selected over other NOACs for both efficacy and safety, the second selected choice was high dose edoxaban regimen. The comparison of major bleeding between apixaban and HDER did not reach statistical significance as it did compared to other NOACs[11].	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Of note, the authors comment on factors that could have contributed to the meta-analysis results which are important to consider when interpreting their results, namely: 1. Patients with CKD enrolled in the ARISTOTLE trial were at lower risk than those enrolled in ENGAGE AF-TIMI 48 and ROCKET-AF, in particular, those included in the ARISTOTLE trial were younger (mean age 77.6 ± 7.1 vs. median age 79 [75–83] vs. 79 [75–82] years, respectively), had lower $CHADS_2$ scores (mean 2.6 vs. 3.1 vs. 3.67, respectively) and less frequently had heart failure (33% vs. 55% vs. 66%, respectively)[12]. 2. Apixaban may be favoured within the network because of the highest relative effect on safety due to the rate of major bleeding in the warfarin arm, which, despite the lower risk population enrolled in the ARISTOTLE trial, was unexpectedly higher (6.44%) compared with those observed in the Warfarin arms of all the other NOACs trials: 5.4% in the RELY trial, which enrolled a population similar to that of ARISTOTLE, 4.7% in ROCKET-AF and 5.3% in ENGAGE AF-TIMI 48[12]. *Andò et al* conclude that apixaban or edoxaban 30mg (dose reduced from HDER regimen) might be more likely considered as reasonable options for AF patients with moderate CKD[12]. Furthermore, they add, "*As a matter of fact, if one considers that Edoxaban High Dose strategy*	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				was tested in a more risky population, this compound can be considered as a first choice in cases with multiple risk factors for bleeding"[12]. We acknowledge the challenges and limitations of such indirect analyses as noted by *Andò et al* in their conclusions and as discussed by *Camm et al* and are thus cognizant of exercising due caution in interpretation of their results. This notwithstanding, it is clear that there is sufficient robust data demonstrating the relative efficacy and safety of edoxaban in patients with mild-moderate CKD, to warrant its inclusion within these guidelines as an additional NOAC that is a viable alternative to warfarin in this high-risk patient cohort. Indeed, there are polypharmacy considerations for patients with renal dysfunction which lend further credence to the argument in favour of a once daily NOAC to aid adherence to prescribed treatment regimens[12]. **References** 1. Giugliano RP, Ruff CT, Braunwald E, et al. *Edoxaban versus warfarin in patients with atrial fibrillation*. N Engl J Med. 2013 Nov 28;369(22):2093-104. 2. Bohula EA, Giugliano RP, Ruff CT, et al. *Impact of renal function on outcomes with edoxaban in the ENGAGE AF-TIMI 48 trial*. Circulation. 2016 Jul 5;134(1):24-36.	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				3. Lixiana® Summary of Product Characteristics accessed February 2021 (https://www.medicines.org.uk/emc/product/6905/) 4. Ruff CT, Giugliano RP, Braunwald E, et al. *Association between edoxaban dose, concentration, anti-Factor Xa activity, and outcomes: an analysis of data from the randomised, double-blind ENGAGE AF-TIMI 48 trial*. Lancet. 2015 Jun 6;385(9984):2288-95. 5. Bae JP, Dobesh PP, Klepser DG, et al. *Adherence and dosing frequency of common medications for cardiovascular patients*. Am J Manag Care 2012;18:139–146. 6. Weeda ER, Coleman CI, McHorney CA, et al. *Impact of once- or twice-daily dosing frequency on adherence to chronic cardiovascular disease medications: a meta-regression analysis*. Int J Cardiol 2016;216:104–109. 7. Laliberte F, Nelson WW, Lefebvre P, et al. *Impact of daily dosing frequency on adherence to chronic medications among nonvalvular atrial fibrillation patients*. Adv Ther 2012;29:675–690. 8. De Groot JR, Weiss TW, Kelly P, et al. *Edoxaban for stroke prevention in atrial fibrillation in routine clinical care: One year follow up of the*	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				prospective observational ETNA-AF-Europe study. Eur Heart J Cardiovasc Pharmacother. 2020 Aug 13;pvaa079 9. Steffal J, Verhamme P, Potpara TS, et al. *The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation*. Eur Heart J. 2018 Apr 21;39(16):1330-1393. 10. Camm AJ, Fox KAA & Peterson E. *Challenges in comparing the non-vitamin K antagonist oral anticoagulants for atrial fibrillation-related stroke prevention*. Europace. 2018 Jan 1;20(1):1-11 11. Andò G, Capranzano P. *Non-vitamin K antagonist oral anticoagulants in atrial fibrillation patients with chronic kidney disease: A systematic review and network meta-analysis*. Int J Cardiol. 2017 Mar 15;231:162-169 Patti G, Haas S. *Non-Vitamin K Antagonist Oral Anticoagulants and Factors Influencing the Ischemic and Bleeding Risk in Elderly Patients With Atrial Fibrillation: A Review of Current Evidence*. J Cardiovasc Pharmacol. 2020 Oct 14;77(1):11-21	
GlaxoSmithKline	Evidence review K	General	General	• We do accept that the review uses the GRADE methodology to evaluate the quality of evidence. However, we are concerned recommendations are based on heterogenous evidence.	Thank you for your comment. Recommendation 1.9.18 was made based on the evidence found in review K: Anaemia – IV iron. The recommendation is specific for haemodialysis because most of the

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				• A key example of this is the of proportions of dialysis types [peritoneal and haemodialysis]. A lot of the papers don't highlight these proportions. • Different dialysis settings lead to different health outcomes. Have recommendations captured different dialysis types?	studies included participants who were on haemodialysis. A research recommendation was made to inform future guidance on intravenous iron for people who are on peritoneal dialysis.
GlaxoSmithKline	Evidence review K	General	General	We note that economic evidence has not been identified. Is there a plan for a denovo economic evaluation?	Thank you for your comment. The committee did not identify this review question for de novo economic modelling (as phosphate binders and risk prediction equations were decided to be higher priorities for modelling in this update of the guidance) and therefore none has been completed. This prioritisation exercise will be repeated the next time the guidance is updated. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
GlaxoSmithKline	Evidence review K	General	General	There are a few publications which do not identify the healthcare settings. We believe that different settings lead to different outcomes and economic implications. Please see references to the studies in comments below.	Thank you for your comment. Study setting was not an inclusion or exclusion criteria for this review, as the committee did not have a strong belief this would meaningfully impact the clinical effectiveness (and therefore cost-effectiveness) of the intervention.
GlaxoSmithKline	Evidence review K	General	General	The question of "amount" doesn't make it clear whether the HCRU associated with administration and frequency as opposed to just dose is taken into account particularly in patients receiving dialysis at home.	Thank you for your comment. We have added a statement in the review to clarify the costs considered.
GlaxoSmithKline	Evidence review K	General	General	This section on GFR and anaemia could be prefaced by a statement indicating that anaemia of CKD can occur across all stages of CKD, starting from CKD2.' This would avoid the risk (albeit an unlikely) that the uninitiated might wrongly infer from the guideline that	Thank you for your comment. We have added a statement to clarify that anaemia of CKD can occur across all stages.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				CKD was never to blame when the eGFR exceeds 60ml/min.	
GlaxoSmithKline	Evidence review K	005	004	The description of the population in the research question doesn't include erythropoiesis stimulating agents (ESAs), however the evidence includes publications which have evaluated patients on ESAs	Thank you for your comment. It is correct that the review question did not include ESAs and the protocol did not exclude ESAs either. Therefore, studies evaluating participants receiving ESAs were not excluded. All studies fulfilling the conditions specified in the protocol included participants on ESAs.
GlaxoSmithKline	Evidence review K	061		It is not clear why the Alcicek et al 1997 paper is included when the study setting is not reported?	Thank you for your comment. Study setting was not an inclusion or exclusion criteria.
GlaxoSmithKline	Evidence review K	071		It is not clear why the Charytan et al 2013 paper is included when the study setting is not reported?	Thank you for your comment. Study setting was not an inclusion or exclusion criteria.
GlaxoSmithKline	Evidence review K	074		It is not clear why the Goldstein et al 2013 paper is included when the study setting is not reported\/	Thank you for your comment. Study setting was not an inclusion or exclusion criteria.
GlaxoSmithKline	Evidence review K	086		It is not clear why the Nissensoon et al 1999 paper is included when the study setting is not reported?	Thank you for your comment. Study setting was not an inclusion or exclusion criteria.
GlaxoSmithKline	Evidence review K	089		It is not clear why the Roe et al 1996 paper is included when the study setting is not reported?	Thank you for your comment. Study setting was not an inclusion or exclusion criteria.
GlaxoSmithKline	Evidence review K	099		It is not clear why the Warady et al 2005 paper is included when the study setting is not reported?	Thank you for your comment. Study setting was not an inclusion or exclusion criteria.
Healthy.io	Guideline	007	020	We are concerned about recommendation 1.1.11. The revised guidance suggests that the 2014 guidance "Do not use reagent strips to identify proteinuria unless they are capable of specifically measuring albumin at low concentrations and expressing the result as an ACR.", should be replaced with ""Do not use reagent strips to identify proteinuria" [1,2]. This revision to the recommendations is inappropriate for 3 reasons.	Thank you for your comment. The committee agreed that evidence was not reviewed for the use of reagent strips in adults. Therefore, we have reinstated (recommendation removed before this consultation in January 2021) the recommendation for adults that was made in 2008 to specify that the use of reagent strips to identify proteinuria in adults should be limited to tests being capable of measuring albumin at low concentrations and expressing the result as an ACR.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				1. The evidence reviewed as part of the development of the 2021 guidance includes only studies that are focused on the use of reagent strips to identify proteinuria *in children.* Therefore, the evidence base of use of reagent strips in adults has not been reviewed and the guidance in relation to adults should not be amended. 2. There is good evidence that semi-quantitative albumin:creatinine ratio (ACR) reagent strips do offer greater sensitivity and specificity for identification of albuminuria and proteinuria than other reagent strips by generating a negative likelihood ratio (LR-) of less than 0.5. The 2014 guidance makes it clear it should be these reagent strips that are used and revised guidance should include this distinction. 3. Prohibiting use of clinically appropriate reagent strips (i.e. those capable of measuring albumin at low concentrations and expressing the result as an ACR) prevents point of care / home-based testing and risks increasing health inequalities for those who cannot access conventional testing via clinic / lab. It impacts accessibility for patients and reduces opportunities for at-risk patients to be identified. Further evidence to support the above assertion is provided below.	

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				1. The evidence reviewed as part of the development of the 2021 guidance includes only studies that are focused on the use of reagent strips to identify proteinuria *in children.* Therefore, the evidence base of use of reagent strips in adults has not been reviewed and the guidance in relation to adults should not be amended. Based on the supporting evidence supplied by NICE as part of the consultation, the studies used to generate the new recommendation, which applies to both adults and paediatrics, is based only upon studies conducted in children and neonates. Further, the new guidance makes a blanket statement regarding proteinuria, despite considering albuminuria and proteinuria as two subsets in the corresponding evidence. In addition, the evidence base reviewed regarding use of reagent strips in children focused on patients that are demographically unrelated to the typical population that would be screened for chronic kidney disease. - One study looks at asphyxiated neonates and compares a stick that only measures albumin (index test) to a "gold standard" of a measurement of serum creatinine (reference test). The literature is clear that microalbuminuria is an early and independent (of eGFR) marker for progression to kidney and	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				heart disease, so a comparison between the presence of urine albumin and a change in serum creatinine as a reference test does align with the broader evidence base. Additionally, the population in question was asphyxiated neonates, a population subset that do not fall into the traditional categories for populations at-risk of CKD.[17] - The second study does relate to a cohort that NICE recommends to screen. This study concerns children with type 1 diabetes and posits a sensitivity of 63% and specificity of 17% for its Clinitek microalbumin semi-quantitative dipstick in comparison to a quantitative test (Cobas-Mira immunoturbidmetry). However, it is unclear what device they are using to read the sticks, as well as which personnel performed the test, and whether it was done at the point of care or in the lab. These variables may go some way to explaining the difference between their experience with the device and a review of the literature using the same stick shown by McTaggart et. al showing sensitivities between 75-91% and specificity between 48%-94%.[8] However, as specified above, many of these studies were performed before 2010 and the technology and thus the accuracy of the semi-quantitative devices have improved since then. **2. There is good evidence that semi-quantitative albumin:creatinine ratio (ACR) reagent strips do offer greater sensitivity and specificity for**	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				identification of albuminuria and proteinuria than other reagent strips by generating a negative likelihood ratio (LR-) of less than 0.5. The 2014 guidance makes it clear it should be these reagent strips that are used and revised guidance should include this distinction. The proposed 2021 NICE guidance does not provide a clear definition about the different types of reagent strips (or urine dipsticks) that have been evaluated or that are recommended. The main types of reagent strips for urinalysis are: • Standard 10 parameter urine test strips. These strips detect all protein and are not sensitive enough to identify albumin at low concentrations. • Albumin test strips. These strips look only for albumin and not creatinine. Without creatinine, the result will be adversely affected by the patient's hydration status e.g. whether the sample is dilute or concentrated. • Protein: creatinine ratio test strips. NICE recommends ACR is used in preference to PCR as PCR detects all protein and is less sensitive for albuminuria, which is the protein used for staging and risk stratification of CKD. • Albumin: creatinine ratio test strips. These strips can detect albuminuria at very low levels and also measure creatinine, resulting in higher sensitivity, specificity and reliability. It is these strips that Healthy.io recommends should be	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				used in line with existing guidance CG182 (2014). In a review of 13 studies that compared semi-quantitative ACR strip testing (using appropriate reagent strips) to quantitative ACR methods, overall median sensitivity and specificity rates were 83.8% and 91.5%. Sensitivity rates reported in more recent studies (i.e., published after 2010) tended to be even higher.[3-15] This evidence highlights the importance of the guidance reflecting the difference between low sensitivity proteinuria sticks and more sensitive and specific semi-quantitative albumin:creatinine ratio dipsticks. A ban on the former due to the likelihood of false positives and negatives when screening for albuminuria on a population basis seems to make sense from a clinical and cost effectiveness point of view. However, these generalisations do not hold for ACR dipsticks. Additionally, if we focus on the metric specified in the evidence reviewed by NICE, a negative likelihood ratio (LR-) of less than 0.5, it is clear that ACR dipsticks do meet this threshold. In a selection of the studies referenced below, urine ACR dipsticks have consistently been able to clear the threshold of a LR- of 0.5, whilst maintaining positive likelihood ratios (LR+) of greater than 2. These studies show that using the criteria that NICE has set out in its most recent consultation, ACR dipsticks are	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				a clinically and cost-effective way of screening for albuminuria in at-risk populations. This has precedent in national guidance with KDIGO 2012 recommending that, "Reagent strip point-of-care testing devices capable of measuring low concentrations of albumin are also available producing both semi-quantitative and fully quantitative ACR results. Reasonable analytical and diagnostic performance has been demonstrated. While studies of these devices have been somewhat limited in size, they demonstrate their potential to play a significant role in the care pathway of patients suspected of having CKD."[16] These sticks already calibrate to the stages of risk stratification of CKD recommended in the existing and upcoming NICE guidance e.g. A1 (<3mg/mmol), A2 (3-30mg/mmol), and A3 (>30mg/mmol). **3. Prohibiting use of clinically appropriate reagent strips (i.e. those capable of measuring albumin at low concentrations and expressing the result as an ACR) prevents point of care / home-based testing and risks increasing health inequalities for those who cannot or do not access conventional testing via clinic / lab. It impacts accessibility for patients and reduces opportunities for at-risk patients to be identified.** For the diagnosis of CKD, KDIGO and NICE guidelines recommend 2 positive tests of uACR >3 mg/mmol. This is important to overcome the high biologic variability of albuminuria (~50% day-to-day variation ~2 SD).	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				However, the literature is clear that compliance to this process has consistently been poor. The National Diabetes Audit noted that from Jan – Sep '20, only 25% of people with type 1 diabetes and 34.5% of people with type 2 diabetes completed this care process.[18] The 2017 CKD audit demonstrated that only 30% of people with high blood pressure compliant with the test.[19] This leaves millions of people at risk of undiagnosed CKD. Studies have postulated that patients often neglect the test due to a variety of reasons, such as the discomfort of producing a sample in the GP practice, not remembering to bring a sample, and not understanding the importance of the urine ACR test.[20-22] Thus, models of care that improve convenience of care and ease of access by allowing near-patient or home-based testing would seem to be more important than ever. Access to semi-quantitative devices and kits could go some way to closing that gap, as indicated in NICE's Medtech Innovation Briefing (2020) of Healthy.io's technology.[23] Healthy.io's home-based ACR test is currently being deployed in the NHS in a number of regions in England, and real-world and clinical studies are underway to assess the impact on improving uptake of the ACR test amongst at-risk patients and particularly those with the greatest need, including people with multiple-morbidity, working age people, BAME communities, socially-deprived localities and people who have no engaged with annual care processes repeatedly for some time.	

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				This evidence will be published in 2021 / 2022, and anecdotal feedback from NHS indicates that home-based testing is improving accessibility for patients, with c.72% of previously untested patients successfully completing the test using this method. The inclusion of all available high-quality methods for uACR testing in the forthcoming guidelines would better support identification, staging, monitoring and treatment of CKD in at-risk patients. It would broaden access to accurate tests that meet the clinical standards of care, including point of care tests, enabling providers to choose the approach that best fits their practice and workflow. References cited: 1 Chronic kidney disease: NICE guideline DRAFT (January 2021) [Internet]. Nice.org.uk. 2021 [cited 1 February 2021]. Available from: https://www.nice.org.uk/guidance/GID-NG10118/documents/draft-guideline 2 Recommendations | Chronic kidney disease in adults: assessment and management | Guidance | NICE [Internet]. Nice.org.uk. 2021 [cited 1 February 2021]. Available from: https://www.nice.org.uk/guidance/cg182/chapter/1-Recommendations#investigations-for-chronic-kidney-disease-2 3 Yang CJ, Chen DP, Wen YH, Lai NC, Ning HC. Evaluation the diagnostic accuracy of albuminuria	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				detection in semi-quantitative urinalysis. Clin Chim Acta 2020;510:177-80. 4 Kim Y, Park S, Kim MH, et al. Can a semi-quantitative method replace the current quantitative method for the annual screening of microalbuminuria in patients with diabetes? Diagnostic accuracy and cost-saving analysis considering the potential health burden. PLoS One 2020;15:e0227694. 5 Shiwa T, Nishimura M, Kato M. The Effectiveness of the Semi-quantitative Assessment of Microalbuminuria Using Routine Urine Dipstick Screening in Patients with Diabetes. Intern Med 2018;57:503-6. 6 Nah EH, Cho S, Kim S, Cho HI. Comparison of Urine Albumin-to-Creatinine Ratio (ACR) Between ACR Strip Test and Quantitative Test in Prediabetes and Diabetes. Ann Lab Med 2017;37:28-33. 7 Cho MC, Ji M, Kim SY, et al. Evaluation of the URiSCAN super cassette ACR semiquantitative urine dipstick for microalbuminuria screening. J Clin Lab Anal 2014;28:281-6. 8 McTaggart MP, Price CP, Pinnock RG, Stevens PE, Newall RG, Lamb EJ. The diagnostic accuracy of a urine albumin-creatinine ratio point-of-care test for detection of albuminuria in primary care. Am J Kidney Dis 2012;60:787-94. 9 Guy M, Newall R, Borzomato J, Kalra PA, Price C. Diagnostic accuracy of the urinary albumin: creatinine ratio determined by the CLINITEK Microalbumin and DCA 2000+ for the rule-out of albuminuria in chronic kidney disease. Clin Chim Acta 2009;399:54-8.	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				10 Croal BL, Mutch WJ, Clark BM, et al. The clinical application of a urine albumin:creatinine ratio point-of-care device. Clin Chim Acta 2001;307:15-21. 11 Sarafidis PA, Riehle J, Bogojevic Z, Basta E, Chugh A, Bakris GL. A comparative evaluation of various methods for microalbuminuria screening. Am J Nephrol 2008;28:324-9. 12 Croal BL, Mutch WJ, Clark BM, et al. The clinical application of a urine albumin:creatinine ratio point-of-care device. Clin Chim Acta 2001;307:15-21. 13 Pickersgill AJ, McInnes EA, Wiener K. Clinitek Microalbumin assay. Diabet Med 2001;18:937-9. 14 Le Floch JP, Marre M, Rodier M, Passa P. Interest of Clinitek Microalbumin in screening for microalbuminuria: results of a multicentre study in 302 diabetic patients. Diabetes Metab 2001;27:36-9. 15 Parsons M, Newman DJ, Pugia M, Newall RG, Price CP. Performance of a reagent strip device for quantitation of the urine albumin: creatinine ratio in a point of care setting. Clin Nephrol 1999;51:220-7. 16 Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter., Suppl. 2013; 3: 1–150. 17 Ochigbo, S.O., Udo, J.J., Nlemadi, A.C. et al. (2017) Comparison of the efficacy of serum 2 creatinine and microalbuminuria in early diagnosis of renal injury in asphyxiated infants in 3 calabar, Southern Nigeria. Iranian Journal of Neonatology 8(2) 18 National Diabetes Audit - Care Processes and Treatment Targets, Quarterly Data Release, January to	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				September 2020 - NHS Digital [Internet]. NHS Digital. 2021 [cited 2 February 2021]. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/national-diabetes-audit/care-processes-and-treatment-targets-2nd-quarter-january-september-2020-data-release 19 National Chronic Kidney Disease Audit [Internet]. Lshtm.ac.uk. 2021 [cited 2 February 2021]. Available from: https://www.lshtm.ac.uk/files/ckd_audit_report.pdf 20 Adams H, Barter R. Type 2 Diabetics miss out on a recommended annual kidney test which can signal irreversible damage that may lead to fatal complications, survey reveals - Napp [Internet]. Napp. 2020 [cited 22 May 2020]. Available from: https://napp.co.uk/news/type-2-diabetics-miss-out-on-a-recommended-annual-kidney-test-which-can-signal-irreversible-damage-that-may-lead-to-fatal-complications-survey-reveals/ 21 Hellemons, M. E., Denig, P., de Zeeuw, D., Voorham, J., & Lambers Heerspink, H. J. (2012). Is albuminuria screening and treatment optimal in patients with type 2 diabetes in primary care? Observational data of the GIANTT cohort. Nephrology Dialysis Transplantation, 28(3), 706–715. https://doi.org/10.1093/ndt/gfs567 22 Willison, A., Tully, V., & Davey, P. (2016). All Patients with Diabetes Should Have Annual UACR Tests. Why is That So Hard? BMJ Quality Improvement Reports, 5(1), u209185.w3747. https://doi.org/10.1136/bmjquality.u209185.w3747 23 Overview | Healthy.io test for home testing of urine albumin to creatinine ratio | Advice | NICE [Internet]. Nice.org.uk. 2021 [cited 11 February 2021]. Available from: https://www.nice.org.uk/advice/mib221	

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
James O'Riordan Medical Centre	Guideline	013	General 1.3.2	Clearer recommendations on the frequency of uACR testing in people diagnosed or at risk of CKD would help to increase testing rates and that this would be of clinical value. If NICE were to recommend **uACR testing to be conducted alongside eGFR testing** as part of the recommended monitoring process then this would in most cases only result in 1 uACR test per patient per year, which appears to be manageable from a primary care perspective.	Thank you for your comment. We have added a note to Table 2 about ACR monitoring which should be individualised based on a person's individual characteristics, risk of progression and whether a change in ACR is likely to lead to a change in management. ACR monitoring was not recommended alongside to eGFR because eGFR is used to define progression rather than ACR and so more frequent monitoring is needed (see recommendations 1.3.5 to 1.3.8 which define progression in adults with the use of eGFR). No specific evidence on ACR monitoring frequency was found but the committee noted that it is a costly test and should not be used every time eGFR is measured, but on an individual basis. The rationale has examples about the frequency of ACR monitoring ACR (more frequently monitoring in people with high ACR categories A2 or A3; or where a change in ACR would affect management). The committee agreed to make a research recommendation to identify the optimal frequency of monitoring ACR in adults, children and young people with CKD.
James O'Riordan Medical Centre	Guideline	021	General 1.5.7	Could NICE have a role in further promoting increased collaboration between primary and secondary care as well as at the MDT level through best practice measures such as virtual triage clinical and consultations to ensure that patients can continue to be managed in the care setting that's right for them and to ensure GPs are not de-skilled. PCN (Primary Care Networks) maybe the way to join this, and with the introduction if ICS (integrated care systems) we could create special	Thank you for your comment. Last bullet point of recommendation 1.5.9 suggests specifying criteria for future referral and re-referral if GP follow up is agreed; and for children and young people, these criteria should be agreed between the GP and secondary care services.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				interest GPs in renal medicine to manage this cohort of patients, across PCNs of 50 000 patients, with direct links with the renal physicians in hospitals.	
James O'Riordan Medical Centre	Guideline	022	022 - 023 1.6.6	The ACR limit of 30 does not represent the full trial evidence for DAPA-CKD which goes down to ACR 20, missing a considerable number of patients that could benefit from dapagliflozin. The lack of a recommendation for SGLT2is in patients without CKD despite the strength of trial evidence from DAPA-CKD in this subgroup and the forthcoming licence timing for dapagliflozin is disappointing. The next opportunity for SGLT2 is to be included in this guideline will likely be several years away when it is next updated. This concerns me, as a lead in diabetes I will obviously be aware, and prescribe to my patients, but those not aware due to not being in the guidelines, maybe doing a disservice to their patients without meaning to.	Thank you for your comment. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. NICE is also currently undertaking a technology appraisal of dapagliflozin for treating chronic kidney disease which will include the DAPA-CKD trial. Therefore, data from DAPA-CKD has been removed from this update. See https://www.nice.org.uk/guidance/indevelopment/gid-ta10808 for details. The NICE CKD guideline will cross refer to this technology appraisal appraising dapagliflozin when it is published.
James O'Riordan Medical Centre	Guideline	023	001 - 002 1.6.6	The recommendation to monitor for eGFR decline could cause confusion and unnecessary termination of treatment. We know initially there maybe a slight decline with an SGLT2. As a GP, I know my colleagues maybe a little keen to check eGFR quite soon after initiation (it's almost a natural response to check kidney function when initiating any medication that will impact the kidney), but some faith and confidence needs to be applied, and potentially check at a later period.	Thank you for your comment. We have included a clarification to the rationale stating that eGFR monitoring should depend on people's circumstances and on the BNF advice of monitoring requirements for people using SGLT2 inhibitors.
Kidney Care UK	Guideline	006	003	We strongly recommend NICE reconsiders the recommendation 'For adults of African-Caribbean or African family origin, multiply eGFR by 4 1.159 if calculated using the CKD-EPI creatinine equation' as it risks exacerbating health inequalities and excluding	Thank you for your comments. Recommendation 1.1.3 has been removed from the guideline. The rationale section includes further advice stating that individualised judgement should be used when interpreting eGFR in people from UK black, Asian

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				people from those ethnic backgrounds from timely specialist assessment, diagnosis and ongoing treatment. Evidence shows that automatically increasing GFR if someone is black may be inaccurate, and can lead to overestimation of kidney function which may mean they are referred for specialised treatment late and inevitably experience poorer outcomes. There is no indication of how to apply such a formula to those of mixed race and this recommendation is not personalised or related to muscle mass. The historic formula is based on an unrepresentative group of African Americans and should not be used to determine access to specialised treatment for adults in the UK in 2021. We note that the US National Kidney Federation and American Society of Nephrology Taskforce has started work to address this problem and "Ensure that GFR estimation equations provide an unbiased assessment of kidney function so that patients, clinicians, laboratories, and public health officials can make informed decisions to ensure equity and personalized care for patients with kidney diseases." We think that this approach should apply in the UK and urge NICE to reconsider the perpetuation of this outdated approach.	and minority ethnic groups and in adults with extremes of muscle mass. The committee agreed to make recommendations for research on appropriate eGFR equations for black, Asian and minority ethnic groups (adults, children and young people) in the UK. They agreed that factors other than ethnicity should also be explored as biomarkers.
Kidney Care UK	Guideline	008	013 - 014	We support the recommendation to offer testing for CKD following incidental finding of unexplained proteinuria on a reagent strip, as it will support the early identification and intervention in chronic kidney disease which is so important to address the growing numbers of people developing the condition.	Thank you for your comment.
Kidney Care UK	Guideline	009	015	We have concerns about the use of the word nephrotoxic without further context and the anxiety this may engender in kidney patients who are prescribed	Thank you for your comment. The term 'nephrotoxic' has been replaced by 'medicines which can adversely affect kidney function'.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				these drugs, particularly tacrolimus which is very widely used amongst transplant recipients. We would recommend an additional statement within this recommendation clarifying that although people with kidney disease may be prescribed drugs that have the potential to be nephrotoxic, this will be after careful consideration of risks and benefits and all patients will be carefully monitored and medication adjusted accordingly to minimise harm. As a good example, NHS Choices explains it this way here in the Who's at risk of AKI section: If "you're taking certain medicines, including non-steroidal anti-inflammatory drugs (NSAIDS, such as ibuprofen) or blood pressure drugs, such as ACE inhibitors or diuretics; diuretics are usually beneficial to the kidneys, but may become less helpful when a person is dehydrated or suffering from a severe illness."	
Kidney Care UK	Guideline	009	018	We query whether liver disease should included in this list of risk factors for kidney disease. See L. Orlić, I. Mikolasevic, Z. Bagic, S. Racki, D. Stimac, S. Milic, "Chronic Kidney Disease and Nonalcoholic Fatty Liver Disease—Is There a Link?", *Gastroenterology Research and Practice*, vol. 2014, Article ID 847539, 6 pages, 2014. https://doi.org/10.1155/2014/847539	Thank you for your comment. The evidence for adults was not reviewed for the list of factors to test for CKD and for the list of factors for referral for specialist assessment because these areas were out of scope of the current update. The committee agreed that evidence is needed before adding liver disease to these recommendations.
Kidney Care UK	Guideline	010	013	We query why 'solitary functioning kidney' is in the list of risk factors for children and young people, but not for adults? During the Covid-19 pandemic Kidney Care UK received a very high number of calls from people with one kidney questioning whether they were at increased risk from Covid, reflecting concern among this group about their health status. If there is no evidence that they	Thank you for your comment. We will pass this information to the NICE COVID-19 team who is responsible for producing guidance that helps people make the right decisions during the COVID-19 pandemic. Evidence for adults was not reviewed during this update and there was no evidence in the

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				are at increased risk, it may be helpful to have a statement clarifying this.	2014 guideline about solitary functioning kidney in adults as a risk factor for developing CKD.
Kidney Care UK	Guideline	011	004	We strongly support recommendation 1.1.25 given the risk of poor outcomes following AKI. Kidney Care UK believes it should be strengthened by a recommendation that patients are made aware of ongoing risk and provided with information tailored to their individual needs on understanding their risk, the need for ongoing monitoring and how they can be involved in self-monitoring. We hear from people who have had AKI who have not had this advice and are not aware of what they can do to protect themselves from acquiring AKI in the future.	Thank you for your comment. NICE guideline on acute kidney injury: prevention, detection and management includes a section on information and support for patients and carers with recommendations about treatment options, monitoring, prognosis and support to people with or who have had acute kidney injury and/or, if appropriate, their parent or carer.
Kidney Care UK	Guideline	013	017	We would like to see the addition of a recommendation that the agreed frequency of monitoring is documented and written confirmation is provided to patients, to support patient understanding and involvement of their own care.	Thank you for your comment. We added a link to the NICE's guideline on patient experience in adult NHS services and the NICE's guideline on shared decision making which recommends to give written information to the patient.
Kidney Care UK	Guideline	014	006	We are unclear whether Table 2 relates just to the minimum number of eGFR creatinine tests, or eGFR creatinine tests and ACR? The title implies it is only eGFR creatinine tests whereas recommendation 1.3.1 stipulates the monitoring involves both. Please can you clarify?	Thank you for your comment. We have added a note to Table 2 about ACR monitoring which should be individualised based on a person's individual characteristics, risk of progression and whether a change in ACR is likely to lead to a change in management. The rationale has examples about the frequency of ACR monitoring (more frequent monitoring in people with high ACR categories A2 or A3; or where a change in ACR would affect management). The committee agreed to make a research recommendation to identify the optimal frequency of monitoring ACR in adults, children and young people with CKD.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Kidney Care UK	Guideline	019	1.5.1	We recommend the addition of 'refer patient to sources of support and information, such as Kidney Care UK.' so that patients can benefit from a wide range of patient friendly and accessible information on risk of CKD and its progression.	Thank you for your comment. Recommendation 1.4.1 says that people with CKD should be offered education and information tailored to the severity and cause of CKD, the associated complications and the risk of progression. We do not wish to endorse a particular source of information in the recommendation as this information has not been reviewed by NICE.
Kidney Care UK	Guideline	019	1.5.1	We note that patients with CKD should be given information about their risk, but this should be supplemented with information about the action a patient can take to reduce their risk. This is vital to empower self-management and reduce the burden of CKD. We suggest that there should also be a separate recommendation that people at risk from CKD are provided with comprehensive information about CKD and why they are at risk/being monitored, as well as the action they can take to reduce their risks from CKD.	Thank you for your comment. There is a section in the guideline about information and education for people with CKD which includes topics like what CKD is and how affects people and what people can do to manage and influence their own condition.
Kidney Care UK	Guideline	021	009	We suggest that the statement is amended to recommend that the care plan should be documented, the patient's understanding of it confirmed, and the patient should be provided with a copy.	Thank you for your comment. The recommendation has been amended to state that the care plan should be documented and dated.
Kidney Care UK	Guideline	021	018	We suggest that patients should be given advice about action they could take to control their blood pressure to enable them to play an active role in their own care.	Thank you for your comment. This is beyond the remit of this guideline and is addressed in the NICE hypertension guideline.
Kidney Care UK	Guideline	022	022 - 023	We note that SGLTs inhibitors are recommended only for people with CKD and diabetes. There is evidence that SGLT inhibitors have benefits from people with CKD with and without diabetes, as discussed in the guideline (DAPA-CKD trial) and, although the technology appraisal for dapagliflozin is not yet complete we note that its scope includes those without diabetes. The	Thank you for your comment. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. NICE is also currently undertaking a

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				development of a new way of treating kidney disease, that shows real benefits, has been of huge interest to patients. We suggest, based on evidence from the DAPA-CKD study, that NICE reconsiders its guidance and maximises the opportunities for those with kidney disease without diabetes to benefit from the SGLT2 drugs now, rather than looking again at an unspecified time in the future.	technology appraisal of dapagliflozin for treating chronic kidney disease which will include the DAPA-CKD trial. Therefore, data from DAPA-CKD has been removed from this update. See https://www.nice.org.uk/guidance/indevelopment/gid-ta10808 for details. The NICE CKD guideline will cross refer to this technology appraisal appraising dapagliflozin when it is published.
Kidney Care UK	Guideline	044	007	We hear from many patients that have problems with phosphate binders and welcome the recommendation to consider switching to the next recommended one. However, there is a risk that patients may not raise these problems with their care team because they are unaware of the side effects are linked to the phosphate binders or may not realise many people cannot tolerate the initial binder prescribed and alternatives are available. Patients may feel they have to tolerate these problems. We would recommend that patients are informed of side effects and when and how to raise problems with the phosphate binder prescribed and that is explained to them that alternatives are available.	Thank you for your comment. Recommendation 1.11.6 has been amended to include your suggestions.
Leeds Teaching Hospitals NHS Trust	Algorithm 1	General	General	The algorithm states that in patients with type 2 diabetes an SGLT2 inhibitor should be added when ACR is 30mg/mmol or greater. This is consistent with the inclusion criteria of the CREDENCE Study with canagliflozin. However, data from the DAPA-CKD trial with dapagliflozin indicate clinical benefit in people with CKD using an inclusion level of ACR of 20mg/mmol or above. We recommend that the ACR threshold in the guidance is amended to reflect this. The DAPA-CKD study provided compelling evidence that dapagliflozin reduces adverse renal events in people with CKD and	Thank you for your comment. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. NICE is also currently undertaking a technology appraisal of dapagliflozin for treating chronic kidney disease which will include the DAPA-CKD trial. Therefore, data from DAPA-CKD has been removed from this update. See

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				ACR of 20-500mg/mmol with and without type 2 diabetes (hazard ratio for the primary endpoint 0.61; 95% confidence interval [CI], 0.51 to 0.72; P<0.001; number needed to treat to prevent one primary outcome event, 19 [95% CI, 15 to 27]).	https://www.nice.org.uk/guidance/indevelopment/gid-ta10808 for details. The NICE CKD guideline will cross refer to this technology appraisal appraising dapagliflozin when it is published.
Leeds Teaching Hospitals NHS Trust	Algorithm 1	General	General	The algorithm does not include a recommendation for treatment with an SGLT2 inhibitor in people without diabetes, despite the evidence that such treatment is protective in this group. The DAPA-CKD study provided compelling evidence that dapagliflozin reduces adverse renal events in people with and without type 2 diabetes (hazard ratio for the primary endpoint 0.61; 95% confidence interval [CI], 0.51 to 0.72; P<0.001; number needed to treat to prevent one primary outcome event, 19 [95% CI, 15 to 27]).	Thank you for your comment. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. NICE is also currently undertaking a technology appraisal of dapagliflozin for treating chronic kidney disease which will include the DAPA-CKD trial. Therefore, data from DAPA-CKD has been removed from this update. See https://www.nice.org.uk/guidance/indevelopment/gid-ta10808 for details. The NICE CKD guideline will cross refer to this technology appraisal appraising dapagliflozin when it is published.
Leeds Teaching Hospitals NHS Trust	Guideline	013	025	The guidance includes measurement of urine albumin creatinine ratio (ACR) in the diagnosis of CKD but makes no recommendation on repeat measurement of ACR nor on the frequency at which this takes place in people with established CKD. We advocate inclusion of repeat ACR measurement at the same intervals as eGFR measurement in Table 2. Because measurement of eGFR and ACR are both integral to assessment of risk in patients with CKD (Table 1), it is necessary for ACR to be measured serially alongside eGFR to help identify disease progression and transition between categories of risk.	Thank you for your comment. We have added a note to Table 2 about ACR monitoring which should be individualised based on a person's individual characteristics, risk of progression and whether a change in ACR is likely to lead to a change in management. ACR monitoring was not recommended alongside to eGFR because eGFR is used to define progression rather than ACR and so more frequent monitoring is needed (see recommendations 1.3.5 to 1.3.8 which define progression in adults with the use of eGFR). No specific evidence on ACR monitoring frequency was

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					found but the committee noted that it is a costly test and should not be used every time eGFR is measured, but on an individual basis. The rationale has examples about the frequency of ACR monitoring ACR (more frequently monitoring in people with high ACR categories A2 or A3; or where a change in ACR would affect management). The committee agreed to make a research recommendation to identify the optimal frequency of monitoring ACR in adults, children and young people with CKD.
Leeds Teaching Hospitals NHS Trust	Guideline	022	022	The guidance states that in patients with type 2 diabetes an SGLT2 inhibitor should be added when ACR is 30mg/mmol or greater. This is consistent with the inclusion criteria of the CREDENCE Study with canagliflozin. However, data from the DAPA-CKD trial with dapagliflozin indicate clinical benefit in people with CKD using an inclusion threshold of ACR of 20mg/mmol or above. The threshold of 30mg/mmol, therefore, does not appropriately reflect the totality of the clinical evidence. Basing a recommendation on this threshold risks excluding a large number of potentially eligible patients from receiving appropriate treatment. We recommend that the ACR threshold in the guidance is amended to reflect this.	Thank you for your comments. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. NICE is also currently undertaking a technology appraisal of dapagliflozin for treating chronic kidney disease which will include the DAPA-CKD trial. Therefore, data from DAPA-CKD has been removed from this update. See https://www.nice.org.uk/guidance/indevelopment/gid-ta10808 for details. The NICE CKD guideline will cross refer to this technology appraisal appraising dapagliflozin when it is published.
Leeds Teaching Hospitals NHS Trust	Guideline	023	002	The recommendation 'monitor for volume depletion and eGFR decline' when prescribing an SGLT2 inhibitor is misleading and may lead to unnecessary discontinuation of therapy by clinicians. A small decline in eGFR is expected after initiation of SGLT2 inhibitor therapy due to the mechanism of action. However, the initial decline	Thank you for your comment. We have included a clarification to the rationale stating that eGFR monitoring should depend on people's circumstances and on the BNF advice of monitoring requirements for people using SGLT2 inhibitors.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				in eGFR precedes long-term protection from progressive decline and reduces the risk of major renal events. We are not aware of evidence that additional monitoring of renal function is required after initiation of SGLT2 inhibitor therapy. We recommend removal of the statement to monitor eGFR from the guidance and inclusion of a brief statement to reassure prescribers that a transient minor decline in eGFR is expected.	
Leeds Teaching Hospitals NHS Trust	Guideline	023	007	We are concerned that no recommendation is made for people with CKD without type 2 diabetes to receive an SGLT2 inhibitor, despite evidence that such treatment is protective in this group. The DAPA-CKD study provided compelling evidence that dapagliflozin reduces adverse renal events in people with CKD and ACR of 20-500mg/mmol with and without type 2 diabetes (hazard ratio for the primary endpoint 0.61; 95% confidence interval [CI], 0.51 to 0.72; P<0.001; number needed to treat to prevent one primary outcome event, 19 [95% CI, 15 to 27]). We are concerned that this evidence of benefit in people with CKD but without type 2 diabetes, which represents an important step-change in therapeutic options available, has been omitted from that considered for this update and has not been considered in the committee's recommendations. We understand a marketing authorisation for dapagliflozin for this indication is expected in May 2021. Omission of this evidence from this update risks this guidance being obsolete almost as soon as it is published.	Thank you for your comment. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. NICE is also currently undertaking a technology appraisal of dapagliflozin for treating chronic kidney disease which will include the DAPA-CKD trial. Therefore, data from DAPA-CKD has been removed from this update. See https://www.nice.org.uk/guidance/indevelopment/gid-ta10808 for details. The NICE CKD guideline will cross refer to this technology appraisal appraising dapagliflozin when it is published.
Liverpool University Hospitals NHS				1. We are concerned that this recommendation has no recommendation has been made for the use of SGLT2is to treat CKD in patients without diabetes	Thank you for your comments. Studies reporting on SGLT2 inhibitors were included in the update of this guideline if they included participants with suspected or diagnosed chronic

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Foundation Trust				2. Question 1: This recommendation will be a challenging change in practice because current recommendation for SGLT2is in people with T2D restricts to ACR ≥30 mg/mmol Our trust has had experience of implementing this approach through our cardiorenal metabolic/heart failure MDT and would be willing to submit its experiences to the NICE shared learning database. In addition current recommendation for SGLT2is in people with T2D states that eGFR should be monitored following treatment initiation This rationale states that There is evidence that Dapa CKD 1. Question 2 recommendations on when to avoid and stop renin-angiotensin-aldosterone system inhibitor (RAASi) therapy in those with or at risk of hyperkalaemia are not aligned to NICE's recommendations for the use of potassium binders Our trust has had experience of implementing this approach through our cardiorenal metabolic/heart failure MDT and would be willing to submit its experiences to the NICE shared learning database.	kidney disease who also had proteinuria or albuminuria. There were 3 randomised controlled trials meeting these inclusion criteria: CANVAS (Neuen 2019), CREDENCE (Perkovic 2019), and DELIGHT (Pollock 2019). There were other studies reporting on SGLT2 inhibitors that did not meet the inclusion criteria: DAPA-HF (McMurray et al. 2019), EMPEROR-Reduced Trial (Anker et al. 2021), and EMPA-REG OUTCOME (Wanner 2020). The recommendation has not changed because the evidence showed that there was a clinically meaningful risk reduction for end stage kidney disease (HR 0.68 [95% CI 0.54, 0.86]), all-cause mortality (HR 0.63 [95% CI 0.43, 0.92]), and hospitalisation for heart failure (HR 0.61 [95% CI 0.47, 0.80]) with canagliflozin compared to placebo in adults with ACR ≥30 mg/mmol. The committee agreed that SGLT2 inhibitors could be recommended as a class of medications to lower proteinuria. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. NICE is also currently undertaking a technology appraisal of dapagliflozin for treating chronic kidney disease which will include the DAPA-CKD trial. Therefore, data from DAPA-CKD has been removed from this update. See https://www.nice.org.uk/guidance/indevelopment/gid-ta10808 for details. The NICE CKD guideline will

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Question 3 no recommendation provided on the frequency of urine albumin to creatinine ratio (uACR) testing in individuals diagnosed with or at high-risk of CKD **Supporting evidence and rationale** 1. For adults with CKD but without diabetes, no recommendation for the use of SGLT2is has been included in the draft guideline. The Committee concluding that **"the evidence was not yet strong enough to make a recommendation, even though it looked promising".** AstraZeneca disagree with this conclusion for the following reasons: • Significant clinical benefit has been demonstrated with dapagliflozin in people without diabetes in the DAPA-CKD trial, [2] representing a step-change treatment option for a population with limited treatment options and high unmet need. A new licence for the treatment of CKD regardless of T2D status is expected in May 2021. • This evidence in people without T2D from DAPA-CKD has been omitted from the evidence synthesis for this guideline update and appears not to have been fully considered in the committees decision making for this sub-population. • In addition to the DAPA-CKD trial, there is strong and consistent evidence that the treatment effect of SGLT2is on both renal and CV outcomes is not modified by baseline HbA1c in individuals with heart failure and varied	cross refer to this technology appraisal appraising dapagliflozin when it is published. Regarding your comment about eGFR monitoring, we have included a clarification to the rationale stating that eGFR monitoring should depend on people's circumstances and on the BNF advice of monitoring requirements for people using SGLT2 inhibitors. Regarding your comments about recommendations 1.6.14 and 1.6.17, recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations but we have added a new recommendation referring to the NICE technology appraisals for treating hyperkalaemia (sodium zirconium cyclosilicate and patiromer). We have also passed your issue on to the surveillance team who will explore whether recommendations 1.6.14 and 1.6.17 (these numbers have been updated to 1.6.15 and 1.6.18 after consultation) need updating in the future. Regarding your comment about recommendations on the frequency of monitoring, we have added a note to Table 2 about the frequency of ACR monitoring stating that ACR monitoring should be individualised based on a person's individual characteristics, risk of progression and whether a change in ACR is likely to lead to a change in management. ACR monitoring was not recommended alongside to eGFR because eGFR is used to define progression rather than ACR

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				diabetes status from both the DAPA-HF trial of dapagliflozin and the EMPEROR-REDUCED trial of empagliflozin. [1-3] • Dapagliflozin is a well-established and well-characterised therapy; there is already extensive clinical experience and RWE for dapagliflozin across it's licenced indications for T2D, T1D and HF. • Preventing or delaying progression to ESRD and CV events in all populations for which there is robust evidence aligns with the prevention focussed NHS Long Term Plan,[4] and represents a major opportunity to reduce the economic burden of kidney disease. • Following the current update of the NICE CKD guidelines it will be several years until the next opportunity for SGLT2is to be included in the NICE CKD guidelines for the non-diabetic population. We understand that NICE is working towards creating more forward looking guidelines. This is evidenced by the 'future-proofed' recommendations already set out in this draft for SGLT2is in patients with T2D. The evidence discussed above (with more detailed provided in our formal response) warrants the same pragmatic approach for patients without T2D. 2. The recommendation for use of SGLT2is in adults with CKD and T2D restricts to ACR ≥30 mg/mmol. The Committee concluding it to be a **"sensible threshold that broadly represented the inclusion**	and so more frequent monitoring is needed (see recommendations 1.3.5 to 1.3.8 which define progression in adults with the use of eGFR). No specific evidence on ACR monitoring frequency was found but the committee noted that it is a costly test and should not be used every time eGFR is measured, but on an individual basis. Regarding your comment about encouraging best practice with respect to communication between primary and secondary care, recommendation 1.5.9 suggests specifying criteria for future referral and re-referral if GP follow up is agreed; and for children and young people, these criteria should be agreed between the GP and secondary care services.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				criteria of the trials". Disagree with this conclusion for the following reasons: • The DAPA-CKD trial provides high quality evidence for the significant treatment effect of dapagliflozin across a range of renal and cardiovascular outcomes measures in patients with an ACR between 20 to 500 mg/mmol. Consistency of treatment effect across the ACR spectrum included in the trial was determined by pre-specified subgroup analysis of the primary endpoint.[2] • Further evidence to support the consistency of treatment effect with dapagliflozin across the ACR range comes from the DECLARE-TIMI trial of patients with T2D in which dapagliflozin reduced the risk of the secondary renal-specific composite outcome (defined as a sustained decline of ≥40% in eGFR to less than 60 mL/min per 1.73m2, end-stage renal disease or death from renal causes) by 47% (95% CI 0·43–0·66; p-value<0.0001), with the treatment effect consistent across all uACR categories including those with normo- (ACR <3mg/mmol) and microalbuminuria (3-30mg/mmol).[5] • Based on an analysis of CPRD and QOF data, it is estimated that at least 80,000 individuals with CKD in England have an ACR between 20 and 30 mg/mmol; dapagliflozin has proven renal and CV benefit in these patients, who left untreated will continue to progress to more severe disease.[6, 7]	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				• 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.[4] 3. Considerable concern amongst nephrologists over the Committee's recommendation to monitor eGFR decline following the initiation of an SGLT2i in patients with T2D, for the following reasons: • The mechanism of action of SGLT2is causes an initial decline of eGFR, which in the long-term helps to protect the glomerulus from damage caused by the high intra-glomerular pressure common to patients with CKD.[8] eGFR subsequently increases again over several months and henceforth the SGLT2i treatment slows progressive eGFR decline as compared with individuals not taking SGLT2is. • Clinical expert opinion is that conducting an eGFR test in the weeks following SGLT2i initiation is not informative and may cause unnecessary concern that could result in termination of treatment, especially amongst primary care physicians who may not be aware of the mechanism of action for this drug class. • Therefore eGFR monitoring should not be recommended in this context, and a clear statement outlining what eGFR decline to	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				expect if renal tests are repeated should be provided. 4. Recommendations on when to avoid and stop RAASi therapy in those with or at risk of hyperkalaemia (1.6.14 and 1.6.17) contradict the recommendations made by NICE in the technology appraisals of potassium binders • RAASi therapy is a cornerstone of CKD treatment and has been shown to reduce blood pressure, renal decline and mortality. Down-titration or discontinuation of RAASi therapy are associated with a loss of these cardio-renal benefits. • Two potassium binders, sodium zirconium cyclosilicate (SZC) and patiromer calcium sorbitex, have been recommended by NICE for the treatment of hyperkalaemia in adults with CKD. NICE TA599 and TA623 recommend the use of SZC and patiromer, respectively, for **treating hyperkalaemia in adults with CKD stage 3b to 5 if they have confirmed serum potassium levels ≥6mmol/litre, are not taking optimised dosage of RAASi because of the HK, and are not on dialysis.**[9, 10] • Potassium binders are a step-change in the management of HK; offering an alternative to down-titration/discontinuation of RAASi therapy whilst maintaining normokalaemia.[11, 12]	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				• SZC and patiromer are recommended in patients with CKD in order to allow continued RAASi therapy in the 2020 Renal Association Guidelines, the 2018 ESC consensus statement and the KDIGO DKD and recently published blood pressure guidelines.[12-15] • Failure to reflect recommendations set out in these NICE TAGs and relevant clinical association guidelines risks patients having their RAASi treatment discontinued or down-titrated unnecessarily, with the potential for major health consequences. 5. Recommendations on the frequency of monitoring in individuals diagnosed with or at high-risk of CKD describe the number of annual eGFR tests by risk group, but not uACR tests. • The current recommendations do not provide clear guidance on the frequency of testing nor do they adequately capture the importance and clinical value of considering ACR alongside eGFR to enable early diagnosis (CKD stages 1&2 are not detectable via eGFR testing), and to accurately assess risk and disease progression. • If NICE were to recommend uACR testing to be conducted alongside eGFR testing as part of the recommended monitoring process this would encourage testing whilst still only resulting in 1	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				uACR test per patient per year in most patients that are managed in primary care. 6. Ensuring the correct management setting for patients with CKD is critical to achieving patient centred care and optimising outcomes at a patient and health system level. • In UK clinical practice, the volume of referrals to specialist care often outweighs the capacity of specialist services for consultations, leading to long waiting times for patients, many of whom can be effectively managed in primary care following specialist advice. • Supports recommendation 1.5.7 in the draft guideline which encourages GPs to seek advice/guidance from a specialist in cases where referral may not be required, but suggest that NICE plays a role in encouraging best practice with respect to communication between primary and secondary care such as virtual CKD clinics and virtual consultations which allow nephrologists to access general practice patient records and enter management suggestions for the PCP which were even quoted in the NHS Long Term Plan.[4] **References**	

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				1. Forxiga 5 mg film coated tablets SmPC [Available from: https://www.medicines.org.uk/emc/medicine/27188#gref. 2. McMurray JJV, Solomon SD, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019;381(21):1995-2008. 3. Anker SD, Butler J, Filippatos G, Khan MS, Marx N, Lam CSP, et al. Effect of Empagliflozin on Cardiovascular and Renal Outcomes in Patients With Heart Failure by Baseline Diabetes Status: Results From the EMPEROR-Reduced Trial. Circulation. 2021;143(4):337-49. 4. National Health Service. The NHS Long Term Plan. 2019. 5. Mosenzon O, Wiviott SD, Cahn A, Rozenberg A, Yanuv I, Goodrich EL, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. The lancet Diabetes & endocrinology. 2019;7(8):606-17. 6. 25/02/21] QdDfCAahwgcucUCA. 7. 2021 ADoFCPRDCacF. 8. Nespoux J, Vallon V. SGLT2 inhibition and kidney protection. Clin Sci (Lond). 2018;132(12):1329-39. 9. National Institute for Health and Care Excellence. Sodium zirconium cyclosilicate for treating hyperkalaemia Technology appraisal guidance [TA599]. 2019 [Available from: https://www.nice.org.uk/guidance/TA599.	

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				10. National Institute for Health and Care Excellence. Patiromer for treating hyperkalaemia Technology appraisal guidance [TA623]. 2020 [Available from: https://www.nice.org.uk/guidance/ta623. 11. National Institute of Clinical and Care Excellence (NICE). Sodium zirconium cyclosilicate for treating hyperkalaemia [ID1293] - ACM1 Committee Papers 2018 [Available from: https://www.nice.org.uk/guidance/gid-ta10307/documents/committee-papers-2. 12. Rosano GMC, Tamargo J, Kjeldsen KP, Lainscak M, Agewall S, Anker SD, et al. Expert consensus document on the management of hyperkalaemia in patients with cardiovascular disease treated with renin angiotensin aldosterone system inhibitors: coordinated by the Working Group on Cardiovascular Pharmacotherapy of the European Society of Cardiology. European heart journal Cardiovascular pharmacotherapy. 2018;4(3):180-8. 13. Alfonzo AH, A.; Baines, R.; et al. . Renal Association Clinical Practice Guidelines Treatment of Acute Hyperkalaemia in Adults. 2020. 14. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. PRACTICE GUIDELINE| VOLUME 98, ISSUE 4, SUPPLEMENT , S1-S115, OCTOBER 01, 2020. 15. KDIGO. Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. 2021. Vol 99 IS, March 2021.	
Napp Pharmaceuticals Limited	Algorithm 2	General	General	Napp suggest that in the main box at the top of this algorithm, NICE make it clear that both eGFR and UACR measurements should be repeated annually at	Thank you for your comment. The committee did not wish to specify a minimum monitoring frequency as this would vary according to the circumstances of

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				minimum in all of the high-risk cohorts listed here. (Please see comment six above for further explanation). This is not clear with the current wording, which could be read as suggesting that these tests only need to be carried out once in each patient.	individual patients. We added to the rationale that the frequency of testing for CKD should be individualised according to the person's circumstances.
Napp Pharmaceuticals Limited	Comments form	Q1	Q1	Napp strongly support the importance of annual albuminuria testing, using appropriate assays, in adults with T2DM. However, we believe that the following two recommendations may be challenging to implement in practice: • 1.1.11 Do not use reagent strips to identify proteinuria. Because use of multi-sensitive reagent sticks is common in clinical practice, it is likely that reagent sticks will still be routinely used (particularly as NICE recommends these are used for detection of haematuria). It may therefore require a concerted effort to educate HCPs that the proteinuria component of the reagent stick should be considered invalid or not relevant. • 1.1.12 Use ACR. The National mean annual ACR testing rate in adults with T2DM was only 69% in 2019/20, despite this diagnostic test comprising one of the nine NICE recommended Key Care Processes for adults with T2DM. There is also a very large regional variation in testing rates at present. Clearly therefore, additional work is required for the recommendation to use ACR for initial detection of proteinuria to be sufficiently implemented across the UK, at least in the subgroup of CKD patients that present with comorbid T2DM.	Thank you for your comment. The recommendation on reagent strips has been split into 2 recommendations: • Do not use reagent strips to identify proteinuria in children and young people (based on evidence from the current update) • Do not use reagent strips to identify proteinuria in adults unless they are capable of specifically measuring albumin at low concentrations and expressing the result as an albumin:creatinine ratio (from guidance in 2008) Regarding your comment on the use of ACR, this will be considered by NICE where relevant support activity is being planned.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Napp Pharmaceuticals Limited	Comments form	Q2	Q2	Increased use of SGLT2i in patients with T2DM and UACR >30mg/mmol would lead to a moderate increase in drug cost in the short term, but also to a significant decrease in overall healthcare costs in the long-term, due to decreased requirements for haemodialysis. Please see comment number 20 below and the hyperlinked cost-modelling study.	Thank you for your response. Your comments will be considered by NICE where relevant support activity is being planned.
Napp Pharmaceuticals Limited	Comments form	Q3	Q3	Napp strongly recommend that NICE consider a multi-stakeholder national initiative to increase UACR testing rates across the UK. Both the pharmaceutical industry and the various CKD and Diabetes academic and professional organisations, as well as patient organisations and charities would be very keen to support this. However, a project of this scope would require the oversight and endorsement of NICE to achieve maximum impact on clinical practice. Napp have funded the authorship of a peer-reviewed journal article that provides several recommendations on this topic, and the recommendations within have been endorsed by several UK professional medical societies. We would also encourage NICE to consider the possibility of endorsing or republishing some or all of this article in the first instance. NICE could also consider using your influence to encourage the re-adoption of the annual T2DM UACR testing QOF indicator (DM005 / NM59), and/or the CKD register annual UACR testing indicator (CKD004),both of which are no longer part of the final set of indicators in the GMS contract.	Thank you for your comment. Your comments will be considered by NICE where relevant support activity is being planned. NICE recommends ACR testing in several situations (children and young people with diabetes receiving individual care processes in the past 12 months; patients with diabetes with a record of an ACR test in the preceding 15 months; patients with diabetes receiving individual care processes in the past 12 months; and identification and monitoring of adults with, or at risk of, chronic kidney disease). However, these recommendations are outside of the scope of this guideline update.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Napp Pharmaceuticals Limited	Comments form	Q4	Q4	Napp recommend that NICE reconsider the utility of at-home semi-quantitative UACR measurements within the context of the ongoing COVID-19 pandemic. Adults with CKD are at particularly high risk of severe outcomes associated with COVID-19 infection, therefore the ability to monitor UACR without in-person contact may offer additional value to the NHS at present – see comment five below for further explanation of this technology.	Thank you for your comment. The committee agreed that evidence was not reviewed for the use of reagent strips in adults. Therefore, we have reinstated (recommendation removed before this consultation in January 2021) the recommendation for adults that was made in 2008 to specify that the use of reagent strips to identify proteinuria in adults should be limited to tests being capable of measuring albumin at low concentrations and expressing the result as an ACR.
Napp Pharmaceuticals Limited	Evidence Review H	General	General	Please reconsider the title of this document and the review question itself in line with Napp's comment number 10 above: None of these interventions are to lower proteinuria, proteinuria lowering is simply a useful biomarker for measuring the ability of these interventions to reduce progression of CKD.	Thank you for your comment. The review questions are determined as part of the scoping process and are consulted on during scoping before being finalised. It is not possible for us to retrospectively change the review question. However, we do not use this wording in the guideline to mean that the review question is all about treating proteinuria as a goal in itself. These are interventions that would be initiated in people with proteinuria. The evidence review considered a range of outcomes, including rates of progression to end stage kidney disease. We amended the title of this section in the guideline to 'Pharmacotherapy for CKD in adults, children, and young people with related persistent proteinuria' and further clarification was added to the rationale for these recommendations.
Napp Pharmaceuticals Limited	Guideline	General	General	Napp are not sure where in guideline this recommendation would best fit, but we strongly suggest a warning is added about the reliability of HbA1c testing in patients with DM and advanced CKD, particularly those with anaemia and receiving ESA. The HbA1c biomarker provides an estimate of mean serum	Thank you for your response. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				glycaemia over a 2-3 month period, however it is based on the assumption of a continuous rate of turnover of erythrocytes. In anaemic patients and particularly those receiving ESA, the turnover rate of erythrocytes will be disrupted - rendering HbA1c results invalid. Please see Figure 5 on page 40 of the KDIGO 2020 guideline: **Practice Point 2.1.2: Accuracy and precision of HbA1c measurement declines with advanced CKD (G4–G5), particularly among patients treated by dialysis, in whom HbA1c measurements have low reliability**	
Napp Pharmaceuticals Limited	Guideline	General	General	Napp would like to draw NICE's attention to the fact that SGLT2i therapy is known to cause small increases in serum phosphate, an observation that may be relevant to include somewhere in this guideline.	Thank you for your comment. The committee agreed that small increases in serum phosphate with the use of SGLT2 inhibitors is not a significant issue. This has been added to the committee's discussion and interpretation of the evidence.
Napp Pharmaceuticals Limited	Guideline	General	General	NICE may wish to consider adding somewhere within this guideline that SGLT2i are not licensed or recommended in patients who have received a renal transplant, even if they meet all the other criteria for SGLT2i initiation as laid out in the product labels and within this guideline. This is because SGLT2i have not been adequately studied in kidney transplant recipients, who are immunosuppressed and may be at increased risk of genitourinary or renal infections or malignancies, which plausibly could be exacerbated by the glucosuria caused by SGLT2i therapy.	Thank you for your comment. The recommendation already specifies that SGLT2i should be used within their licensing authorisation.
Napp Pharmaceuticals Limited	Guideline	General	General	Please see the following comment numbers for background information & rationale on suggested amendments to this algorithm:	Thank you for your comment. The algorithm and recommendations have been updated. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				• Comment 7: Napp suggest addition of a recommendation to review glycaemic targets in adults with T2DM and UACR 3 mg/mmol or more • Comment 9: Napp strongly suggest an additional box is added to this flowchart, after "Offer an ACEi or ARB", and before "Add an SGLT2i…" This additional box should simply say "Titrate ACEi / ARB to maximum tolerated or licensed dose" This statement could also be added to the recommendations on initiating RAAS blockade in nondiabetic adults, in the two boxes on the right hand side of the flowchart. • Comment 11: Please consider making type 1 and type 2 diabetes more clearly separated in the algorithm • Comment 12: Please consider giving separate recommendations for SGLT2i initiation in T2DM patients based on whether or not they are at target HbA1c. • Unrelated to previous comments: Please change the term "microalbuminuria" to "ACR" in the box giving recommendations for adults with diabetes and an ACR <3 mg/mmol. "Microalbuminuria" is an outdated term that is not generally recommended to be used.	recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021.
Napp Pharmaceuticals Limited	Guideline	007	020	Napp strongly support the recommendation to avoid classic urinalysis reagent strips due to their low sensitivity to albuminuria <30mg/mmol. However, we also suggest that NICE add an additional recommendation making it clear that semi-quantitative assays that incorporate reagent strips, such as those from healthy.io, are recommended by NICE for detection of clinically relevant proteinuria. I.e. that it is only the classic urinalysis reagent strips (that only detect severe proteinuria) that NICE do not recommend.	Thank you for your comment. The committee agreed that evidence was not reviewed for the use of reagent strips in adults. Therefore, we have reinstated (recommendation removed before this consultation in January 2021) the recommendation for adults that was made in 2008 to specify that the use of reagent strips to identify proteinuria in adults should be limited to tests being capable of measuring albumin at low concentrations and expressing the result as an ACR.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				These semi-quantitative assays are generally considered to represent an acceptable alternative to lab-based UACR testing: Recently NHSX has agreed to commission 500k of them for at-home ACR testing over the next three years, and endorsement by NICE would likely lend significant credence to this project.	
Napp Pharmaceuticals Limited	Guideline	014	006	Although Napp agree with the minimum testing intervals for eGFR as determined by the most recent eGFR and ACR category, table 2 doesn't provide guidance on frequency of UACR testing in these groups. This greatly limits the utility of the recommendations in the table, as decisions on frequency of eGFR monitoring may therefore be based on old and irrelevant UACR data. We strongly suggest revising the table title and supporting text to make it clear that these recommended minimum monitoring intervals apply to both eGFR and UACR testing. It is also worth noting that in KDIGO 2012 where this advice originally appeared it does specifically make it clear that it is referring to both eGFR and UACR monitoring. Annual measurement of UACR in all T2DM patients is also recommended in by the peer-reviewed journal article mentioned in comment three, and is also recommended as one of the NICE nine essential care processes for T2DM, as assessed in the National Diabetes Audit. The numbering system used in this table is inconsistent and somewhat confusing as there are three different formats used: "**X"; "X or more"; "X to Y"**.	Thank you for your comment. We have added a note to Table 2 about ACR monitoring which should be individualised based on a person's individual characteristics, risk of progression and whether a change in ACR is likely to lead to a change in management. ACR monitoring was not recommended alongside to eGFR because eGFR is used to define progression rather than ACR and so more frequent monitoring is needed (see recommendations 1.3.5 to 1.3.8 which define progression in adults with the use of eGFR). No specific evidence on ACR monitoring frequency was found but the committee noted that it is a costly test and should not be used every time eGFR is measured, but on an individual basis. The rationale has examples about the frequency of ACR monitoring ACR (more frequently monitoring in people with high ACR categories A2 or A3; or where a change in ACR would affect management). The committee agreed to make a research recommendation to identify the optimal frequency of monitoring ACR in adults, children and young people with CKD. Table 2 was reformatted to take account of the new accessibility standards.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				As the table is intended to show the **minimum** recommended monitoring interval, the "**X to Y**" and "**X or more**" wording is redundant as this is implied but the fact that this is a minimum recommended interval. Therefore, all cells should just contain a single number or just revert to the numbering system previously used in CG182 which recommended a **specific** testing interval for each group rather than a **minimum** one.	
Napp Pharmaceuticals Limited	Guideline	021	017	Napp suggest the addition of a section regarding review of glycaemic control and glycaemic targets in people with diabetes and CKD, as this may need to change if CKD has been newly diagnosed. This section could simply cross-reference other NICE guidance on management of DM, but we would suggest some reference is made to this aspect of pharmacotherapy, which is critical to get right in people with DM to prevent further loss of eGFR. See Figure 9, Page S45 of KDIGO guidelines on diabetes management in patients with CKD. Ideally Napp would suggest the addition of some direct recommendations on glycaemic targets, as well as a cross reference to NG28, in an analogous manner to how hypertension is addressed in this guideline. This would then be a consistent approach to addressing the two most common comorbidities that cause or contribute to CKD progression.	Thank you for your comment. We have added a cross reference to other NICE guidelines on management of type 1 and type 2 diabetes.
Napp Pharmaceuticals Limited	Guideline	022	015	Napp suggest that NICE could consider a specific recommendation here that SGLT2 inhibitors should be considered in patients with T2DM; CKD and sub-optimally controlled hypertension, where those patients are already treated with a RAASi. Although SGLT2i are	Thank you for your comment. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				not specifically licensed as antihypertensives, they have demonstrated a robust clinical efficacy comparable to other antihypertensives and will also confer both glycaemic and (evidenced for some agents only at present) direct disease-modifying effects on CKD in conjunction with RAASi in these patients. Therefore, this may represent a sensible use of resources, as although the SGLT2i are generally of higher price than traditional antihypertensives, use in this specific sub-population could potentially replace the use of three separate alternative agents.	September 2021, and the review will publish in November 2021. NICE is also currently undertaking a technology appraisal of dapagliflozin for treating chronic kidney disease which will include the DAPA-CKD trial. Therefore, data from DAPA-CKD has been removed from this update. See https://www.nice.org.uk/guidance/indevelopment/gid-ta10808 for details. The NICE CKD guideline will cross refer to this technology appraisal appraising dapagliflozin when it is published.
Napp Pharmaceuticals Limited	Guideline	022 022 023 023 013	015 020 005 008 013	At the five locations noted here, the recommendation is given to "Offer an ARB or ACEi" for various types of patient depending on the level of their UACR biomarker. Napp do not disagree with this statement, however the guideline is lacking a critical additional piece of information at every appearance of this recommendation: ARB or ACEi therapy must be titrated to the maximum licensed or tolerated dose in each patient. E.g. Losartan is licensed to be initiated at a dose of only 50 mg/day, but is licensed to be titrated up to a maximum dose of 100 mg/day. Therefore, for this commonly used agent, approximately half the therapeutic benefit may not be realised if the agent is not appropriately titrated. Napp do not have any formal evidence to support the importance of this assertion, but anecdotally many nephrologists and diabetologists have raised this concern when discussing management of comorbid T2DM and CKD, and we would urge NICE to consult further with HCPs on this point if this is omission is not noticed by other stakeholders in their consultation responses.	Thank you for your comments. We have amended the recommendations to include the titration of ARB or ACEi therapy and this has been added to the algorithm as well.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				It is worth noting that this recommendation is specifically made in KDIGO 2020: Recommendation 1.2.1: We recommend that treatment with an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) be initiated in patients with diabetes, hypertension, and albuminuria, and that these medications be titrated to the highest approved dose that is tolerated (1B).	
Napp Pharmaceuticals Limited	Guideline	022	019	Napp would like to suggest a rewording of the subtitle of this section. Although it is true that proteinuria is the diagnostic marker for patients that can benefit from pharmacotherapy for CKD, the pharmacotherapy is not for proteinuria. I.e. proteinuria in and of itself (unless massive e.g. nephrotic syndrome), is not harmful, and is not involved in the pathology of CKD. C.f. the previous section, hypertension, where the targeted pathology is not just a biomarker of renal damage, but a direct contributor to the disease pathology. Instead a better title for this section would be something like Pharmacotherapy for CKD in adults with related persistent proteinuria. This is also important as "Proteinuria" is a broad term which encompasses protein in the urine from any cause. Transient proteinuria due to infection is relatively common, whereas persistent proteinuria is less so and more likely to be (although not necessarily) related to CKD. It is therefore important to be clear that these recommendations only apply to people with CKD and related persistent proteinuria.	Thank you for your comment. The title of the section has been amended.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Napp Pharmaceuticals Limited	Guideline	022	020	Napp strongly recommend that NICE separate out the pharmacotherapy recommendation here for T1 and T2DM. We make this suggestion in order to ensure the guideline is not misread as recommending SGLT2i use in T1DM - to be clear the content of the recommendation here is correct, we are just suggesting restructuring this into separate sections to reduce the potential for any confusion. This is an important consideration for patient safety as SGLT2i use in T1DM is only licensed in extremely specific circumstances and under the supervision of a specialist, due to the significantly increased risk of DKA with SGLT2i in T1DM vs T2DM. Napp suggest two separate recommendations in this format: *1.6.6 For adults with CKD and type 1 diabetes:* *- Offer an ACE inhibitor or an ARB if ACR is 3 mg/mmol or more* *- Do not offer an SGLT2 inhibitor* *1.6.7 For adults with CKD and type 2 diabetes, offer:* *- an ACE inhibitor or an ARB if ACR is 3 mg/mmol or more* *- an SGLT2 inhibitor, in addition to an ACE inhibitor or an ARB, if they have an ACR of 30 mg/mmol or more and meet the criteria in the marketing authorisation*	Thank you for your comment. Recommendation 1.6.6 has been separated into 2 parts. The first part (recommendation 1.6.6) is to offer an ACE inhibitor or an ARB (titrated to the highest approved dose that is tolerated) to adults with CKD and diabetes (type 1 or type 2) if ACR is 3 mg/mmol or more. The second part (recommendation 1.6.7) is to offer an SGLT2 inhibitor, in addition to an optimised dose of ACE inhibitor or an ARB, to people with type 2 diabetes, an ACR of 30 mg/mmol or more and meet the criteria in the marketing authorisation (including relevant eGFR thresholds); monitor for volume depletion and eGFR decline. We have also added MHRA alerts on canagliflozin and SGLT2 inhibitors under recommendation 1.6.7.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				(including relevant eGFR thresholds); monitor for volume depletion and eGFR decline.	
Napp Pharmaceuticals Limited	Guideline	022	020	Further to Napp's suggestion that T1DM and T2DM are split into separate sections here, Napp would like to further suggest that T2DM is split into two further separate sections, giving distinct advice for patients that have controlled vs uncontrolled T2DM. The rationale for this suggested change is as follows: In patients with an ACR of 30mg/mmol or more, there is clear primary outcome evidence (from the CREDENCE trial) of significant mortality and morbidity benefits - irrespective of glycaemic control. This therefore supports the current recommendation here that SGLT2i is started in patients with ACR > 30 mg/mmol. The recommendation does not extend to patients with an ACR 3-30mg/mmol, as there is not primary outcome evidence in this subgroup. However, there is a great deal of secondary and exploratory outcome evidence for renal benefits of SGLT2i in patients with ACR 3-30mg/mmol from the SGLT2i CVOTS: CANVAS; DECLARE-TIMI; EMPA-REG; & VERTIS-CV. According to NICE's published methods, this evidence is not robust enough to support a primary recommendation, however NICE contend that this evidence is strong enough to influence the choice of agent where additional glycaemic control is required. I.e., in patients with CKD, ACR 3-30 mg/mmol & uncontrolled T2DM who already require additional glycaemic therapy, Napp contend that the evidence for SGLT2i renal benefits in this group of patients would be	Thank you for your comments. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. NICE is also currently undertaking a technology appraisal of dapagliflozin for treating chronic kidney disease which will include the DAPA-CKD trial. Therefore, data from DAPA-CKD has been removed from this update. See https://www.nice.org.uk/guidance/indevelopment/gid-ta10808 for details. The NICE CKD guideline will cross refer to this technology appraisal appraising dapagliflozin when it is published. Recommendation 1.6.6 has been separated into 2 parts. The first part (recommendation 1.6.6) is to offer an ACE inhibitor or an ARB (titrated to the highest approved dose that is tolerated) to adults with CKD and diabetes (type 1 or type 2) if ACR is 3 mg/mmol or more. The second part (recommendation 1.6.7) is to offer an SGLT2 inhibitor, in addition to an optimised dose of ACE inhibitor or an ARB, to people with type 2 diabetes, an ACR of 30 mg/mmol or more and meet the criteria in the marketing authorisation (including relevant eGFR thresholds); monitor for volume depletion and eGFR decline.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				sufficient to render SGLT2i the agent class of choice, as all other classes of antihyperglycaemic therapy have shown no benefit in preventing or reducing the progression of CKD. Use of SGLT2i for glycaemic control in a general T2DM population has already been recommended by NICE in TA315 and TA390, therefore is considered cost-effective by NICE even in the absence of consideration of the additional renal benefits. Napp suggest that these sections could appear as follows: *1.6.7 For adults with CKD and type 2 diabetes who are at glycaemic target, offer:* *- an ACE inhibitor or an ARB if ACR is 3 mg/mmol or more* *- an SGLT2 inhibitor, in addition to an ACE inhibitor or an ARB, if they have an ACR of 30 mg/mmol or more and meet the criteria in the marketing authorisation (including relevant eGFR thresholds); monitor for volume depletion and eGFR decline* *1.6.8 For adults with CKD and type 2 diabetes who require additional antihyperglycaemic therapy, offer:* *- an ACE inhibitor or an ARB if ACR is 3 mg/mmol or more*	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				- an SGLT2 inhibitor, in addition to an ACE inhibitor or an ARB, if they have an ACR of 3 mg/mmol or more and meet the criteria in the marketing authorisation (including relevant eGFR thresholds); monitor for volume depletion and eGFR decline Napp acknowledge that this clinical decision exists at the intersection of T2DM management and CKD management, and NICE may already be planning to incorporate this recommendation into the upcoming review of NG28. However, we assert that this recommendation is sufficiently relevant to both guideline documents that it should be included in both. Finally, Napp would like to highlight the significant divergence between the approach recommended by NICE for SGLT2i in CKD & T2DM, and the approach recommended by other authoritative clinical guidelines in this area: • In this guideline NICE have suggest that SGLT2i should **only** be used in people with CKD and T2DM where their UACR is >30 mg/mmol • Napp have suggested extending this recommendation to include patients with UACR 3-30 mg/mmol where additional antihyperglycaemic therapy is required, as existing NICE advice already supports the cost-effectiveness of SGLT2i, irrespective of any additional renal benefits	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				• ADA/EASD recommend that SGLT2i therapy should be considered in **all** T2DM patients (irrespective of glycaemic control) with **either** eGFR 30-60 ml/min/1.73m^2 **or** UACR >3mg/mmol, with particular emphasis on the importance of SGLT2i use where UACR >30mg/mmol. • KDIGO make an even stronger recommendation that **all** patients (unless specifically contraindicated or not tolerated) with T2DM, CKD and an eGFR >30ml/min/1.782m^2 should be treated with an SGLT2i, irrespective of achievement of glycaemic target, and in fact that other antihyperglycaemic therapies should be discontinued in order to allow initiation of an SGLT2i if the patient is already at glycaemic target and receiving therapy/therapies that increase the risk of hypoglycaemia. From KDIGO: **Recommendation 4.2.1: We recommend treating patients with T2D, CKD, and an eGFR ‡30 ml/min per 1.73 m2 with an SGLT2i (1A)** **Practice Point 4.2.2: For patients in whom additional glucose-lowering may increase risk for hypoglycemia (e.g., those treated with insulin or sulfonylureas and currently meeting glycemic targets), it may be necessary to stop or reduce the dose of an antihyperglycemic drug other than metformin to facilitate addition of an SGLT2i.**	

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Napp Pharmaceuticals Limited	Guideline	023	002	Napp strongly advise against the inclusion of advice to monitor eGFR decline with SGLT2i without further explanation of why this is recommended. In a directly analogous process to ACE/ARB therapy, eGFR will typically transiently decline by <5ml/min upon initiation of SGLT2i therapy. This does **not** represent a worsening of CKD, rather it represents a decrease in the intraglomerular pressure and consequent renal filtration rate - i.e. a reduction in renal physiological stress and a beneficial effect on the progression of CKD. Without this important context, a simple recommendation to monitor eGFR decline may lead to treatment being unnecessarily terminated in many patients. https://www.sciencedirect.com/science/article/abs/pii/S175199181830010X From KDIGO: **Practice Point 4.2.6: A reversible decrease in the eGFR with commencement of SGLT2i treatment may occur and is generally not an indication to discontinue therapy**	Thank you for your comment. We have included a clarification to the rationale stating that eGFR monitoring should depend on people's circumstances and on the BNF advice of monitoring requirements for people using SGLT2 inhibitors.
Napp Pharmaceuticals Limited	Guideline	023	003	Napp are aware that NICE try to avoid mention of specific pharmacological agents, however it would be most factually accurate and helpful for the reader of the guideline to have a more specific statement here, i.e. something to the effect of "*In June 2021 only canagliflozin is currently licensed for this indication; but development of other SGLT2i for this indication is in progress. These recommendations should be considered to apply to any SGLT2i that is authorised and licensed in this indication at the time of reading"*	Thank you. The committee was aware that licensing extensions are in process for other SGLT2 inhibitors and so would make guideline out of date quickly if this was added. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. NICE is also currently undertaking a technology appraisal of

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					dapagliflozin for treating chronic kidney disease which will include the DAPA-CKD trial. Therefore, data from DAPA-CKD has been removed from this update. See https://www.nice.org.uk/guidance/indevelopment/gid-ta10808 for details. The NICE CKD guideline will cross refer to this technology appraisal appraising dapagliflozin when it is published.
Napp Pharmaceuticals Limited	Guideline	062	009	Please refer to comment number 12 above. Napp agree that a threshold ACR of 30 mg/mmol is appropriate when considering prescription of an SGLT2i solely for its renal benefits. However, this restriction may not be appropriate in CKD patients who also require additional antihyperglyaemic and/or antihypertensive therapy. In these patients the evidence of renal benefit in patients with ACR <30mg/mmol is generally considered to be strong enough to warrant selection of SGLT2i before other antihyperglycaemic or antihypertensive therapies.	Thank you for your comment. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. NICE is also currently undertaking a technology appraisal of dapagliflozin for treating chronic kidney disease which will include the DAPA-CKD trial. Therefore, data from DAPA-CKD has been removed from this update. See https://www.nice.org.uk/guidance/indevelopment/gid-ta10808 for details. The NICE CKD guideline will cross refer to this technology appraisal appraising dapagliflozin when it is published.
Napp Pharmaceuticals Limited	Guideline	062 - 063	029 - 008	This paragraph also needs amending or removing as it is based on the incorrect assumption explained in comment 20.	Thank you for your comment. We have amended the rationale to note that the benefits are not expected to be the same for blood glucose control in people with diabetes and CKD as in people with diabetes but without CKD. The committee were confident that the overall clinical benefit in people with diabetic kidney disease would be as large as the benefits estimated in the technology appraisals for people with diabetes but without CKD.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Napp Pharmaceuticals Limited	Guideline	067	011	The statement that SGLT2i are *"not suitable for everyone"* and "*should only be used within their MA"* seems somewhat subjective and redundant - surely these general considerations apply for any pharmacological agent used for any condition? Suggest removing.	Thank you for your comment. The statement was kept in the rationale to highlight that relevant eGFR thresholds should be applied when prescribing SGLT2 inhibitors in line with the advice of the BNF.
Napp Pharmaceuticals Limited	Guideline	067	012	Napp are unsure what NICE intend to convey by the statement that people taking SGLT2i *"should have monitoring"*; this is a vague and likely unhelpful statement for prescribers. Napp believe the committee were probably referring to the below recommendation which appears in the SGLT2i SmPCs. Please either remove this statement or update to reflect the full SmPC wording: *Monitoring of renal function is recommended as follows:* *- Prior to initiation of SGLT2i and at least annually thereafter.* *- Prior to initiation of concomitant medicinal products that may reduce renal function and periodically thereafter.*	Thank you for your comment. We have included a clarification to the rationale stating that eGFR monitoring should depend on people's circumstances and on the BNF advice of monitoring requirements.
Napp Pharmaceuticals Limited	Guideline	067	014	Napp strongly object to this statement and request its removal. Firstly, the unqualified use of the word 'high' when referring to cost of SGLT2i is subjective and does not provide any useful information to the reader, on the contrary it may discourage uptake in this indication even where the guideline specifically endorses it.	Thank you for your comment. Regarding your comment about "High Cost Drugs" we have changed the wording and removed the term. This paper was published after the searches were completed. Regarding your comment about the new cost effectiveness analysis of canagliflozin, this was

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Secondly, the term "High Cost Drugs" is usually used within the NHS to refer to drugs that have been excluded from routine commissioning and are instead funded centrally by NHS England. This is not the case for SGLT2i. Thirdly, a robust cost-effectiveness analysis of the use of canagliflozin for CKD in patients with T2DM was published in December 2020 in Diabetes Therapy, showing to a high degree of confidence that not only is canagliflozin cost-effective in this population - it is actually probably cost saving over time horizons over five years. - i.e. ICER less than £0. Please either remove this statement; appropriately qualify it (i.e. high cost relative to...); or ideally quote the actual gross drug cost and net overall healthcare costs associated with the use of these agents, allowing the reader to make an informed decision for themselves.	presented to the committee at the post-consultation meeting and is now included in the evidence review, and the committee agreed that the paper further supports the recommendations on SGLT2 inhibitors made in the guideline.
Napp Pharmaceuticals Limited	Guideline	067	017	This assumption is invalid as it contains a serious flaw: The glycaemic efficacy of SGLT2i is reduced in patients with decreased eGFR - in fact glycaemic efficacy decreases linearly with loss of eGFR, as the antihyperglycaemic MoA depends on renal filtration rate. Therefore, it is not correct or accurate to assume equal effectiveness, and hence cost-effectiveness, of SGLT2i in patients with CKD. This was the reason that an entirely new cost effectiveness model for the use of canagliflozin in T2DM & CKD was constructed - a model which assumes zero antihyperglyaemic effect in this cohort.	Thank you for your comment. The committee noted that the doses of SGLT2 used in people with diabetes and CKD were lower than the doses used in people without renal impairment. They were nonetheless confident these drugs would still have some effect for blood glucose control in this population and would therefore provide benefits on diabetes control to those in the non-CKD population. In addition, there would then be further benefits on renal outcomes, as demonstrated in the RCTs included in this review, and therefore the overall clinical benefit in a population of people with diabetic kidney disease would be larger than the benefit

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					estimated in the technology appraisals for people with diabetes but not CKD. The committee also noted the cost-effectiveness study of the use of canagliflozin in T2DM and CKD showed that even with zero antihyperglycemic effect the treatment is cost effective. They therefore felt confident that, with a larger benefit for a similar cost, it was appropriate that these drugs be available earlier in the treatment pathway for people with diabetes and CKD, and that this would represent a cost-effective use of NHS resources.
Napp Pharmaceuticals Limited	Membership of Kidney Suite Guideline Committee	General	General	Although two lay members are mentioned in the Committee membership list, it does not appear that any individuals with CKD themselves are included in committee. Napp would like to check if this is correct, and if so suggest that the perspective of CKD patients would be a useful addition to the committee.	Thank you for your comment. We cannot comment on the personal circumstances of committee members but there was representation from people living with CKD on the guideline committee.
NHS England & Improvement Renal Transplantation Programme	Comments form	Q1	Q1	**Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why.** Prevention of or delay to progressive CKD to the point of needing renal replacement therapy is a major ambition of the RSTP. The emerging outcome data in those living with CKD (both diabetic & non-diabetic CKD) treated with SGLT2i offers the first major advance in this area for over 20 years. For those living with stage 3 and potentially 4 proteinuric (ACR 20 – 30mg/mmol or more) CKD, local (ICS) commissioners should ensure they have a suitable plans to increase population uptake of	Thank you for your response. Your comments will be considered by NICE where relevant support activity is being planned.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				this class, with appropriate education and information, supported by capable clinical teams	
NHS England & Improvement Renal Transplantation Programme	Comments form	Q2	Q2	**Would implementation of any of the draft recommendations have significant cost implications?** Yes, drug costs of SGLT2i, associated clinical and educational time, aiming for 90% uptake in those suitable.	Thank you for your response. Your comments will be considered by NICE where relevant support activity is being planned.
NHS England & Improvement Renal Transplantation Programme	Guideline	006	003	We do not support the recommendation to adjust CKD-EPI eGFR for adults of African-Caribbean or African family origin. This population is already subject to health inequalities as a result of late identification and an increased prevalence of risk factors associated with CKD. There is also variation within the cohort e.g. a Brazilian study suggested that a correction factor may not be appropriate in a cohort made up of 61% African Brazilians [Rocha et al IJN 2020]. The literature review does not focus on populations representative of the UK, where the accuracy & utility of a correction factor in black non-African American populations on long-term outcomes has not been undertaken. The impact of using correction factors may disadvantage those expecting preparation for dialysis, pre-emptive transplantation, or access to NICE-funded drugs such as SGLT2i. See recent NEJM editorial [Vyas et al, NEJM 2020].	Thank you for your comments. Recommendation 1.1.3 has been removed from the guideline and therefore any potential disadvantage for those preparing for dialysis, transplant or access to NICE-funded drugs should no longer be an issue. The rationale section includes further advice stating that individualised judgement should be used when interpreting eGFR in people from UK black, Asian and minority ethnic groups and in adults with extremes of muscle mass. The committee agreed to make recommendations for research on appropriate eGFR equations for black, Asian and minority ethnic groups (adults, children and young people) in the UK. They agreed that factors other than ethnicity should also be explored as biomarkers.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
NHS England & Improvement Renal Transplantation Programme	Guideline	007	020 -	The use of reagent strips +/- semi-quantitative digital reads are currently being marketed and used by primary care as an alternative to urine ACR or reagent strips for patients with diabetes. We recommend explicitly stating the use of a quantitative urine ACR as measured in mg/mmol.	Thank you for your comment. The committee agreed that evidence was not reviewed for the use of reagent strips in adults. Therefore, we have reinstated (recommendation removed before this consultation in January 2021) the recommendation for adults that was made in 2008 to specify that the use of reagent strips to identify proteinuria in adults should be limited to tests being capable of measuring albumin at low concentrations and expressing the result as an ACR.
NHS England & Improvement Renal Transplantation Programme	Guideline	014	007	The table provides guidance on eGFR monitoring. We recommend clearer guidance on frequency of urine ACR monitoring re	Thank you for your comment. We have added a note to Table 2 about ACR monitoring which should be individualised based on a person's individual characteristics, risk of progression and whether a change in ACR is likely to lead to a change in management. The rationale has examples about the frequency of ACR monitoring ACR (more frequently monitoring in people with high ACR categories A2 or A3; or where a change in ACR would affect management). The committee agreed to make a research recommendation to identify the optimal frequency of monitoring ACR in adults, children and young people with CKD.
NHS England & Improvement Renal Transplantation Programme	Guideline	019 020	027 001 - 012	We believe there is an opportunity to clarify the referral criteria further. Referral criteria should consider co-morbidities and functional status. For example, a referral may not add value irrespective of KFRE if the patient has advanced dementia and is bed bound or has end stage heart failure.	Thank you for your comments. The first part of the recommendation includes the importance of taking comorbidities and wishes into account when referring adults with CKD for specialist assessment. We have amended the bullet point to clarify that diabetes is already 'appropriately treated' and a reference has been added to see recommendations 1.6.6 and 1.6.7.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				"an ACR of 70 mg/mmol or more, unless known to be caused by 2 diabetes and already treated". Clarity needs to be provided on 'treated'. For example the prescription of low dose ramipril may be considered as treated. Consider specifically referring readers to the treatments section.	
NHS England & Improvement Renal Transplantation Programme	Guideline	023	007 - 012	We note that SGLT2i (specifically dapagliflozin) now has evidence of significant benefit in adults with CKD but **without** diabetes. For those with living with an eGFR 25 - 75ml/min with proteinuria (ACR >20mg/mmol), similar benefits have been described in DAPA-CKD (NEJM, 2020), with a decreased risk of kidney failure, and decreased risk of death from CV causes or hospitalisation for HF. We believe that SGLT2i should be recommended on current evidence for use in all proteinuric patients living with CKD within scope of this Guideline.	Thank you for your comment. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. NICE is also currently undertaking a technology appraisal of dapagliflozin for treating chronic kidney disease which will include the DAPA-CKD trial. Therefore, data from DAPA-CKD has been removed from this update. See https://www.nice.org.uk/guidance/indevelopment/gid-ta10808 for details. The NICE CKD guideline will cross refer to this technology appraisal appraising dapagliflozin when it is published.
NHS England & Improvement Renal Transplantation Programme	Guideline	027	001	We note that patients may be referred to renal services without completing appropriate anaemia investigations. Haematinics and TSAT measurement and correction should be recommended prior to referral. The reader can be directed to section 1.7.3 around iron deficiency diagnostic testing.	Thank you for your comment. A cross reference to recommendation 1.7.3 has been added into recommendation 1.7.2.
NHS England & Improvement Renal	Guideline	044	023	We note the wording 'control serum phosphate levels'. Please clarify the threshold as there is limited evidence to suggest controlling serum phosphate translates to	Thank you for your comment. We have clarified that the thresholds should be age-adjusted. We also added a comment to the rationale about the influence of pre-existing vascular calcification on binder choice.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Transplantation Programme				improved outcomes. KDIGO CKD-MBD 2017 recommends towards normal range. The totality of evidence suggests that calcium loading may be a contributor towards adverse outcomes. The evidence for this is stronger (RCTs) that than the evidence for phosphate lowering towards the normal range (observational data). Comment on the influence of pre-existing vascular calcification on binder choice. .	
NHS England & Improvement Renal Transplantation Programme	Guideline	052 053 054	002 015 001 - 004	Recommend include diagnostic accuracy of cystatin-C equations at extremes of weight. Is controlling phosphate relevant in non-dialysis CKD? What are the treatment thresholds in all groups including 5D? Recommend recruitment to clinical trials in the absence of evidence Refer to KDIGO 2017. Also consider evaluating the effects of extended release calcifediol on outcomes in comparison to current therapies. Evaluate impact of national recommendations for vitamin D supplementation (as a result of COVID19) in patients with CKD. What is the role of anticoagulation in non-valvular AF in patients with eGFR < 30mls/min?	Thank you for your comment. We have added weight as a subgroup of interest to the research recommendation on the accuracy of cystatin C-based equations to estimate GFR as a measurement of kidney function in adults, children and young people in the UK. The rest of the research that you suggest was not part of this update and therefore we cannot add them. We have passed your suggestions on to the surveillance team who will explore whether these research recommendations need adding in the future.
NHS England/NHS Improvement	Guideline	007	020	We welcome the guidance with regards to investigations for proteinuria (PC)	Thank you for your comment
NHS England/NHS Improvement	Guideline	008	010	We welcome the guidance with regards to when to use PCR as an alternative to ACR (PC)	Thank you for your comment.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
NHS England/NHS Improvement	Guideline	009	013	Important clarification on who should be tested for CKD (PC)	Thank you for your comment.
NHS England/NHS Improvement	Guideline	019	010	"Give adults with CKD and their family members or carers (as appropriate)" – suggest inclusion of what information should be provided to children and young people here as part of their risk assessment. (NP)	Thank you for your comment. The recommendation specifies what information they should be given "Give adults with CKD and their family members or carers (as appropriate) **information about their absolute risk and their 5-year risk of needing renal replacement therapy**"
NHS England/NHS Improvement	Guideline	019	010	Patient friendly resource on explaining the 'risk' would be helpful (PC)	Thank you for your comment. We believe this is adequately addressed by the referral to the NICE guideline on shared decision-making and by recommendations 1.5.2 to 1.5.4.
NHS England/NHS Improvement	Guideline	021	007	Shared Care arrangements between secondary care and general practice will need to be created, negotiated and commissioned if there is any transfer of care (PC)	Thank you for your response. Your comments will be considered by NICE where relevant support activity is being planned.
NHS England/NHS Improvement	Guideline	021	008	What is expected where individuals decline referral as the 'shared care' element inferes a referral must be made in order to receive this opportunity? (NP)	Thank you for your comment. We added a link to the NICE's guideline on patient experience in adult NHS services which recommends to 'respect and support the patient in their choice of treatment, or if they decide to decline treatment.'
NHS England/NHS Improvement	Guideline	021	013	A shared care template for this would be beneficial (PC)	Thank you for your comment. We added a link to recommendation 1.5.9 to the NICE's guideline on shared decision making which has more details about share decision making in everyday health care.
NICE GP Reference Panel	General			NOTE: The GP reference panel were asked to comment specifically on recommendations 1.5.1. and 1.5.5 at the request of the guideline developer. They were also asked as always to make any general or wider comments. These are summarised below.	Thank you for your comment.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Direct quotes/comments are in plain text. Notes from the Panel Moderator (JT) are in bold.	
NICE GP Reference Panel	Guideline	General		Clarity on the term renal replacement therapy would be helpful as this is one that most patients will not be familiar with. **Note: I wonder if this GP is more comfortable with the term End-stage renal disease. I suspect most of us are more used to using this.**	Thank you for your comment. We have added a definition of renal replacement therapy to the section of 'Terms used in this guideline'.
NICE GP Reference Panel	Guideline	General		**Overdiagnosis in CKD (comments from one GP)** Main area of concern I would highlight is the lack of discrimination with the current guidance around what is true CKD and what is an expected age related drop off of eGFR/creatinine clearance. These tools/formulae to guide diagnosis/identification of patients has the potential to label a cohort of patients whose renal function reflects the natural ageing process. Presently the GP Practice QOF includes a domain for "CKD" but in some practices this generates a large amount of monitoring/bloods/urine testing for asymptomatic patients.	Thank you for your comment. We did not review evidence about overdiagnosis in CKD because this was outside of the scope of the current update. The NICE surveillance team identified new evidence related to the classification of chronic kidney disease. They concluded that the evidence supported the use of the Tangri risk equation (kidney failure risk equation [KFRE]) in predicting end stage renal disease in people with chronic kidney disease and that this had a potential impact on recommendations related to the classification of chronic kidney disease. During the update of the guideline, it was agreed that KFRE is an equation that can be used for determining the risk of progression rather than for the classification of CKD.
NICE GP Reference Panel	Guideline	General		**Guideline complexity** This guidance is very extensive, please could you make clear which parts of this are for secondary care and which applies to primary care, I felt confused reading it as I did not clearly understand what is expected of the GP.	Thank you for your comment. The care pathways are going to differ in different areas and with different local arrangements, so we do not feel it is possible to be specific in each area whether things should be done in primary or secondary care. We acknowledge that the guideline is complex and extensive. We

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				This sentiment was also expressed by another GP who highlighted the section on anaemia in particular	have produced 3 flowcharts summarising the recommendations on identifying chronic kidney disease, managing proteinuria, and use of phosphate binders that we hope will make the recommendations easier to follow.
NICE GP Reference Panel	Guideline	019	008>	These referral criteria seem reasonable and in line with current practice **(one GP)** **Another GP commented:** 1) There is no paragraph about excluding patients who are palliative care 2) What is the difference in actual age between a child, young person, young adult and adult? Should not all those under 25 years be under the care of a renal specialist and all treatment decisions be made by that team as standard?	Thank you for your comment. The decision about referring patients receiving palliative care is a clinical judgment. For the purposes of NHS services an adult is normally aged 18 or over, and the committee did not agree that all under 25s should be cared for by the renal team.
NICE GP Reference Panel	Guideline	019	010 - 016	Use of this risk equation would need an automated, simple and understandable score to be generated by GP clinical systems to be practical. **3 GPs made this point** Are GPs expected to have this conversation with everyone with CKD? This is a large number of patients. This will need a significant amount of consultation time. **2 GPs made this point** **One GP felt it was outside their expertise to have conversations about risk of renal replacement therapy**	Thank you for your comment. The committee did not expect that primary care would be performing these calculations, but rather that medical laboratories would use existing systems to report a KFRE value (see more details about committee's discussion on implementation issues in evidence review F: The best combination of measures to identify increased risk of progression in adults, children and young people; pages 18 and 19). We recognise that there may be a delay in implementing the KFRE calculation in some laboratory systems and during this period existing referral criteria will need to be used. We

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				One expressed concern about generating anxiety when communicating 5 year risk of needing RRT	have added this to the rationale section for this recommendation. We have added a link to the NICE's guideline on shared decision making and the NICE's guideline on patient experience in adult NHS services. Both guidelines have recommendations on how to communicate risk to the patient.
NICE GP Reference Panel	Guideline	021	018> Rec 1.6.1-3	**Clarify BP targets to include home BP measurements:** BP targets-this needs clarifying. The guidance needs to specify if home BP readings are acceptable, as you know the Nice guidance on Hypertension now strongly advises that diagnosis and monitoring are ideally based on home readings, not clinic ones. Many patients now monitor their BP at home-are the clinic targets you specify the same for home readings? The guidance also need to clarify whether we should treat to standing BP in the elderly and those known to have a postural drop in BP.	Thank you for your comment. The preferred measure to monitor blood pressure is clinic blood pressure (see recommendation 1.4.15 in the NICE's guideline on hypertension in adults). There are nuances related to blood pressure measurement which are included in recommendations 1.4.17 to 1.4.19, 1.4.22 and 1.4.45 within the NICE's guideline on hypertension in adults. This has been clarified under the section of 'Blood pressure control' in the updated NICE guideline on chronic kidney disease. The NICE BP guideline has recommendations on measurement and treatment for people with symptoms of postural hypotension.
NICE GP Reference Panel	Guideline	026	009 - 016	**Specific question on NOAC recommendation:** Why do you specify Apixaban as the Doac to use for AF with a gfr 30-50? I assume you mean the gfr calculated using the Cockroft Gault formula as required in the BNF? I do not think this is correct, Edoxaban can be used down to a gfr of 15 ml/min and is the first choice DOAC in many CCG's including ours.	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations. We have passed your issue on to the NICE surveillance team who will explore whether this recommendation needs updating in the future.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
NICE GP Reference Panel	Guideline	027	009 - 020	**Increase in routine blood testing** You imply that we should "monitor for iron deficiency every 3 months" in patients with a gfr 30-60, I am afraid this frequency of testing is just not possible currently in general practice. If this is needed we would have to pass this back to secondary care, there is just not the phlebotomy capacity in the community. You also imply that this monitoring should be with FBC, ferritin and transferrin saturation- for us this would mean requesting FBC and iron studies each time. Our lab locally is very reluctant to do repeated iron studies, again, this would need to be passed back to secondary care. **Another GP repeated a similar concern about increased testing**	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.
NICE GP Reference Panel	Guideline	031	001 >	**One GP suggested a recommendation about whether patients could self-administer EPO in the context of challenges providing district nursing cover to do this in a rural community**	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.
NICE GP Reference Panel	Guideline	048	010	**Lack of routine bicarbonate testing in primary care** You refer to starting bicarbonate if gfr<30 and serum bicarbonate<20, just for information- the e/u results that come down to general practice no longer include bicarbonate in our area and I expect this applies to many labs in the UK.	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.
North Central London Joint Formulary Committee	Guideline	022	021	A NICE TA is scheduled for later this year for 'Canagliflozin for adults with type 2 diabetes and diabetic kidney disease with albuminuria' Please comment on whether is appropriate for an NG to pre-empt a TA.	Thank you for your comment. NICE's Topic Selection Oversight Panel determined that canagliflozin would be best assessed and included in the chronic kidney disease and Type 2 diabetes in adults: management update. Therefore the appraisal was suspended from the Technology Appraisal work programme in

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					December 2020 (https://www.nice.org.uk/guidance/indevelopment/gid-ta10555).
North Central London Joint Formulary Committee	Guideline	022	021	The rationale for not requiring a cost-effectiveness evaluation of SGLT2is for proteinuria appears misguided. At a basic level, NICE has already taken a view that a cost-effectiveness evaluation *is* required because 'Canagliflozin for adults with type 2 diabetes and diabetic kidney disease with albuminuria' is being considered through the NICE TA programme (despite already having TAs in place as an antihyperglycemic in type 2 diabetes). https://www.nice.org.uk/guidance/indevelopment/gid-ta10555 At a more detailed level, NICE TA315 / TA572 / TA336 / TA288 advise that SGLT2 inhibitors are cost-effective for patients with type 2 diabetes in whom sulfonylureas are unsuitable, as an alternative to other antihyperglycemic agents, to reduce HbA1c and ultimately microvascular and macrovascular conditions. Data informing these decisions are from clinical studies which mostly/all excluded people with renal impairment. TA315 specifically excludes patients with CrCl < 60mL/min (in line with the SPC at the time). To summarise the PICO for these NICE TAs: • Population: Type 2 diabetes with good renal function • Intervention: SGLT2i	Thank you for your comment. NICE's Topic Selection Oversight Panel determined that canagliflozin would be best assessed and included in the chronic kidney disease and Type 2 diabetes in adults: management update. Therefore the appraisal was suspended from the Technology Appraisal work programme in December 2020 (https://www.nice.org.uk/guidance/indevelopment/gid-ta10555). NICE is undertaking an additional review to consider the effectiveness and cost effectiveness of SGLT2 inhibitors in people with CKD and type 2 diabetes. This work will include economic modelling and will be broader in scope than the current review, in that it will include all people with CKD and type 2 diabetes, not only those with proteinuria. See https://www.nice.org.uk/guidance/## for details. This work may amend the current recommendation on SGLT2 inhibitors in the CKD guideline.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				• Comparator: Other oral antihyperglycemic agents • Outcome: HbA1c mainly, + BP and body weight to predict micro and macrovascular complications The effectiveness, as measured by placebo adjusted HbA1c lowering effect, of SGLT2i with normal renal function (CrCL >60 mL/min) is 0.6% at 52 weeks (https://www.nice.org.uk/guidance/ta315/documents/diabetes-type-2-canagliflozin-appraisal-consultation-document) In contrast, the placebo adjusted HbA1c lowering effect of SGLT2i in CREDENCE (CrCl 30-60 mL/min + ACR >34 mg/mmol), is much smaller at 0.25%. The PICO for proteinuria is therefore quite different: • Population: Type 2 diabetes with kidney disease and proteinuria • Intervention: SGLT2i • Comparator: Best supportive care • Outcome: Worsening CKD, need for dialysis, cardiovascular death It appears therefore that the proteinuria cohort described in this draft guidance would all have been excluded from the previously published NICE TAs. Further, the comparators and outcomes are different. It is therefore unclear that SGLT2i have demonstrated cost-effectiveness in this new place in therapy.	

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Novartis Pharmaceuticals UK Limited	Guideline	General	General	The Kidney Disease Improving Global Outcomes (KDIGO) Consensus Conference on Nomenclature for Kidney Function and Disease (June 2019) had the primary objective of standardising and refining the nomenclature for describing kidney function and disease 'to create a patient-centred and precise glossary of terms related to kidney disease to promote greater uniformity in medical practice, research, and public health.' Its relevance to a UK-audience is reflected in the participation of a number of preeminent medical experts from the UK in the development and subsequent publication of the outputs from the consensus conference. The consensus report includes the following:[1] • 'kidney' should be employed in lieu of 'renal' or 'nephro-' when referring to kidney disease and kidney function • 'kidney failure' should be accompanied by appropriate descriptions of presence/absence of symptoms, signs, and treatment in lieu of 'end-stage kidney disease' • to employ the KDIGO definition and classification of chronic kidney disease (CKD) rather than alternative descriptions to define and classify severity of CKD • and to utilize specific kidney measures (such as albuminuria or decreased GFR rather than 'abnormal' or 'reduced' kidney function when describing alterations in kidney structure/function)	Thank you for your comments. The nomenclature for kidney function and disease has been updated.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Although the report does caution against a 'wholesale switch' of terms, for instance in contexts where 'renal' may be considered 'less awkward', it does advocate, where possible, usage of 'kidney', as it is perceived to be more patient-centric. In addition, 'end-stage' as a descriptor for kidney disease should be avoided, as it is felt to be both non-specific and stigmatising/demoralising for patients (furthermore, the implication of 'imminent death' was recognised as being 'outdated'). Whilst the NICE CKD draft guideline is aligned with respect to the classification of CKD and embraces the utilisation of specific kidney measures, it does not always reflect the recommended nomenclature with respect to the first and second points above. By standardising terms, there may be an improvement in adherence to definitions and an avoidance of errors, which will help foster consistency in trial design/execution/reporting, etc. It would, therefore, be worthwhile considering more widespread adoption of the nomenclature, where it is felt to be practical and appropriate. Furthermore, a desire to be patient-centric in communicating with patients is underscored by the NICE CKD draft guideline (page 19, lines 17-18) which encourages 'use [of] every day, jargon-free language to communicate information on risk. If technical terms are	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				used, explain them clearly.' A more widespread adoption of patient-centric nomenclature within the guideline may thus be a consideration. 1. Levey AS, Eckardt KU, Dorman NM, et al. Nomenclature for kidney function and disease: report of a Kidney Disease: Improving Global Outcomes (KDIGO) Consensus Conference. Kidney Int 2020;97(6):1117-1129.	
Novartis Pharmaceuticals UK Limited	Guideline	009	016	Consider insertion of an 'or' between 'lithium' and 'NSAIDs', as the current draft text may be read as all of the aforementioned rather than any single mentioned drug.	Thank you for your comment. we have replaced 'and' by 'or'.
Novartis Pharmaceuticals UK Limited	Guideline	022 023 062 063	020 – 023 001 - 002 003 - 031 001 - 021	The draft guideline recommends use of an SGLT2 inhibitor in adults with type 2 diabetes and CKD who have an ACR of 30 mg/mmol or more and meet the criteria in the marketing authorisation. Existing NICE technology appraisal guidance for SGLT2 inhibitors in adults with type 2 diabetes (NICE TA288, TA315, TA336, TA390, TA418, TA572, TA583), however, restricts the eligible patient population compared to the marketing authorisations of these medicines, for example, by requiring another diabetes drug to be considered or tried first. We are concerned that the recommendation in the draft guideline would thus expand the use of SGLT2 inhibitors to type 2 diabetes populations in whom they have been deemed not cost-effective in the relevant technology appraisals. We are not aware of any assessment whether the inclusion of renal benefits would make SGLT2 inhibitors a cost-effective treatment option in	Thank you for your comment. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. NICE is also currently undertaking a technology appraisal of dapagliflozin for treating chronic kidney disease which will include the DAPA-CKD trial. Therefore, data from DAPA-CKD has been removed from this update. See https://www.nice.org.uk/guidance/indevelopment/gid-ta10808 for details. The NICE CKD guideline will cross refer to this technology appraisal appraising dapagliflozin when it is published. Regarding your concern about 'the recommendation in the draft guideline would thus expand the use of SGLT2 inhibitors to type 2 diabetes populations in

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				type 2 diabetes patients who are not currently covered by technology appraisal guidance recommendations. The guideline committee assumed that SGLT2 inhibitors provide similar benefits for diabetes control in people with diabetes and CKD, as in people without CKD. However, the summaries of product characteristics (SmPC) of several SGLT2 inhibitors seem to contradict that. For example, the SmPC of dapagliflozin (section 4.4) notes that *"the glycaemic efficacy of dapagliflozin is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and is likely absent in patients with severe renal impairment"*. The SmPC of canagliflozin highlights that addition of further anti-hyperglycaemic agents may be required to achieve glycaemic control in patients with moderate or severe renal impairment. SmPCs also report an increased risk of adverse events and additional monitoring requirements in patients with renal impairment, which would have to be taken into account in cost-effectiveness analyses, alongside the reduced glycaemic treatment effect. The guideline committee's conclusion that SGLT2 inhibitors are likely to be even more cost-effective in diabetes patients with CKD than in diabetes patients without CKD, may therefore be specious. On that basis, we do not agree that the committee's considerations laid out in the draft guideline provide a sufficient basis for concluding that the proposed recommendation of SGLT2 inhibitors would represent a cost-effective use of NHS resources. Especially when taking into account the substantial cost impact the proposed recommendation would have (as	whom they have been deemed not cost-effective in the relevant technology appraisals.' These technology appraisals were not on people with type 2 diabetes and chronic kidney disease. Therefore, there is no evidence in the technology appraisals that those SGLT2 inhibitors were not cost-effective in people with type 2 diabetes and chronic kidney disease.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				acknowledged by the committee), a formal, systematic and evidence-based assessment of clinical and cost effectiveness in the target population seems necessary. In addition, we would like to draw the guideline authors' attention to a proposed NICE technology appraisal of dapagliflozin in CKD [ID3866]. Under the suggested remit to appraise the clinical and cost effectiveness of dapagliflozin for treating CKD, which also includes consideration of a subgroup of patients with diabetes (see draft scope), the content of this technology appraisal will overlap with the draft guideline recommendation regarding SGLT2 inhibitor use. Given the expected timing, the present draft guideline recommendation – if maintained in the final version of the guideline – could thus either inappropriately pre-empt the outcome of technology appraisal ID3866 or potentially result in a contradiction between NICE technology appraisal guidance and a NICE guideline. As specified in the 2019 Voluntary Scheme for Branded Medicines Pricing and Access, extensions to marketing authorisations that represent a significant new therapeutic indication will undergo an appropriate NICE appraisal. We strongly believe that the planned extension of the dapagliflozin marketing authorisation to CKD meets this criterion. Therefore, we contend that any recommendation for dapagliflozin or any other SGLT2 inhibitor that goes beyond the existing technology appraisal guidance in diabetes should only be made as a result of an appropriate technology appraisal, involving all relevant stakeholders.	

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Pharmacosmos UK Limited	Guideline	036	019 - 020	Table 3 provides an example of high-dose intravenous iron regimen for adults with stage 5 chronic kidney disease. As this is intended to serve as general guidance for any intravenous iron therapy, it would be better to not specify a particular intravenous iron preparation, as done for iron sucrose in the header of the table and below the table. We suggest simply stating intravenous iron. Thereby, the paragraph that is stated in the Rational and Impact section (page 66, lines 28-29 to page 67, lines 1-3) can be reduced to *"The committee agreed that the type of intravenous iron was not relevant and that there was no reason to recommend a specific preparation. ~~An example regimen for adults using iron sucrose was taken from the evidence to help guide practice, however the choice of preparation should be based on local availability and policies.~~"*	Thank you for your comment. The committee acknowledged the difficulty of bioequivalence in iron products. Therefore, the rationale now includes more detail about this difficulty and that a pharmacist should be consulted for bioequivalent doses when considering iron preparations. The rationale also states that the committee agreed that the type of intravenous iron was not relevant and that there was no reason to recommend a specific preparation. Table 3 provides an example from the PIVOTAL trial, but other bioequivalent doses might be used based on local availability and policies.
Pharmacosmos UK Limited	Guideline	040	005 - 007	Based on the current recommendation in this guideline, **high-dose intravenous iron regimen** is recommended for correcting iron deficiency in adults and children with stage 5 CKD on **in-centre haemodialysis**. We are concerned that the recommendation stated below from the guidelines, could be deemed contradictory to the above mentioned rationale as it recommends a low dose, high frequency intravenous iron regimen in the same patient group. We suggest that the recommendation stated below is deleted from the guidelines to avoid confusion.	Thank you for your comment. The recommendation has been deleted. This has been clarified in the discussion of evidence review K on managing anaemia with IV iron in people with GFR category G5 who are on dialysis.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				*"Intravenous iron administered at a **low dose and high frequency** may be more appropriate for all children and for adults who are having **in-centre haemodialysis**."*	
Polycystic Kidney Disease Charity	Guideline	General	General	We welcome the updated guideline.	Thank you for your comment.
Polycystic Kidney Disease Charity	Guideline	019	017	We welcome the recommendation to use everyday language with clear explanations. We would like to see this adopted consistently however as soon as possible. We see too many examples of clinic letters that lack clarity, are full of jargon and measurements without explanation, and sometimes not addressed directly to the patient (as per current best practice but to the GP).	Thank you for your comment.
Polycystic Kidney Disease Charity	Guideline	020	013 & 020	Children with polycystic kidney disease often need referral to other non-kidney specialities, such as hepatology, GI, and genetics. We would like this be specified in the guideline. Parents are often unaware of potential co-morbidities and kidney doctors don't always mention them at kidney clinic appointments	Thank you for your comment. The management of specific conditions, in this case polycystic kidney disease in children, is outside the scope of this update.
Polycystic Kidney Disease Charity	Guideline	019 & 020	025 & 011	Adults with polycystic kidney disease often need referral to other, non-kidney specialities, such as hepatology, neurology and genetics. We would like this be specified in the guideline. Patients are often unaware of potential co-morbidities and kidney doctors don't always mention them at kidney clinic appointments.	Thank you for your comment. This recommendation is about referral to specialist assessment of renal related outcomes based on evidence. The evidence for referral to other non-kidney specialities was not reviewed. Therefore, the recommendation is specific to renal related outcomes.
Primary Care Diabetes Society	Guideline	007	025	Suggest add "Early morning samples are the most accurate for assessing ACR but the initial sample may be collected any time of the day. If the ACR if between 3 and 70, then confirm in an early morning sample"	Thank you for your comments. We have added more details to the committee's discussion and interpretation of the evidence about ACR variation (see evidence review B: Accuracy of albumin:creatinine ratio versus protein:creatinine

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					ratio measurements to quantify proteinuria in children and young people with CKD). The committee highlighted that people's circumstances should be considered when interpreting ACR levels and that ACR may vary by time of day. This is why confirmation should be done using a subsequent early morning sample when ACR is between 3 mg/mmol and 70 mg/mmol in the initial detection of proteinuria.
Primary Care Diabetes Society	Guideline	009	018	1.1.21 Should it not specify testing for CKD at least annually in those with the specified risk factors?	Thank you for your comment. We added to the rationale that the frequency of testing for CKD should be individualised according to the person's circumstances.
Primary Care Diabetes Society	Guideline	011	004	1.1.25 It would be useful to state how soon after AKI and then how frequently this should be monitored?	Thank you for your comment. The timing and frequency of CKD monitoring after CKD should be individualised to the person's circumstances.
Primary Care Diabetes Society	Guideline	013	016	Table refers to freq of eGFR monitoring but do we also need to state freq of ACR monitoring. In 1.3.1 in mentions that freq of monitoring both markers should be discussed. I often get asked in clinical practice (primary care) how often ACR should be checked.	Thank you for your comment. We have added a note to Table 2 about ACR monitoring which should be individualised based on a person's individual characteristics, risk of progression and whether a change in ACR is likely to lead to a change in management. The rationale has examples about the frequency of ACR monitoring ACR (more frequently monitoring in people with high ACR categories A2 or A3; or where a change in ACR would affect management). The committee agreed to make a research recommendation to identify the optimal frequency of monitoring ACR in adults, children and young people with CKD.
Primary Care Diabetes Society	Guideline	019	012	1.5.1 It would be useful to have a calculator for working out the 4 variable kidney failure risk? Include what conversion should be used for ACR to get to mg/g	Thank you for your comment. The committee thought that the risk equations would be completed in the laboratories and then the KFRE would be inputted to

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				required for this tool. Calculation too complex for primary care use - an automatic version will be necessary if it is to be widely used.	the primary care systems (see more details about committee's discussion on implementation issues in evidence review F: The best combination of measures to identify increased risk of progression in adults, children and young people; pages 18 and 19). The committee did not envision that primary care physicians would be calculating the KFRE for themselves (which they agreed would be problematic).
Primary Care Diabetes Society	Guideline	020	001	1.5.5 Clinicians worry about the advice not to refer to specialist if ACR ≥70 and caused by diabetes and diabetes is optimally managed – consider a link to "optimum management" or summarise key points.	Thank you for your comments. The first part of the recommendation includes the importance of taking comorbidities and wishes into account when referring adults with CKD for specialist assessment. We have amended the bullet point to clarify that diabetes is already 'appropriately treated' and a reference has been added to see recommendations 1.6.6 and 1.6.7.
Primary Care Diabetes Society	Guideline	022	015	1.6.5 Surely should specify that Urinary ACR should be measured at least annually in those with hypertension and where it is persistently >30mg/mmol ACE/ARB should be offered? 1.6.5 Should people with diabetes be in the list or is this covered in the Hypertension link in 1.6.4?	Thank you for your comment. We have added a note to Table 2 about ACR monitoring which should be individualised based on a person's individual characteristics, risk of progression and whether a change in ACR is likely to lead to a change in management. The rationale has examples about the frequency of ACR monitoring ACR (more frequently monitoring in people with high ACR categories A2 or A3; or where a change in ACR would affect management). The committee agreed to make a research recommendation to identify the optimal frequency of monitoring ACR in adults, children and young people with CKD. NICE's guideline on hypertension in adults applies to all adults, including those with type 2 diabetes.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Primary Care Diabetes Society	Guideline	022	020	1.6.6 KDIGO make the distinction between recommending ACE/ARB if diabetes hypertension and albuminuria and only offering it if diabetes and albuminuria but no hypertension.	Thank you for your comment. Recommendation 1.6.6 has been separated into 2 parts. The first part (recommendation 1.6.6) is to offer an ACE inhibitor or an ARB (titrated to the highest approved dose that is tolerated) to adults with CKD and diabetes (type 1 or type 2) if ACR is 3 mg/mmol or more. The second part (recommendation 1.6.7) is to offer an SGLT2 inhibitor, in addition to an optimised dose of ACE inhibitor or an ARB, to people with type 2 diabetes, an ACR of 30 mg/mmol or more and meet the criteria in the marketing authorisation (including relevant eGFR thresholds); monitor for volume depletion and eGFR decline.
Primary Care Diabetes Society	Guideline	022	022	SGLT2 inhibitor only recommended if ACR >30mg/mmol – this may not be specified in the licence for Dapagliflozin??? (further to Dapa HF) and importantly the SGLT2 inhibitor Dapagliflozin will be licenced for those without diabetes too - this is not included. The body of evidence for renal protection with the SGLT2i class is now substantial and continues to grow. Canagliflozin can already be initiated at eGFR > 45 for renal protection, regardless of ACR. I do feel the guidelines needs to go further in its recommendations to consider SGLT2i in people with CKD (all stages) in view of renal protective evdicene, in line of course with current licence restrictions. We now have a systematic review and meta-analysis (Neuen et al Lancet Diabetes & Endo 2019) of large studies in people with type 2 diabetes. SGLT2i appear to be reno-protective across all levels of Since the original recommendation for the treatment of ACEi/ARBs, at least in the use as reno-protective in type 2 diabetes,	Thank you for your comments. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. NICE is also currently undertaking a technology appraisal of dapagliflozin for treating chronic kidney disease which will include the DAPA-CKD trial. Therefore, data from DAPA-CKD has been removed from this update. See https://www.nice.org.uk/guidance/indevelopment/gid-ta10808 for details. The NICE CKD guideline will cross refer to this technology appraisal appraising dapagliflozin when it is published.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				was based on similar of evidence then I think serious consideration should be made for the use of SGL2Ti in CKD with ACR>3.	
Primary Care Diabetes Society	Guideline	023	002	No evidences of the need to monitor eGFR decline in relation to addition of an SGLT2i (nothing beyond recommended normal monitoring), no evdicene of inc AKI or renal decline. I think this recommendation will worry clinicians about potential renal toxicity. Post-hoc data from CREDENCE would suggest as long as the eGFR drop was less than 30% from baseline within 3 months of initiation all is well.	Thank you for your comment. We have included a clarification to the rationale stating that eGFR monitoring should depend on people's circumstances and on the BNF advice of monitoring requirements for people using SGLT2 inhibitors.
Primary Care Diabetes Society	Guideline	023	005	1.6.7 Do they have robust guidance on contraception for these potentially teratogenic drugs in young people and young female adults? Could go in at 1.6.10	Thank you for your comment. We have added your suggestion to recommendation 1.6.11.
Primary Care Diabetes Society	Guideline	062	029	The committee noted that the doses of SGLT2 inhibitor used in people with diabetes and CKD were lower than in people without renal impairment. However, they were confident that these drugs would still be effective for blood glucose control in people with diabetes and CKD, and would therefore provide similar benefits for diabetes 1 control as in people without CKD – would challenge this as it is NOT supported by the evidence – most likely inadequate blood glucose lowering efficacy where eGFR < 45 mL/min/1.73 m2. There needs to be a clear specification of the reason for prescribing – is it glycaemic control or renal benefit?	Thank you for your comment. We have amended the rationale to note that the benefits are not expected to be the same for blood glucose control in people with diabetes and CKD as in people with diabetes but without CKD. The committee were confident that the overall clinical benefit in people with diabetic kidney disease would be as large as the benefits estimated in the technology appraisals for people with diabetes but without CKD.
Race & Health	Evidence Review A	General	General	On behalf of Race & Health (https://raceandhealth.org/) – a global network of medical and non-medical professionals working to highlight the impact of racism, xenophobia, and discrimination on health through streams of work in advocacy, education, and academia, we welcome this consultation for the upcoming NICE	Thank you for your comments. Recommendation 1.1.3 has been removed from the guideline. The rationale section includes further advice stating that individualised judgement should be used when interpreting eGFR in people from UK black, Asian and minority ethnic groups and in adults with

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				guideline for Chronic Kidney Disease. We are commenting on "Evidence review A – Diagnostic accuracy of eGFR calculations in black, Asian and other minority ethnic groups". We were disappointed to find the committee's statement 1.1.9.3. "Benefits and harms" contradictory and unsatisfactory. The committee acknowledged that variations based on ethnicity were "likely due to other biomarkers, for example body density rather than family origin" but insisted that "in the absence of appropriate robust new evidence, the existing guideline recommendation should be retained which recommends to multiply eGFR by 1.159 if calculated using the CKD EPI creatinine equation" in "people from black African and Caribbean family origin". The oversimplified use of race as a flawed and inconsistent shortcut for a far more complex fusion of underlying social, cultural, and ancestral differences is endemic in medicine[1,2]. Structural racism is coded into the very care algorithms we employ in daily practice[3]. The CKD EPI calculation for estimating GFR is a prominent example, based on an erroneous perception amongst physicians that Black patients and patients from other racial or ethnic minorities have homogenous creatinine physiology based on biological differences [4,5]. Such assumptions have impacts on patient outcomes: delays to specialist care, delays to transplant listing, delays to vascular access formation and so on. While we recognise the troubling imperfections of serum creatinine measurement to estimate GFR, this does not	extremes of muscle mass. The committee agreed to make recommendations for research on appropriate eGFR equations for black, Asian and minority ethnic groups (adults, children and young people) in the UK. They agreed that factors other than ethnicity should also be explored as biomarkers.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				justify the inappropriate and crude use of race-adjustment which may result in reinforcing prejudicial beliefs about biology amongst health professionals as well as delays in care for Black patients. We have been following developments in the US, where colleagues have challenged this status quo. Several hospitals have abolished the use of the race multiplier[6]. Vitally it has sparked serious discussions around differential health outcomes between communities of colour and their white counterparts[7]. Earlier this month, the National Kidney Foundation/American Society of Nephrology Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Diseases released a statement from its leaders in agreement that "race modifiers should not be included in equations to estimate kidney function"[8]. This year's NICE guideline is an opportunity to follow suit in leading the way in leaving behind practice of race adjustment. NICE has raised in this consultation with regards "[w]hich areas will have the biggest impact on practice…?". We strongly feel it is the care of Black patients that will be most negatively affected by maintaining the status quo. As this approach is being increasingly discredited, it is only by refreshing important national and international guidelines that changes in practice can have a wider reach through implementation across different settings and disciplines, and in providing the imperative for much-needed research into improving GFR estimation in clinical practice. At this historical juncture, it would be irresponsible of NICE to obviate its	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				responsibilities to these ends in favour of legitimising the existing flawed and impractical formula within its updated recommendations. **References** 1. Saini, A. Stereotype threat. *Lancet* **395**, 1604–1605 (2020). 2. Adigbli, G. Race, science and (im)precision medicine. *Nature Medicine* (2020). doi:10.1038/s41591-020-1115-x 3. Vyas, D. A., Eisenstein, L. G. & Jones, D. S. Hidden in Plain Sight — Reconsidering the Use of Race Correction in Clinical Algorithms. *N. Engl. J. Med.* **383**, 874–882 (2020). 4. Eneanya, N. D., Yang, W. & Reese, P. P. Reconsidering the Consequences of Using Race to Estimate Kidney Function. *JAMA - Journal of the American Medical Association* **322**, 113–114 (2019). 5. Ahmed, S. *et al.* Examining the Potential Impact of Race Multiplier Utilization in Estimated Glomerular Filtration Rate Calculation on African-American Care Outcomes. *J. Gen. Intern. Med.* 1–8 (2020). doi:10.1007/s11606-020-06280-5 6. Push to remove racist bias from kidney testing gains new ground. Available	

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				at: https://www.statnews.com/2020/07/17/egfr-race-kidney-test/. 7. American Society of Nephrology | Kidney Week - [Session] Race and Ethnicity Considerations in CKD. Available at: https://www.asn-online.org/education/kidneyweek/2020/program-session-details.aspx?sessId=356596. 8. National Kidney Foundation/American Society of Nephrology Letter to members. Available at: https://www.asn-online.org/g/blast/files/NKF-ASN-eGFR-March2021.pdf (Accessed: 17 March 2021)	
Renal Nutrition Group of the British Dietetic Association	Guideline	General	General	We are very pleased to see a dietary intervention section	Thank you for your comment.
Renal Nutrition Group of the British Dietetic Association	Guideline	017	011	We understand that the content of this guideline is not in the scope of this review. We do ask that the panel consider : We would suggest to add a specific questions: How should I change my diet and lifestyle if I have CKD?	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.
Renal Nutrition Group of the British Dietetic Association	Guideline	018	015	We understand that the content of this guideline is not in the scope of this review. We do ask that the panel consider specifically that renal dietitians should be involved in the dietary management of complex patients with CKD : If dietary advice is agreed ensure a renal dietitian is involved in the management of complex patients with CKD	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Renal Nutrition Group of the British Dietetic Association	Guideline	043	001	We would suggest that the following point is added Take into account patient preference and the ease of administration, as well as the clinical circumstances, when offering a phosphate binder in line with recommendations Rationale: we feel it is important to consider patient preference for the type of binder, this can often aid compliance. This statement also acknowledges that for some patients the pill burden of taking phosphate binders might outweigh the risks of hyperphosphataemia , such as in end of life care.	Thank you for your comment. We have added recommendation 1.11.7 which recommends that patients' preferences should be considered when offering phosphate binders and the importance of this approach has been explained in the rationale.
Renal Nutrition Group of the British Dietetic Association	Guideline	044	005	We suggest consideration is given to changing this sentence to: • the timing and distribution of binders; explain the exact timing (ie before, with or after food) depending on the binder type, and the need to take with snacks containing phosphate (for example high protein snacks) Rationale: it is important to take the phosphate binder at the correct time, some need to be taken before meals, some after and some with. It is also important to ensure the number of binders is appropriate for the size and content of the meal as this will affect the amount of phosphate eaten:	Thank you for your comment. Recommendation 1.11.6 has been amended to include your suggestions.
Renal Nutrition Group of the British Dietetic Association	Guideline	045	005	We note that calcium acetate is recommended as the first line binder. It appears that the evidence is weak or very weak and this contradicts the KDIGO and RA	Thank you for your comment. The recommendations were updated based on the results of the cost-effectiveness modelling done for this review question, which did find robust evidence calcium acetate was

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				guidelines / statements which favour non calcium binders as first line in order to restrict calcium https://renal.org/sites/renal.org/files/FINAL-KDIGO-CKD-MBD-commentary-Final-for-publication.pdf https://kdigo.org/wp-content/uploads/2017/02/2017-KDIGO-CKD-MBD-GL-Update.pdf	the best first-line option. This has been clarified in the rationale when explaining the choice of phosphate binders.
Renal Nutrition Group of the British Dietetic Association	Guideline	045	017	We queried whether there is sufficient robust evidence to recommend sucroferric oxyhydroxide over lanthanum. The evidence on efficacy is of low quality and the costs vary	Thank you for your comment. The committee were satisfied that sucroferric oxyhydroxide is an effective and cost-effective next option for people in whom sevelamer carbonate is not suitable. Lanthanum carbonate has a high cost and relatively low efficacy versus the other non calcium-containing binders. The committee felt that, although it should not be put forward as an 'offer' recommendation, it should not be removed as an option entirely, and they therefore recommend it only for people who cannot tolerate all other options.
Renal Nutrition Group of the British Dietetic Association	Guideline	045	020	We feel there should be clear guidance on the timing of binders as this will improve efficacy and would recommend adding in: calcium carbonate is pH dependent and should be taken 10-15 minutes before food and not after	Thank you for your comment. Recommendation 1.11.6 has been reworded to clarify about the timing of binders.
Renal Nutrition Group of the British Dietetic Association	Guideline	046	007	As well as checking whether the binder is taken correctly we feel the following should be checked: For those on dialysis ensure maximum adequacy is achieved. Consider reviewing the dose of active vitamin D	Thank you for your comment. The committee agreed to add to the rationale that renal physicians assess several factors at clinical reviews for people who are taking phosphate binders (including parathyroid hormone, vitamin D and serum calcium).
Renal Nutrition Group of the	Guideline	046	019	We recommended that medications which might affect serum phosphate levels for example alfacalcidol and calcitriol are included in this list	Thank you for your comment. The wording 'medications which might affect serum phosphate' has been added to recommendation 1.11.18.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
British Dietetic Association					
Renal Nutrition Group of the British Dietetic Association	Guideline	051	008	We feel that it would be beneficial to have evidence as to whether the use of phosphate binders and the control of serum phosphate are linked to the delay in CKD-MBD or survival, we suggest adding: Is the usage of phosphate binder in CKD 4 -5 linked to improve survival in patients with CKD/ delay CKD-MBD? Does the improvement of phosphate levels towards normal range have an impact on survival?	Thank you for your comment. The research that you suggest was not part of this update and therefore we cannot add them.
Renal Nutrition Group of the British Dietetic Association	Guideline	067	017	We note that calcium acetate is recommended as the first line binder. It appears that the evidence is weak or very weak and this contradicts the KDIGO and RA guidelines / statements which favour non calcium binders as first line in order to restrict calcium https://renal.org/sites/renal.org/files/FINAL-KDIGO-CKD-MBD-commentary-Final-for-publication.pdf https://kdigo.org/wp-content/uploads/2017/02/2017-KDIGO-CKD-MBD-GL-Update.pdf	Thank you for your comment. The recommendations were updated based on the cost-effectiveness of the evidence. Which concluded "When first- and second-line binder options are taken into account, the base-case economic model results suggest that calcium acetate is likely to be the preferred first-line phosphate binder for the management of hyperphosphataemia in people with CKD stage 5 who are on dialysis. If people experience hypercalcaemia, the most cost-effective strategy is to switch them to sevelamer carbonate. If sevelamer carbonate is not an option, sucroferric oxyhydroxide may provide a cost-effective alternative." This has been clarified in the rationale when explaining the choice of phosphate binders.
Renal Nutrition Group of the British Dietetic Association	Guideline	068	021	This statement is not correct, several units in the UK are using Sucroferric oxyhydroxide	Thank you for your comment. We have clarified that the use of sucroferric oxyhydroxide currently varies across the UK.
Royal College of General Practitioners	Guideline	007	021 - 027	Can the committee clarify that the first ACR is RANDOM, does not need to be early morning and should be carried out in the absence of Urinary tract	Thank you for your comment. We have added more details to the committee's discussion and interpretation of the evidence about ACR variation

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				symptoms. If the ACR is raised, can the committee clarify whether a urine dipstick or culture be performed to rule out infection? If this is not required, can the committee specifically state this?	(see evidence review B: Accuracy of albumin:creatinine ratio versus protein:creatinine ratio measurements to quantify proteinuria in children and young people with CKD). The committee highlighted that people's circumstances should be considered when interpreting ACR levels because ACR can be affected by different factors (for example, urinary tract infections). It was also highlighted that ACR may vary by time of day. This is why confirmation should be done using a subsequent early morning sample when ACR is between 3 mg/mmol and 70 mg/mmol in the initial detection of proteinuria.
Royal College of General Practitioners	Guideline	007	026	Can the committee confirm the exact meaning of early morning urine? Do you mean the first urine on waking which is a slightly different thing, especially if people who work permanent night shifts.	Thank you for your comments. We have added more details to the committee's discussion and interpretation of the evidence about ACR variation (see evidence review B: Accuracy of albumin:creatinine ratio versus protein:creatinine ratio measurements to quantify proteinuria in children and young people with CKD). The committee highlighted that people's circumstances should be considered when interpreting ACR levels and that ACR may vary by time of day. This is why confirmation should be done using a subsequent early morning sample when ACR is between 3 mg/mmol and 70 mg/mmol in the initial detection of proteinuria.
Royal College of General Practitioners	Guideline	008	001	Can the committee confirm that this is in the absence of a urine infection?	Thank you for your comment. We have added more details to the committee's discussion and interpretation of the evidence about ACR variation (see evidence review B: Accuracy of albumin:creatinine ratio versus protein:creatinine

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					ratio measurements to quantify proteinuria in children and young people with CKD). The committee highlighted that people's circumstances should be considered when interpreting ACR levels because ACR can be affected by different factors (for example, urinary tract infections). It was also highlighted that ACR may vary by time of day. This is why confirmation should be done using a subsequent early morning sample when ACR is between 3 mg/mmol and 70 mg/mmol in the initial detection of proteinuria.
Royal College of General Practitioners	Guideline	008	005	Can the committee confirm, when the haematuria testing is required Is this for everyone with proteinuria or everyone being tested for CKD as per 1.1.14? It is not currently clear who requires this testing.	Thank you for your comment. We have clarified that haematuria should be tested in the same people as recommended in 1.1.14.
Royal College of General Practitioners	Guideline	009	014	Can the committee confirm whether all people taking NSAIDs need GFR annually or only those taking regular NSAIDs? If it is regular NSAIDs, what frequency would be the right threshold to begin annual testing? NSAIDs are frequently taken on a PRN basis or intermittently for things such as headaches, dysmenorrhoea and MSK pain and are largely over the counter medication rather than prescribed.	Thank you for your comment. The committee confirmed that the monitoring is for people with long-term chronic use of NSAIDs. This has been added to recommendation 1.1.20.
Royal College of General Practitioners	Guideline	009	018	Can the committee confirm if this is a one off test *at* diagnosis of these conditions, rather than annual screening? The first seems reasonable, the latter has significant workload implications (especially hypertension and CVD). Clarity on the frequency that this test is recommended would be valuable.	Thank you for your comment. We added to the rationale that the frequency of testing for CKD should be individualised according to the person's circumstances.
Royal College of General Practitioners	Guideline	009	018	Would the committee consider adding gout to the list of risk factors for CKD as the both commonly co-exist.	Thank you for your comment. Gout has been added to the list of risk factors to test for CKD in adults.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Royal College of General Practitioners	Guideline	011	004	We are concerned about the monitoring burden contained within this recommendation and there is a lack of detail and evidence associated with it. How often should people be monitored? Is there good evidence that AKI stage 1 needs 3 years of monitoring? If someone with AKI stage 3 is back to baseline after a few weeks, do they really need longer than 3 years of monitoring? The wording associated with the recommendation is unusual in that it doesn't have a qualifier 'offer' or 'consider'. Therefore the wording is quite strong considering the lack of detail.	Thank you for your comment. The committee discussed the frequency of monitoring in people with AKI and they agreed that monitoring should be individualised. Most of the studies did not report data on each AKI stage but there was evidence from one study about the risk of developing CKD at 5 years post-hospital discharge in children and young people who had AKI stage 1 during hospitalisation (HR 2.2; 95% CI 1.1 to 4.5; Hessey 2019). During the 2014 update of the guideline, the committee referred to a study (Jones et al. 2012) which showed that people making a complete recovery from their AKI episode who had no prior evidence of CKD had a significantly increased incidence of subsequent new onset CKD compared to people without AKI at a median of 2.5 years follow-up. Therefore, in 2014, the committee concluded that even people making a complete recovery to a normal baseline level of kidney function should be followed up for a period of 2 to 3 years after an episode of AKI. During the update of the guideline in 2021, the committee did not have concerns about the costs of monitoring after AKI which would not be a significant addition to current workload because this should not be a change in practice since the 2014 recommendations should be followed.
Royal College of General Practitioners	Guideline	019	010 - 023	We do not believe that recommendation 1.5.1 is appropriate for everyone. Could the committee consider revising this? It may be better to ensure the risk assessment is calculated for everyone, with a recommendation that a calculator is integrated into the electronic GP records and then offer a threshold for	Thank you for your comment. The committee did not expect that primary care would be performing these calculations, but rather that medical laboratories would use existing systems to report a KFRE value. The risk assessment should be individualised to the

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				discussion with the patient. If you are recommending a detailed risk communication conversation with every patient with CKD every time their GFR is calculated this becomes a huge and largely unnecessary burden on primary care. Many patients will have such a low risk of progression of their CKD that this conversation is essentially meaningless. A very typical women, aged 75, GFR 55 and ACR 2 would have a risk of 0.23% over 5 years – what does that mean to a patient? The comment in the rationale (P59L11) stating risk assessments 'help[ing] them to proactively manage their own risk' implies that the committee had evidence that patients who know their risk beneficially change their behaviour. There is no evidence to our knowledge that it does, and so we request that the committee review this recommendation to ensure the burden on primary care to provide this intervention, does so only of there is evidence of patient benefit.	person's circumstances (for example, when there is a clinical reason for doing it).
Royal College of General Practitioners	Guideline	019	025 onwards	These referral criteria for a adults and children are useful for primary care. Can the committee consider developing a flowchart/infographic of these.	Thank you for your comment. NICE does not routinely produce infographics or algorithms for lists of criteria where there are no decision points. An infographic would only replicate the lists in the guideline.
Royal College of General Practitioners	Guideline	022	004 - 006	In the rationale section, it says that this recommendation was made with a lack of evidence of benefits of lower BP targets. Can the committee review this to determine if it should therefore be a "consider" recommendation? Ideally with a clearer narrative in the rationale section about why the committee recommend this.	Thank you for your comment. We have amended the rationale to clarify that the evidence was limited and that these recommendations were consistent with clinical practice and with recommendations from NICE guideline on hypertension in adults.
Royal College of Nursing	General	General	General	The Royal College of Nursing (RCN) welcome the proposal to develop NICE guidance for Chronic kidney disease: assessment and management.	Thank you for your comment.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				The RCN invited members who work with people in these settings and care for people with this condition to review and comment on the draft guidelines on our behalf. The comments below, reflect the views of our reviewers.	
Royal College of Nursing	General	General	General	What future evidence will be made available for UK Black / Asian and minority ethnic groups?	Thank you for your comment. The committee made specific research recommendations for people from black, Asian and other minority ethnic groups with chronic kidney disease living in the UK. These research recommendations are on estimated GFR calculations; biomarkers or factors, other than ethnicity to improve the diagnostic accuracy of eGFR calculations; and the accuracy of the 4-variable Kidney Failure Risk Equation.
Royal College of Nursing	General	General	General	There is no mention of KQuIP KQuIP Home - The Kidney Quality Improvement Partnership (thinkkidneys.nhs.uk)	Thank you for your comment. The committee did not specifically discuss quality improvement in renal services as this is not something they were specifically tasked with for this update. We will pass this comment to the quality standards team at NICE, who will be updating the NICE quality standard on chronic kidney disease in adults.
Royal College of Nursing	Guideline	005	002	It would be helpful to include other examples of multisystem disease	Thank you for your comment. The committee agreed that an example was sufficient because the list could be too long to include in the recommendation.
Royal College of Nursing	Guideline	012	General	Include family impact / dynamic changes	Thank you for your comment. The guideline includes a section on information and education for people with CKD and their family members and their carer, as appropriate.
Royal College of Nursing	Guideline	018	1.4.4	To include renal specialist as relevant i.e.- Renal nurses	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.
Royal College of Nursing	Guideline	018	1.4.5	Signposting to relevant charity support as appropriate e.g.- Kidney Care UK. British Renal association/ National Kidney Federation	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.
Royal College of Nursing	Guideline	018	1.4.6	Referral to public health agencies where relevant	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.
Royal College of Nursing	Guideline	018	1.4.8	Suggest including dietetic input and advice here	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.
Royal College of Nursing	Guideline	019	1.5.2	Add: 'Technical and medical terms'	Thank you for your comment. We have added 'technical and medical terms' as you suggested.
Royal College of Nursing	Guideline	026	1.7	Should other haemoglobin disorders be included?	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.
Royal College of Nursing	Guideline	029	1.8.15	To include safe disposal	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.
Royal College of Nursing	Guideline	029	1.8.7	What is best practice on how often this should be reviewed?	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.
Royal College of Paediatrics and Child Health	Guideline	General	General	The reviewer is happy with this comprehensive guideline.	Thank you for your comment
Royal College of Paediatrics and Child Health	Guideline	General	General	From the perspective of a paediatrician with a special interest in renal disease who sees a number of children with CKD, supported by colleagues from GOSH, it was noted that the statements in the guideline relating to children seem very sensible and in keeping with the reviewers current understanding of best practice.	Thank you for your comment
Royal College of Paediatrics and Child Health	Guideline	005		Paediatrics should use the Schwartz bedside 2009 formula (or even better the new 2021 formula). The paediatric formula should be validated using a UK based cohort.	Thank you for your comment. This is outside the scope of this update.
Royal College of Paediatrics and Child Health	Guideline	006		Section 1.1.4 should include children.	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.
Royal College of Paediatrics	Guideline	006	010 1.1.23	Does the investigation of children with a hearing loss need to be added to this list as the current practise is to	Thank you for your comment. The factors listed on recommendation 1.1.23 were considered clinically

Stakeholder	Document	Page No	Line No	Comments	Developer's response
and Child Health				investigate for renal problems such as Alports disease and Brachio-oto-renal syndrome? References: 1. Characterization of Sensorineural Hearing Loss in Children with Alport Syndrome. Jan Boeckhaus,1,† Nicola Strenzke,2,† Celine Storz,1,2 Oliver Gross,1 2. Guidelines into the investigation of children with mild/moderate and severe hearing loss. BAAP 3. Guidelines for aetiological investigation into progressive permanent childhood hearing impairment January 2018 (cited 14/03/2021) https://www.baap.org.uk/uploads/1/1/9/7/119752718/guideline_progressive_hl_final.pdf 4. Guidelines for aetiological investigation into mild to moderate bilateral permanent childhood hearing impairment April 2015(cited 14/03/2021) https://www.baap.org.uk/uploads/1/1/9/7/119752718/guidelines_for_aetiological_investigation_into_mild_to_moderatebilateral_permanent_childhood_hearing_impairment.pdf 5. Guidelines for aetiological investigation into severe to profound bilateral permanent childhood hearing impairment April 2015 (cited14/03/2021) https://www.baap.org.uk/uploads/1/1/9/7/119752718/guidelines_for_aetiological_investigation_into_severe_to_profoundbilateral_permanent_childhood_hearing_impairment.pdf	important factors by the committee and most of these factors were extrapolated from the evidence for adults. This means that the factors you suggest were not found in the evidence or were not considered clinically important to be added to the list of risk factors for testing CKD in children and young people.
Royal College of Paediatrics	Guideline	007		Section 1.1.9 should include children.	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were

Stakeholder	Document	Page No	Line No	Comments	Developer's response
and Child Health					outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.
Royal College of Paediatrics and Child Health	Guideline	008		Section 1.1.14, it was questioned why are some of these groups restricted to adults? Should all these groups not be adults and children? Age-appropriate creatinine reference ranges should not be used but converted to Paediatric eGFR.	Thank you for your comment. This update reviewed evidence in children and young people. The review of evidence in adults was outside the scope of this update. Therefore, recommendation 1.1.14 was amended to incorporate evidence from children and young people keeping the recommendation already made for adults.
Royal College of Paediatrics and Child Health	Guideline	009		Section 1.1.18 these appropriate age groups should be specified rather than just referring to somewhere else to make the guideline usable by clinicians.	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.
Royal College of Paediatrics and Child Health	Guideline	011		Section 1.1.25 should specify what staging of AKI, does it also include stage 1? It might be excessive for stage I for children, on 1.1.6 of evidence D the studies do not divide to AKI 1 and are all of very low quality. It seems to conflict with: Acute kidney injury: prevention, detection and management NICE guideline [NG148] Published date: 18 December 2019 https://www.nice.org.uk/guidance/ng148/chapter/Recommendations#managing-acute-kidney-injury section 1.5.12 'Do not refer adults, children or young people to a nephrologist or paediatric nephrologist when there is a clear cause for acute kidney injury and the condition is responding promptly to medical management, unless they have a renal transplant. [2013]'.	Thank you for your comment. Most of the studies did not report data on each AKI stage but there was evidence from one study about the risk of developing CKD at 5 years post-hospital discharge in children and young people who had AKI stage 1 during hospitalisation (HR 2.2; 95% CI 1.1 to 4.5; Hessey 2019). Therefore, no changes were made to recommendations on specific AKI staging to monitor for the risk of CKD.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Royal College of Paediatrics and Child Health	Guideline	017		Section 1.4.2 should it just say involve 'patients and families' rather than adults?	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.
Royal College of Paediatrics and Child Health	Guideline	018		Section 1.4.6 again it should be patients with CKD rather than adults, children and young people should not be excluded from the narrative.	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.
Royal College of Paediatrics and Child Health	Guideline	018		Section 1.4.9 'please consult paediatric dietitian', in children it should say that they should receive sufficient protein for growth.	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.
Royal College of Paediatrics and Child Health	Guideline	018		Section 1.4.10 and 1.4.11 again it states adult thus excluding children, young people and families of children and young people.	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.
Royal College of Paediatrics and Child Health	Guideline	019	019 1.5.2	Information on communication, insertion of deaf awareness and the fact that some deaf patients may be extremely reliant on lip reading or may need a BSL interpreter may be helpful. This need does not always readily come to mind.	Thank you for your comment. Recommendation 1.5.1 refers to the NICE guidance on patient experience in adult NHS services which includes a section on communication and recommendation 1.5.4 is about establishing the most effective way of communicating with each person and exploring ways to improve communication including the use of sign language.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Royal College of Paediatrics and Child Health	Guideline	020		Section 1.5.6 could specify what the specialist is, as it could be a general paediatrician for the most basic sieve, then general paediatrician with a nephrology interest or paediatric nephrology specialist for some of them.	Thank you for your comment. The specialist was not specified because the exact referral pathway may differ locally.
Royal College of Paediatrics and Child Health	Guideline	021	1.5.9	It can be with a general paediatrician as well as a GP.	Thank you for your comment. Paediatrician has been added to recommendation 1.5.9.
Royal College of Paediatrics and Child Health	Guideline	024		Section 1.6.12 and 1.6.14 this should apply to all patients.	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.
Royal College of Paediatrics and Child Health	Guideline	025		Section 1.6.18 should apply in children also. Points 1.6.18, 19 and 20 are confusing as it seems to be saying the same thing. Can it be simplified?	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.
Royal College of Paediatrics and Child Health	Guideline	033	1.9.11	The reviewer was not aware of any evidence that suggests adverse outcomes in children where normal haemoglobin levels are targeted. Therefore, what is the rationale for targeting lower levels? Is this based on adult evidence? Children (particularly younger ones) are unique and care needs to be taken when advising sub-normal Hb levels, as they can lose a lot of blood and drop Hb quickly (e.g. lost HD circuit) and then require transfusion, with the adverse effects this gives including sensitisation.	Thank you for your comment. The committee was aware that while the current recommendations are in line with MHRA guidance, which was based on two studies which did not include findings from a paediatric population or from young people. This information has been passed to the MHRA, and we would update the guideline in the future should the MHRA advice change. Furthermore, current NICE recommendations on optimal Hb levels for children and young people were based on the view that this population could in general be expected to benefit

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				It is therefore difficult to understand the rationale for targeting sub-normal Hb levels. In addition the comment about avoiding levels of Hb >120g/L is based on adult evidence, to the reviewers knowledge there is no evidence for adverse events in children, therefore this statement should be changed to reflect the fact that it can only be applied to adults (in an evidence based way).	from similar Hb levels to adults. However, the committee highlighted that coagulation risks in children and young people are very different to those in adults. The committee noted that the current recommendation of Hb levels may be too low for children as in practice higher targets of between 110 -130 g/litre are being used but was unable to draft new recommendations about higher Hb levels because there was no new evidence. The committee agreed that further research in this area was important and highlighted that audit or registry data may also be useful as this would allow data on safety and efficacy to be captured for different Hb targets currently being used in practice. It made a research recommendation to support further research in this area.
Royal College of Paediatrics and Child Health	Guideline	044	1.11.9	In infants with CKD care should be taken to ensure that the higher than normal reference ranges for calcium and phosphate are applied. Also, that phosphate levels are not allowed to drop below the normal range as this risks the development of rickets.	Thank you for your comment. Based on clinical experience, the committee said that in growing children and young people, calcium is often maintained close to, but not above the upper limit of the age-related reference range. This have been added to the rationale.
Royal College of Paediatrics and Child Health	Guideline	046	1.11.17	This should also include an assessment of alkaline phosphatase when considering phosphate levels.	Thank you for your comment. Assessment of alkaline phosphatase has been added to recommendation 1.11.17 (this number has been updated to 1.11.8 after consultation).
Royal College of Physicians and Surgeons of Glasgow	Guideline	General	General	The Royal College of Physicians and Surgeons of Glasgow although based in Glasgow 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	Thank you for your response. Your comments will be considered by NICE where relevant support activity is being planned.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				including Scotland. They should be considered by the relevant Ministers of the devolved governments. The College welcomes this update on guidance on Chronic Kidney disease, its assessment and management. While comments were not requested on text in the shaded areas, it should be pointed out that many clinicians do not recognise that creatinine levels are related to muscle bulk and most levels are measured without patients being advised to avoid meat in the previous 12 hours. (page 6, 6-14) This is an important message.	
Royal College of Physicians and Surgeons of Glasgow	Guideline	009	018	Recommendations 1.1.20 to 1.1.25 There are resource implications to the advice: "Offer testing for CKD using eGFR creatinine and ACR to adults with any of 18 the following risk factors: • diabetes • hypertension • acute kidney injury" etc. Our reviewer considers there needs to be more clarity on when this testing should take place in relation to AKI. If ACR is tested at the time AKI is first identified, there may be false positives because albuminuria is a non-specific feature of febrile illness. There may also be false elevation of ACR in someone who has acutely deteriorating kidney function because the urine creatinine concentration is lower than would be expected at steady state because of deteriorating GFR and urine creatinine concentration is the denominator. If the intention is to screen patients who have had AKI for	Thank you for your comment. With regard to the resource implications of recommendations 1.1.20 to 1.1.25 the committee acknowledged that the new recommendations may increase the number of patients being tested and thus increase the costs. This is due to some patients being lost to follow up and there being no mechanism in primary care to flag previous AKI. However, the costs of the tests themselves are unlikely to significantly increase costs and any patients with CKD who are identified should then follow a cost effective treatment plan.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				evidence of CKD then the utility is likely to be optimal in the convalescent period not at any time after AKI diagnosed.	
Royal College of Physicians and Surgeons of Glasgow	Guideline	010	005 and 021	Multi system disease should include Systemic Sclerosis and its variants. The presence or possibility of renal disease and its monitoring is often omitted.	Thank you for your comment. The committee agreed that an example was sufficient because the list could be too long to include in the recommendation.
Royal College of Physicians and Surgeons of Glasgow	Guideline	011	004	Recommendation 1.1.25 "Monitor adults, children and young people for the development or progression of CKD for at least 3 years after acute kidney injury (longer for people with acute kidney injury stage 3) even if eGFR has returned to baseline." The utility of this is uncertain and I disagree with the committee that "The recommendations are in line with current practice, so no additional resources should be needed." This paper suggests the health gain from this recommendation will be negligible: https://pubmed.ncbi.nlm.nih.gov/28391314/	Thank you for your comment. During the 2014 update of the guideline, the committee referred to a study (Jones et al. 2012) which showed that people making a complete recovery from their AKI episode who had no prior evidence of CKD had a significantly increased incidence of subsequent new onset CKD compared to people without AKI at a median of 2.5 years follow-up. Therefore, in 2014, the committee concluded that even people making a complete recovery to a normal baseline level of kidney function should be followed up for a period of 2 to 3 years after an episode of AKI. During the update of the guideline in 2021, the committee did not have concerns about the costs of monitoring after AKI which would not be a significant addition to current workload because this should not be a change in practice since the 2014 recommendations should be followed.
Royal College of Physicians and Surgeons of Glasgow	Guideline	053	026	While this recommendation has been in the document since 2014, management of gout and hyperuricaemia has changed and this needs to be considered in the main document. Titration of serum urate to urate-lowering drugs is now the norm and needs to be discussed. (UK and European guidance on management of Gout).There is some early evidence that prolonged	Thank you for your comment. The research recommendation on uric acid-lowering agents has been removed.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				untreated hyperuricaemia may lead to significant Coronary Heart Disease.	
Royal College of Physicians of Edinburgh				It is mentioned criteria for ultrasound scan – one should also add that in young patients a history of deafness or eye problems should urge one to consider ultrasound scan in addition to the urine dip stix	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.
Royal College of Physicians of Edinburgh				Monitoring – this may need to be adjusted to accommodate the increase in primary care use of virtual consultations.	Thank you for your comment. We do not specify face to face monitoring. Therefore, this would be up to individual clinicians or local areas discretion.
Royal College of Physicians of Edinburgh				We note the research question on cystatin C based equations but the use of cystatin C based equations is of value in those with and eGFR around 60ml/min for accurate assessment and wonder why this is no longer suggested. We note the committee suggested that this has led to an increased in false negatives as their argument but given no data on this. We would request that clarifications are detailed for clarity. If we compare the recent recommendations from KDIGO for eGFR 45-59 they recommend Cystatin C. "There is a low number needed to test with cystatin C to avoid CKD misclassification. In a meta-analysis of 90750 participants across 16 cohort studies 23% of patients with an eGFR 60-74 based on creatinine had an eGFR <60ml/min based on cystatin C , Indeed among person with an eGFR of 45-49 by creatinine 42% had eGFR >60 by cystatin C. This is supported by data from the UK biokank study of 440526 participants. Shiplack MG NEJM 2013, 3, 369, 932-943 and Ebert N Curr Opin Nephrol Hypert 2020; 29; 591-598.	Thank you for your comment. The committee concluded that there was uncertainty, from the included studies, as to the risk posed by these equations for producing false positive and false negative results, particularly when used in people with lower-stage kidney disease. The committee also highlighted that cystatin-c has not been widely used in clinical practice and that no longer recommending its use would not have an impact on daily practice (where creatinine is used to estimate GFR). We have checked the references you mention in your comment. Our protocol restricted study design to diagnostic cross-sectional studies. Diagnostic cross-sectional studies are the most robust design for assessing diagnostic test accuracy, which is why we included inly those. None of the UK biobank studies were diagnostic cross-sectional studies, and so they were not included in the evidence review. The committee made a research recommendation to gather more evidence on the accuracy of cystatin C-based equations to estimate GFR as a measurement

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					of kidney function in adults, children and young people.
Royal College of Physicians of Edinburgh				We welcome the revised guidance and algorithm on use of phosphate binders in clinical practice	Thank you for your comment.
Royal College of Physicians of Edinburgh				We did not see any recommendation to the use of statins in CKD for secondary CV protection. This is important given the data from the SHARP study.	Thank you for your comment. This was outside the scope of this update, however, please see recommendation 1.6.23 about the use of statins for cardiovascular protection in people with CKD.
Royal College of Physicians of Edinburgh			1.125	The need to monitor AKI after "complete" biochemical recovery for 3 years will have a significant impact on workload and this needs to be considered carefully. Fellows are unclear on the evidence base for this recommendation.	Thank you for your comment. During the 2014 update of the guideline, the committee referred to a study (Jones et al. 2012) which showed that people making a complete recovery from their AKI episode who had no prior evidence of CKD had a significantly increased incidence of subsequent new onset CKD compared to people without AKI at a median of 2.5 years follow-up. Therefore, in 2014, the committee concluded that even people making a complete recovery to a normal baseline level of kidney function should be followed up for a period of 2 to 3 years after an episode of AKI. During the update of the guideline in 2021, the committee did not have concerns about the costs of monitoring after AKI which would not be a significant addition to current workload because this recommendation should already be happening in current practice, since it has been in place since 2014.
Royal College of Physicians of Edinburgh			1.38	Chronic use of PPI should be considered as a risk factor for potential renal progression and the possibility of acute interstitial nephritis at any time point.	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					Therefore, we cannot make substantive changes to these recommendations.
Royal College of Physicians of Edinburgh			1.47	Dietary Advice: I would change the language to stress a general advice to minimise salt intake or indeed avoid salt and in particular not to use LoSalt. Similar to KDIGO an aspiration to aim for a salt reduction to <2g/day would be useful.	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.
Royal College of Physicians of Edinburgh			1.66	SGLT-2 use should be extended to non-diabetic CKD based on DAPA-CKD – we realise that the SMPC has yet to change but this is an important advance and should be rapidly adopted in primary care. We note the committee considered this and would not have the benefit of the data from the recent DAPA-CKD study and as the committee indicated this is a fast moving field in which it would appear use of these drugs are potentially a game changer in reducing renal progression, cardiovascular events and mortality in this high risk population.	Thank you for your comment. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. NICE is also currently undertaking a technology appraisal of dapagliflozin for treating chronic kidney disease which will include the DAPA-CKD trial. Therefore, data from DAPA-CKD has been removed from this update. See https://www.nice.org.uk/guidance/indevelopment/gid-ta10808 for details. The NICE CKD guideline will cross refer to this technology appraisal appraising dapagliflozin when it is published.
Royal College of Physicians of Edinburgh			1.6.1	Fellows would suggest it would be better and more effective to simplify the recommendations on target blood pressure to a single target of <130/80 mmHg for all CKD, irrespective of proteinuria. We note the rational on page 60 but the increasing evidence suggest that the lower the blood pressure the better the outcome, acknowledging that one should be cautious in the frail elderly patients. Moe importantly simplicity is key to successful implementation and complaince.	Thank you for your comment. The committee highlighted the importance of taking into account people's characteristics to individualise blood pressure targets and that having options on the targets would help them to make decisions in clinical practice. They noted for some patients, a low blood pressure target could have an unacceptably high treatment burden, in terms of extra medication and side effects, and so targets should be considered

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					individually. Therefore, the committee did not think it was appropriate to change the recommendation.
Royal College of Physicians of Edinburgh			1.6.12	Need to add more information on use of K binders which are now NICE approved.	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations, but we have added a new recommendation referring to the NICE technology appraisals for treating hyperkalaemia (sodium zirconium cyclosilicate and patiromer). We have also passed your issue on to the surveillance team who will explore whether recommendation 1.6.12 (this number has been updated to 1.6.13 after consultation) needs updating in the future.
Royal College of Physicians of Edinburgh			1.6.13	Needs implementing	Thank you for your response. Your comments will be considered by NICE where relevant support activity is being planned.
Royal College of Physicians of Edinburgh			1.10.7	For PRCA – add in exclude hyperparathyroidism and consider discontinuation of ACEi if on this medication depending on the benefits	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.
Royal College of Physicians of Edinburgh			1.1.2.8	We would recommend based on the landmark studies that bicarbonate supplementation should be considered when the bicarbonate value is less than 22mmol/L. This is also the case in the updated the KDIGO guidelines. It is not clear where the value of 20 mmol/l came form in the current recommendations.	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Royal College of Physicians of Edinburgh	Guideline	General		There needs to be a statement of the importance of all CKD patients receiving both the flu vaccine and COVID-19 vaccine, as these are high risk and in many cases extremely vulnerable groups. In addition, patients should receive the pneumococcal vaccine and Hepatitis B vaccine.	Thank you for your comment. Vaccinations for people with CKD are outside the scope of this update. The NICE guideline on vaccine uptake in the general population is being developed (https://www.nice.org.uk/guidance/indevelopment/gid-ng10139). The guideline will cover interventions, barriers and facilitators for the identification and recording of a person's vaccination eligibility and status and for increasing the uptake of routine vaccines.
Royal College of Physicians of Edinburgh	Guideline	007	1.1.12	The Advice to use ACR to diagnose proteinuria and not use reagent strips, the Advice that ACR of 3 or more is 'clinically important' and advice that ACR of 3-70 mg/mmol requires a confirmatory EMU for repeat ACR make no allowance for the patient's context. An ACR of 3 or more, may be clinically important – however Fellows suggest that for the majority of patients, it will not be – for example patients with significant comorbidities, frailty, extensive vascular disease and other life limiting conditions. The recommendation to use uACR rather than uPCR will create additional cost to health services and Fellows are not convinced of the benefit. The advice not to use reagent strips is again questioned as to whether that is a pragmatic approach given the demands on primary care, labs and added cost.	Thank you for your comments. We have added more details to the committee's discussion and interpretation of the evidence about ACR variation (see evidence review B: Accuracy of albumin:creatinine ratio versus protein:creatinine ratio measurements to quantify proteinuria in children and young people with CKD). The committee highlighted that people's circumstances should be considered when interpreting ACR levels and that ACR may vary by time of day. This is why confirmation should be done using a subsequent early morning sample when ACR is between 3 mg/mmol and 70 mg/mmol in the initial detection of proteinuria. The committee also agreed that evidence was not reviewed for the use of reagent strips in adults. Therefore, we have reinstated (recommendation removed before this consultation in January 2021) the recommendation for adults that was made in 2008 to specify that the use of reagent strips to identify proteinuria in adults should be limited to tests being capable of measuring albumin at low concentrations and expressing the result as an

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					ACR. During the update of the guideline in 2021, the committee did not have concerns about the costs of using ACR which would not be a significant addition to current workload because this recommendation should already be happening in current practice, since it has been in place since 2014.
Royal College of Physicians of Edinburgh	Guideline	011	1.2	Need to consider SGLT2 in the algorithm of management of delaying renal progression. This is a rapidly advancing area which NICE need to be aware of and implement rapidly.	Thank you for your comment. SGLT2 inhibitors have been recommended under section 1.6 Pharmacotherapy and as part of the algorithm to manage proteinuria.
Royal College of Physicians of Edinburgh	Guideline	013 - 014	1.3.2	Section 1.3.2 Table 2 sets an expectation of a 'minimum number' of monitoring clinics depending on eGFR and uACR. Again this recommendation makes no allowance for the context of the patient, and seems to offer no latitude for shared decision making about benefits/harms and burdens of monitoring. There will be many patients who would not gain value from this approach. Later para 1.5.9 addresses importance of SDM, but that seems to be in relation to other aspects of care. Discussion about when to start preparation for renal replacement therapy is limited, but is referenced NG 107, and covered there.	Thank you for your comment. Recommendation 1.3.1 includes the agreement of the frequency of monitoring with adults, children and young people who have CKD and with their family members or carers, as appropriate.
Royal College of Physicians of Edinburgh	Guideline	053	026	Uric acid lowering therapy has now been shown to be none effective in delaying renal progression – see negative trial in NEJM which studied 363 patients with stage 3-4 CKD and no history of gout given allopurinol 100-300mg or placebo over 1.5 years (NEJM 2020, 382; 2504-2513. And also the PERL study in 530 participants with DM and renal disease and a high uric acid level – this trial showed a 3ml/min loss in GFR vs 2.5ml/min	Thank you for your comment. The research recommendation on uric acid-lowering agents has been removed.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				loss per year (not significant). In addition, there was no significant difference in secondary outcomes (NEJM 2020; 382, 2493-2503.). Although one could argue that these trials are not generalisable and thus one could say further studies are warranted as a minimum to tease out the correct answer in the future.	
South Asian Health Foundation	General comment			The committee have asked to consider the impact of Covid -19 on the implementation of the guideline. We are of the view that there is at present no convincing evidence to link the use of ACE inhibitors or ARBs and the risk of Covid infection. We therefore feel these agents can continue to be prescribed. In relation to the use of SGLT2i we would recommend temporary discontinuation in patients hospitalised with severe Covid -19 infection until full clinical recovery. It would also be good to emphasize sick day rules for patients receiving SGLT2i.	Thank you for your comment. The COVID-19 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. People who are receiving SGLT2 inhibitors would be expected to be 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

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					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. We have not added additional information about sick day rules for taking SGLT2 inhibitors, as this issue is covered in the Summary of product characteristics for individual medicines (e.g. https://www.medicines.org.uk/emc/medicine/28400#gref) and applies to all people taking these treatments not just those who have CKD and diabetes.
South Asian Health Foundation	General Comment			In the proposed recommendations we did not find any circumstances that would limit access or conditions that apply to specific ethnic groups. We are also not aware any adverse events that are more common in any ethnic group. We therefore feel there are no restrictions to be made with regards to the use of SGLT2 inhibitors in any ethnic group. However, people of south Asian ethnicity with diabetes are at a disproportionately higher risk of cardiovascular disease as well as chronic kidney disease compared to those of white European ethnicity. It is therefore useful for the NICE recommendations to emphasise the benefits of using these agents in preference to other glucose lowering therapies that do not have similar degree of cardiovascular or renal protection in people with south Asian ethnicity .	Thank you for your comment. The use of glucose lowering therapies is being updated as part of the update of the NICE guidance on type 2 diabetes in adults: management. The update covers adults with type 2 diabetes and specific consideration will be given to people in specific ethnic groups. In addition, NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. This update will also consider whether and specific consideration will be given to people in particular ethnic groups.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Reference: 1: Hanif W, Ali SN, Bellary S, Patel V, Farooqi A, Karamat MA, Saeed M, Sivaprasad S, Patel K, Khunti K. Pharmacological management of South Asians with type 2 diabetes: Consensus recommendations from the South Asian Health Foundation. Diabet Med. 2020 Dec 10:e14497.	
South Asian Health Foundation	General Comment			It is not uncommon for patients with type 2 diabetes to be on a combination of ACE/ARB and a diuretic. The use of SGLT2i in these patients may exacerbate volume depletion. Some guidance around the optimisation and monitoring in patients on this combination would be useful.	Thank you for your comment. We have included a clarification to the rationale stating that volume depletion might be a particular issue for frail people which may result in falls, and that clinicians should take this into account on an individual basis.
South Asian Health Foundation	Guideline	007	021	The guidance describes the tests to be used to detect proteinuria. However, we feel the need for regular assessment and the frequency for undertaking these tests in high risk patients should be highlighted	Thank you for your comment. There is guidance on the frequency of ACR in recommendation 1.3.1 which recommends that 'If an adult, child or young person has CKD, or is at risk of it, agree the frequency of monitoring (eGFRcreatinine and ACR) with them (and their family members or carers, as appropriate), bearing in mind that CKD is not progressive in many people'.
South Asian Health Foundation	Guideline	009	018	Please can you recommend the frequency at which these need to be undertaken	Thank you for your comment. We added to the rationale that the frequency of testing for CKD should be individualised according to the person's circumstances.
South Asian Health Foundation	Guideline	021	001	The NHS long term plan cites use of virtual MDTs as practised in East London as an example of best practice. If patients do not need to see a specialist, could this option be considered and made clearer in the guideline?	Thank you for your comment. This is not within the remit of this guideline.
South Asian Health Foundation	Guideline	022	023	In the section 1.6.6 pharmacotherapy for proteinuria, the guideline recommends offering SGLT2 inhibitors for patients with type 2 diabetes. Although it is	Thank you for your comment. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				understandable that the proposed recommendations reflect the patient cohorts of large randomised control trials that included patients with low eGFR and significant proteinuria, we feel an important opportunity is being missed by not including those with moderate renal impairment (eGFR 60-30ml/min) and microalbuminuria (ACR 3-30mg/mmol). Currently, patients who have eGFR greater than 60ml per minute and have no proteinuria may still be treated with SGLT2 inhibitors (on glucose lowering indication). The proposed guideline now includes those with a eGFR of less than 60 ml per minute but have significant proteinuria albeit for reasons of reno protection but leaves out those with eGFR less than 60 and ACR < 30mg/mmol. Given that patients with microalbuminuria represent a cohort that have high cardiovascular risk and risk of progressive renal disease, we feel these patients must also be considered for treatment with SGLT2i. It will also make the algorithm simpler as many patients who have an ACR <30mg/mmol will otherwise have to be discontinued SGLT2i if eGFR falls below 45ml only to be re-started when the ACR increases to above 30. This approach will not only disadvantage patients but will be a missed opportunity to tackle the cardiovascular and renal risk in these patients.	recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. NICE is also currently undertaking a technology appraisal of dapagliflozin for treating chronic kidney disease which will include the DAPA-CKD trial. Therefore, data from DAPA-CKD has been removed from this update. See https://www.nice.org.uk/guidance/indevelopment/gid-ta10808 for details. The NICE CKD guideline will cross refer to this technology appraisal appraising dapagliflozin when it is published.
South Asian Health Foundation	Guideline	022	023	Canagliflozin is available in 100mg and 300mg. The guideline should clarify the correct dose i.e. 100mg daily to be used when indicated for reno protection.	Thank you for your comment. Clinicians should prescribe in accordance with national prescribing guidelines and the medicines license.
South Asian Health Foundation	Guideline	023	001 - 003	There is comment 'Monitor for volume depletion and eGFR decline'. It would be useful to clarify whythese should be monitored and what should be done if there is indeed volume contraction.	Thank you for your comment. We have included a clarification to the rationale stating that eGFR monitoring should depend on people's circumstances and on the BNF advice of monitoring requirements for people using SGLT2 inhibitors.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
South Asian Health Foundation	Guideline	023	007	Section 1.6.8 . The proposed guideline and the accompanying treatment algorithm recommend the use of SGLT2i patients with type 2 diabetes and proteinuria > 30mg/mmol in accordance with most of the clinical trial data. However, we are unsure why the use of these agents with non -diabetic patients with CKD has not been recommended. While we appreciate that the algorithm does take into consideration the current evidence with regards to the use of SGLT2i from recently published renal outcome trials (CREDENCE, DAPA CKD trials), we would like to draw attention to the data from the DAPA CKD study which showed non-diabetic patients had similar benefits to those without diabetes. Considering the available evidence, we feel the benefit of SGLT2i must be offered to non-diabetic patients with CKD.	Thank you for your comment. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. NICE is also currently undertaking a technology appraisal of dapagliflozin for treating chronic kidney disease which will include the DAPA-CKD trial. Therefore, data from DAPA-CKD has been removed from this update. See https://www.nice.org.uk/guidance/indevelopment/gid-ta10808 for details. The NICE CKD guideline will cross refer to this technology appraisal appraising dapagliflozin when it is published.
St George's Healthcare – London Kidney Network	Comments form	Q1	Q1	**Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why.** Endorsement of SGLT2i with diabetic and potentially, non-diabetic CKD with proteinuria will be an important implementation challenge to optimise. ICS commissioning decisions and local prescribing guidance for primary care will need to reflect the updated evidence available in order to realise the clinical and financial benefits of this class of medications for people who have shown to have significantly improved outcomes. Additional challenge will be in ensuring that non-diabetologists in secondary care are confident to optimally prescribe.	Thank you for your response. Your comments will be considered by NICE where relevant support activity is being planned.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
St George's Healthcare – London Kidney Network	Comments form	Q2	Q2	**Would implementation of any of the draft recommendations have significant cost implications?** Expanded prescribing of SGLT2i will incur a cost, but significant long term savings are anticipated, associated with decreased risk of kidney failure, decreased risk of death from CV causes or hospitalisation for HF.	Thank you for your response. Your comments will be considered by NICE where relevant support activity is being planned.
St George's Healthcare – London Kidney Network	Comments form	Q3	Q3	**What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or examples of good practice.)** With respect to SGLT2i: Stakeholders have indicated that NICE support in the form of the CKD Guidelines will facilitate prescribing in in primary care settings, and for non-diabetologists in secondary care. Through discussions with stakeholders across London, we understand that additional support in the form of prescribing guidance and education on the appropriate initiation, monitoring and cessation of SGLT2 inhibitors will be essential for all prescribing clinicians, in both primary and secondary care. As a network we intend to provide this support and would be happy to share examples of good practice and outcomes with our national peers.	Thank you for your response. We will pass this information to our local practice collection team. More information on local practice can be found here (https://www.nice.org.uk/about/what-we-do/into-practice/shared-learning-case-studie).
St George's Healthcare – London Kidney Network	Evidence Review A	General	General	This is an important opportunity to take action to improve kidney outcomes for people of Black ethnicities in the UK. Ongoing use of the eGFR adjustment factor is likely to contribute to ethnicity associated CKD health	Thank you for your comments. Recommendation 1.1.3 has been removed from the guideline. The rationale section includes further advice stating that individualised judgement should be used when interpreting eGFR in people from UK black, Asian

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				inequalities. Until further relevant data are available, we should not be continuing to extrapolate findings from very different study cohorts to guide clinical practice in the UK. Rationale: • Based on the rationale and impact section we do not feel that the literature review methodology has facilitated a comprehensive oversight of the current literature relevant to the UK. For example, 20 out of the 27 studies were from China. There are three important studies including people of black ethnicity demonstrating that the adjustment factor substantially overestimates GFR compared to measured GFR, which have been excluded as the 'Outcome does not match those specified in the protocol' - (Arlet et al / Bukabau et al / Wyatt et al) and another excluded due to its retrospective design (Moodley et al). There are four further relevant studies which have not been mentioned in the literature review (Agoons et al, Madala et al, Seape et al and Flamant et al) which similarly suggest that use of the adjustment factor is inaccurate in Black non-African American populations. There are considerable challenges in conducting robust research in black communities for both low- and high-income countries. The amount and level of evidence is likely to be lower but should not be prohibit appropriate interpretation of existing literature.	and minority ethnic groups and in adults with extremes of muscle mass. The committee agreed to make recommendations for research on appropriate eGFR equations for black, Asian and minority ethnic groups (adults, children and young people) in the UK. They agreed that factors other than ethnicity should also be explored as biomarkers.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				• In the UK, people of African ancestry are likely to include more people from North, East and South African with lower muscle mass than people in the USA. Therefore, studies from other regions of Africa should be considered in the NICE review. Current evidence supporting use of adjustment factors is derived predominantly from African Americans (MDRD - 197 African Americans (8% of cohort); CKD EPI - 1737 African Americans (32% of cohort)) but more contemporaneous data from over 1,300 black people in Africa and Europe, i.e., more relevant to the UK, consistently suggest that eGFR without adjustment is more accurate in these populations. • A recent study has been undertaken exploring accuracy of eGFR equations in a black UK cohort. The paper is currently under review for publication and was an oral presentation at the American Society of Nephrology in 2020. The authors would be pleased to share their work with the panel. They demonstrated that a substantial number of people of African ancestry in the UK could have delayed work-up for RRT and transplantation if the use of adjustment factors continues. In addition, CKD Stage 3 is likely to be underdiagnosed in this population, leading to missed opportunities for preventative strategies. Despite the adjustment factors being derived from predominantly African American cohorts, there is now a	

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				US National Kidney Federation and American Society of Nephrology Taskforce to explore how to change practice. Several world leading institutions in the USA - Massachusetts General Hospital, University of Washington, Brigham and Women's Hospital, Zuckerberg San Francisco General Hospital, Beth Israel Deaconess Medical Center - no longer use the adjustment factor due to inaccuracy leading to a detrimental impact on care.	
St George's Healthcare – London Kidney Network	Guideline	005	010	We suggest that the panel adapt the statement to include the text in bold – "eGFRcreatinine may be less reliable in certain situations (for example, acute kidney injury, pregnancy, oedematous states, muscle wasting disorders and in adults who are malnourished **or those with higher muscle mass**)" to assist clinicians in interpreting eGFR estimates.	Thank you for your comment. We have added your suggestion to the recommendation.
St George's Healthcare – London Kidney Network	Guideline	006	003	We urge that the directive to use an adjustment factor when using eGFR CKD EPI creatinine equation in adults of African-Caribbean or African family origin is removed.	Thank you for your comments. Recommendation 1.1.3 has been removed from the guideline. The rationale section includes further advice stating that individualised judgement should be used when interpreting eGFR in people from UK black, Asian and minority ethnic groups and in adults with extremes of muscle mass. The committee agreed to make recommendations for research on appropriate eGFR equations for black, Asian and minority ethnic groups (adults, children and young people) in the UK. They agreed that factors other than ethnicity should also be explored as biomarkers.
St George's Healthcare – London Kidney Network	Guideline	007	General	It would be helpful to have standardised nomenclature throughout the document with respect to eGFR- there is variation from eGFR to GFR; we presume throughout it	Thank you for your comment. Most of the guideline refers to eGFR but there are some recommendations referring to GFR. The section of 'Terms used in this guideline' has a definition of the GFR and eGFR

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				should be eGFR that is being referred to as it is a clinical guideline.	abbreviations. Therefore, no changes were made regarding the use of GFR or eGFR abbreviations.
St George's Healthcare – London Kidney Network	Guideline	007	020	"Do not use reagent strips to identify proteinuria" Does this statement also apply to semi-quantitative ACR testing in adults or just children? There is concern that the children and young adult data review may have been extrapolated to adults - when there are robust data to support semi-quantitative assessment for screening.	Thank you for your comment. The committee agreed that evidence was not reviewed for the use of reagent strips in adults. Therefore, we have reinstated (recommendation removed before this consultation in January 2021) the recommendation for adults that was made in 2008 to specify that the use of reagent strips to identify proteinuria in adults should be limited to tests being capable of measuring albumin at low concentrations and expressing the result as an ACR.
St George's Healthcare – London Kidney Network	Guideline	022	022	We ask that the committee reconsider the statement: • *an SGLT2 inhibitor, in addition to an ACE inhibitor or an ARB, if they have type 2 diabetes, an ACR of 30 mg/mmol or more and meet the criteria in the marketing authorisation (including relevant eGFR thresholds); monitor for volume depletion and eGFR decline.* We urge that the statement is replaced with: Offer: • an SGLT2 inhibitor, in addition to an ACE inhibitor or an ARB, if they have type 2 diabetes, an ACR of 30 mg/mmol or more and meet the criteria in the marketing authorisation (including relevant eGFR thresholds). • In patients with Type 2 diabetes and adequate renal function (eGFR >45ml/min) the addition of	Thank you for your comments. We have included a clarification to the rationale stating that eGFR monitoring should depend on people's circumstances and on the BNF advice of monitoring requirements for people using SGLT2 inhibitors. We have also added MHRA alerts on canagliflozin and SGLT2 inhibitors under recommendation 1.6.7.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				an SGLT2i may increase the risk of hypoglycaemia if used concurrently with insulin, sulphonureas or glinides. Adjustment of the other diabetic therapies may be required to mitigate this risk. • It is not necessary to monitor eGFR more than the standard of care for diabetic patients (typically 3 monthly) as this is anticipated and is not associated with harm. • Caution should be taken when prescribing SGLT2i for people with risk factors for diabetic ketoacidosis (DKA), that is, individuals with previous DKA, pancreatic cancer/pancreatitis and patients who rapidly progressed to insulin treatment within 1 year of diagnosis. If in doubt consider referral to specialist diabetes team for guidance. • Clinicians should test for *capillary* ketones in anyone with suspected DKA (even if euglycaemic). Discontinue use if DKA is confirmed. Rationale: All published studies show no evidence of harm or increased adverse events in subjects with a reduction in eGFR >10% v those without. In those treated with SGLT2i, AKI risk was in fact decreased. Monitoring for eGFR decline following initiation of SGLT2i is unhelpful as decline is anticipated and not associated with harm. RA/ABCD guidance supports this assertion. We are	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				concerned specifically with placing additional barriers to prescribing in primary care, which would impact the take-up of this beneficial treatment. With respect to people at risk of DKA, we feel there should be more clarity provided on who poses the greatest risk of developing DKA with flozin use. Additionally, urine ketones (acetoacetate) may be less sensitive at detecting DKA, particularly in the presence of an SGLT2i due to increased tubular ketone reabsorption.	
St George's Healthcare – London Kidney Network	Guideline	023	007 - 012	For adults with CKD but without diabetes: We urge the guideline panel to include the following recommendation, after the guidance for ACEi and ARB therapy after line 12. • Offer Dapagliflozin if eGFR is ≥ 25ml/min and ≤75ml/min *and* ACR is >20mg/mmol. Offer this in addition to optimal ACEi or ARB therapy (where RAAS blockade agent is tolerated). Rationale: We are encouraged by significant study outcomes in this area, with reference to the recently published DAPA-CKD trial. We feel assured by the data that Dapagliflozin has proven to be of equal benefit in non-diabetic and diabetic CKD populations, with respect to the following clinically important endpoints: • Decreased risk of kidney failure • Decreased risk of death from CV causes or hospitalisation for HF • Prolonged survival	Thank you for your comment. NICE is currently undertaking a technology appraisal of dapagliflozin for treating chronic kidney disease which will include the DAPA-CKD trial. Therefore, data from DAPA-CKD has been removed from this update. See https://www.nice.org.uk/guidance/indevelopment/gid-ta10808 for details. The NICE CKD guideline will cross refer to this technology appraisal appraising dapagliflozin when it is published. NICE are also reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				We assert that Dapagliflozin has demonstrated a good safety profile and is globally well tolerated, even at the lower end of the studied eGFR range (25-30ml/min). We understand that economic modelling is likely to support projected health system savings associated with a reduction of patients reaching RRT. Additional health system savings are forecast related to cardiovascular morbidity. These benefits are in addition to those seen in patients on ACEi/ARBs only. We suggest that excluding the non-diabetic CKD patients from the benefits of SGLT2i in the NICE guidelines will limit the confidence of integrated care systems to include them in local prescribing protocols. This has considerable implications for people living with CKD and proteinuria, at risk of eGFR decline. With the next review of these guidelines unlikely to be earlier than 3-5 years, failure to include this recommendation represents a missed opportunity for significantly improved outcomes for this cohort.	
St George's Healthcare – London Kidney Network	Guideline	024	018 - 019	We understand that the content of this guideline is not in the scope of this review. We do ask that the panel consider consolidating the key guidance below from NICE TA599 (Sodium Zirconium Cyclosilicate) within the NICE Guideline for CKD, to ensure clinicians caring for people with CKD are aware of the recommendations around the use of potassium binding agents. Sodium zirconium cyclosilicate is recommended as an option for treating hyperkalaemia in adults with CKD 3b-5 only if used:	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations, but we have added a new recommendation referring to the NICE technology appraisals for treating hyperkalaemia with potassium binders (sodium zirconium cyclosilicate and patiromer). We have also passed your issue on to the NICE surveillance team who will explore whether recommendation 1.6.15 (this number has been

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				• in emergency care for acute life-threatening hyperkalaemia alongside standard care *or* • in outpatient care for people with persistent hyperkalaemia and chronic kidney disease stage 3b to 5 or heart failure, if they: – have a confirmed serum potassium level of at least 6.0 mmol/litre – are not taking an optimised dosage of renin-angiotensin-aldosterone system (RAAS) inhibitor because of hyperkalaemia and – are not on dialysis.	updated to 1.6.16 after consultation) needs updating in the future.
St George's Healthcare – London Kidney Network	Guideline	026	009 - 011	We are aware that this section is proposed to be out of scope for this review; however we recommend this section of the guideline is updated due to *changes in available safety data*. Apixaban can now be used to an GFR of 15ml/min. eGFR MDRD equation is also not recommended to be used to estimate renal function when dosing DOACs such as Apixaban. This is following an MHRA drug safety update. CrCl (Cockroft & Gault) is recommended. See: Direct-Acting oral anticoagulants (DOACs): reminder of bleeding risk, including availability of reversal agents (via www.gov.uk)	Thank you for your comment. We have reviewed the drug safety update and do not believe that the update suggests that the current recommendations in this area are unsafe. The current recommendation refers to an eGFR of 30-50 ml/min/1.73 m^2 and does not specify how eGFR should be estimated. Therefore, we have not made changes to this recommendation as it was not part of this guideline update and evidence was not reviewed in this area.
St George's Healthcare – London Kidney Network	Guideline	034	005	We are aware that this section is proposed to be out of scope for this review, however we recommend considering the inclusion of the following sentence after line 5: Clear documentation needed in patient's records if responsible clinician has chosen to accept the lower Hb levels so that continuity of care is maintained in all clinical settings.	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
St George's Healthcare – London Kidney Network	Guideline	045	005 - 006	Can the panel clarify if they include Ca acetate/Mg binder (Osvaren) in the first line recommendation of Ca acetate? We believe this should be included as one of the first line choices available to patients.	Thank you for your comment. The committee discussed evidence on the combination of calcium acetate and magnesium carbonate which showed that results could not differentiate between this combination and the rest of interventions for serum phosphate levels at 3 months or at 6 months or for serum calcium levels at 3 months or 6 months or for discontinuation due to adverse events. Longer term outcomes and adverse events were not reported for the combination of calcium acetate and magnesium carbonate. The committee agreed to replace magnesium carbonate with calcium acetate plus magnesium carbonate in a research recommendation on its effectiveness and safety in adults with stage 5 CKD who are on dialysis (minimum 12 months follow-up).
St George's Healthcare – London Kidney Network	Guideline	047	002	Considering that Mimpara is now off patent, would the panel consider including guidance on the appropriate use of calcimimetics where hyperparathyroidism is worsening despite intervention with vitamin D and/or phosphate binders? We suggest that this is considered even outside of its existing license. Or could the panel take this into consideration for incorporation into the CKD MBD guidance or NICE TA117 on Cinacalcet?	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.
Stanningley Pharma Limited	Algorithm PO4 Binder	General	All	Though the importance of specialist renal dietetic support is highlighted in the draft guidelines (p40.L5,1.11.1, p43.L23.1.11.5, p68 L10) the algorithm shows as the first step a move to using a binder. In practice it is more likely that the first step would be to provide specialist renal dietetic support. This could start with dietary advice to help reduce PO4 intake and then potentially move on to support with specialist	Thank you for your comment. The algorithm is specific for the use of phosphate binders this is why the first step is the use of a binder.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				supplements which may be specifically formulated for the needs of renal patients, i.e. high protein, low volume, low PO4 and low K+. It may be helpful to stress that this specialist renal dietetic support should be both the first step and ongoing.	
Stanningley Pharma Limited	Guideline	068	006	The comment regarding taste and patient choice is helpful as it will potentially lead to patients being offered the treatment that they are most likely to be concordant with.	Thank you for your comment.
The Renal Association	Evidence Review A	General	General	This is an important opportunity to take action to improve kidney outcomes for people of Black ethnicities in the UK. Ongoing use of the eGFR adjustment factor is likely to contribute to ethnicity associated CKD health inequalities. Until further relevant data are available, we should not be continuing to extrapolate findings from very different study cohorts to guide clinical practice in the UK. Rationale: • Based on the rationale and impact section we do not feel that the literature review methodology has facilitated a comprehensive oversight of the current literature relevant to the UK. For example, 20 out of the 27 studies were from China. There are three important studies including people of black ethnicity demonstrating that the adjustment factor substantially overestimates GFR compared to measured GFR, which have been excluded as the 'Outcome does not match those specified in the	Thank you for your comments. Recommendation 1.1.3 has been removed from the guideline. The rationale section includes further advice stating that individualised judgement should be used when interpreting eGFR in people from UK black, Asian and minority ethnic groups and in adults with extremes of muscle mass. The committee agreed to make recommendations for research on appropriate eGFR equations for black, Asian and minority ethnic groups (adults, children and young people) in the UK. They agreed that factors other than ethnicity should also be explored as biomarkers.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				protocol' - (Arlet et al / Bukabau et al / Wyatt et al) and another excluded due to its retrospective design (Moodley et al). There are four further relevant studies which have not been mentioned in the literature review (Agoons et al, Madala et al, Seape et al and Flamant et al) which similarly suggest that use of the adjustment factor is inaccurate in Black non-African American populations. There are considerable challenges in conducting robust research in black communities for both low- and high-income countries. The amount and level of evidence is likely to be lower but should not be prohibit appropriate interpretation of existing literature. • In the UK, people of African ancestry are likely to include more people from North, East and South African with lower muscle mass than people in the USA. Therefore, studies from other regions of Africa should be considered in the NICE review. Current evidence supporting use of adjustment factors is derived predominantly from African Americans (MDRD - 197 African Americans (8% of cohort); CKD EPI - 1737 African Americans (32% of cohort)) but more contemporaneous data from over 1,300 black people in Africa and Europe, i.e., more relevant to the UK, consistently suggest that eGFR without adjustment is more accurate in these populations. • A recent study has been undertaken exploring accuracy of eGFR equations in a black UK cohort. The paper is currently under review for	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				publication and was an oral presentation at the American Society of Nephrology in 2020. The authors would be pleased to share their work with the panel. They demonstrated that a substantial number of people of African ancestry in the UK could have delayed work-up for RRT and transplantation if the use of adjustment factors continues. In addition, CKD Stage 3 is likely to be underdiagnosed in this population, leading to missed opportunities for preventative strategies. Despite the adjustment factors being derived from predominantly African American cohorts, there is now a US National Kidney Federation and American Society of Nephrology Taskforce to explore how to change practice. Several world leading institutions in the USA - Massachusetts General Hospital, University of Washington, Brigham and Women's Hospital, Zuckerberg San Francisco General Hospital, Beth Israel Deaconess Medical Center - no longer use the adjustment factor due to inaccuracy leading to a detrimental impact on care.	
The Renal Association	Further Recommendations for Research	052	012 - 015	Managing proteinuria. We agree that direct comparisons between ACEi and ARB treatment for patients with proteinuria are lacking but do not agree that conducting trials to evaluate this would be of substantial benefit to patients. There is evidence of efficacy for both ACEi and ARB. It would require very large and expensive trials to investigate this issue and we are not convinced that this would be good use of limited research resources.	Thank you for your comment. The research recommendation on managing proteinuria has been removed.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
The Renal Association	Guideline	General	General	There is no mention in the pharmacotherapy section on the indication for use of potassium binders. We feel this is a missed opportunity to give guidance on potassium binders, especially if the next iteration of this guideline takes as long to emerge as this one has (six years).	Thank you for your comment. We have added a new recommendation referring to the NICE technology appraisals for treating hyperkalaemia with potassium binders (sodium zirconium cyclosilicate and patiromer).
The Renal Association	Guideline	General	General	There is no mention in the pharmacotherapy section on the use of finerenone, demonstrated to improve outcomes for T2DM with eGFR 25 - 75 and ACR > 34 (NEJM Dec 3 2020)	Thank you for your comment. NICE is currently undertaking a technology appraisal of finerenone for treating chronic kidney disease in people with type 2 diabetes. See https://www.nice.org.uk/guidance/indevelopment/gid-ta10820 for details. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
The Renal Association	Guideline	General	General	It would be helpful to have standardised nomenclature throughout the document with respect to eGFR- there is variation from eGFR to GFR; we presume throughout it should be eGFR that is being referred to as it is a clinical guideline.	Thank you for your comment. Most of the guideline refers to eGFR but there are some recommendations referring to GFR. The section of 'Terms used in this guideline' has a definition of the GFR and eGFR abbreviations. Therefore, no changes were made regarding the use of GFR or eGFR abbreviations.
The Renal Association	Guideline	005	010	We suggest that the panel adapt the statement to include the text in bold – "eGFRcreatinine may be less reliable in certain situations (for example, acute kidney injury, pregnancy, oedematous states, muscle wasting disorders and in adults who are malnourished **or those with higher muscle mass**)" to assist clinicians in interpreting eGFR estimates.	Thank you for your comment. We have added your suggestion to the recommendation.
The Renal Association	Guideline	006	003	We urge that the directive to use an adjustment factor when using eGFR CKD EPI creatinine equation in adults of African-Caribbean or African family origin is removed. Please see detailed rationale below in comments on Evidence Review A.	Thank you for your comments. Recommendation 1.1.3 has been removed from the guideline. The rationale section includes further advice stating that individualised judgement should be used when interpreting eGFR in people from UK black, Asian and minority ethnic groups and in adults with

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					extremes of muscle mass. The committee agreed to make recommendations for research on appropriate eGFR equations for black, Asian and minority ethnic groups (adults, children and young people) in the UK. They agreed that factors other than ethnicity should also be explored as biomarkers.
The Renal Association	Guideline	007	020	"Do not use reagent strips to identify proteinuria" Does this statement also apply to semi-quantitative ACR testing in adults or just children? There is concern that the children and young adult data review may have been extrapolated to adults - when there are robust data to support semi-quantitative assessment for screening.	Thank you for your comment. The committee agreed that evidence was not reviewed for the use of reagent strips in adults. Therefore, we have reinstated (recommendation removed before this consultation in January 2021) the recommendation for adults that was made in 2008 to specify that the use of reagent strips to identify proteinuria in adults should be limited to tests being capable of measuring albumin at low concentrations and expressing the result as an ACR.
The Renal Association	Guideline	016	012	Although this is in a section blanked out for comment, we noticed the citation of BAME representing a risk factor for which health optimisation should be given. I fear that this is difficult and is the only non-modifiable risk factor in the section. Furthermore, I fear it might imply that non-BAME should not receive work to optimise their health. I wonder if it is best removed?	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.
The Renal Association	Guideline	016	022	SGLT2i are only recommended if T2DM and ACR >30 The DAPA-CKD trial has shown benefit in non-diabetic patients with eGFR 25 - 75 and ACR >22.6 (NEJM Oct 8 2020) "Monitor for volume depletion and reduction in eGFR" - should more specific recommendations be made?	Thank you for your comments. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. NICE is also currently undertaking a technology appraisal of dapagliflozin for treating chronic kidney disease which will include the DAPA-

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					CKD trial. Therefore, data from DAPA-CKD has been removed from this update. See https://www.nice.org.uk/guidance/indevelopment/gid-ta10808 for details. The NICE CKD guideline will cross refer to this technology appraisal appraising dapagliflozin when it is published. Regarding your comment about eGFR monitoring, we have included a clarification to the rationale stating that eGFR monitoring should depend on people's circumstances and on the BNF advice of monitoring requirements for people using SGLT2 inhibitors.
The Renal Association	Guideline	016	022	The draft suggests that SGLT2 inhibitors should be prescribed only when the UACR is 30mg/mmol or more and yet the DAPA-CKD study showed benefit down to an inclusion UACR of 22.6mg/mmol. It also suggests monitoring for eGFR decline. In our recent ABCD-RA guideline for management of hyperglycaemia in diabetic kidney disease, we advise against "routine assessment of renal function within 6–8 weeks of SGLT-2 initiation since there is likely to be a transient deterioration and this is not a reason to withdraw the drug".	Thank you for your comment. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. NICE is also currently undertaking a technology appraisal of dapagliflozin for treating chronic kidney disease which will include the DAPA-CKD trial. Therefore, data from DAPA-CKD has been removed from this update. See https://www.nice.org.uk/guidance/indevelopment/gid-ta10808 for details. The NICE CKD guideline will cross refer to this technology appraisal appraising dapagliflozin when it is published. Regarding your comment about eGFR monitoring, we have included a clarification to the rationale stating that eGFR monitoring should depend on people's circumstances

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					and on the BNF advice of monitoring requirements for people using SGLT2 inhibitors.
The Renal Association	Guideline	019	010 - 012	We have concerns over the recommendation to refer all those with KFRE risk greater than 5% for specialist review. The Major 2019 paper which looks at modelling suggests that referral at this level has a "Sensitivity" of 6% - ie 94% of referrals would not progress to ESKD - and sensitivity of 99.7% (ie this would detect 99.7% of all ESKD patients from the group over the next 5 years), but that baseline referrals would be 615 (of whom ~575-580 would never develop ESKD. However, if the KFRE threshold of 15% were used, baseline referrals would drop to 144 (over 75% reduction in referrals on this criterion). "Sensitivity" would be 16% and specificity would drop by only 0.1%. We wonder why the threshold was chosen at 5%? This quadruples the referrals to increase specificity by 0.1% to 99.7%. As a nephrologist, I recognise the importance of early detection and preparation for RRT, but question whether a 4-fold increase in referral rate really is justified for such a small increment; at the 15% risk level for referral, still 84% of the referrals would never need such specialist treatment, but at least 75% of referrals are spared the disruption of referral and review. I wonder whether all those referrals and time spent by specialists undertaking review would meet the NICE threshold of cost-utility? Would the 15% KFRE risk threshold not seem more appropriate? Furthermore, there are then listed another 7 referral criteria which should lead to referral, and I wonder how	Thank you for your comment. In the model having a KFRE ≥ 15% produced the lowest net monetary benefit and was therefore the least cost-effective option. This is because a KFRE ≥ 15% threshold will miss a significant number of patients who will then not have time to adequately prepare for renal replacement therapy, and this incurs increased costs and lower outcomes for the patient. While using a KFRE ≥ 5% does increase the number of referrals to secondary care (compared to the KFRE ≥ 15%), the cost of these appointments was included in the model and it still appeared to be the most cost effective option. Therefore, the committee decided that having the limit of 5% was the preferred option. The committee also noted that the new referral criteria are expected to refer less people than those in the previous 2014 guidance due to higher sensitivity and specificity, and therefore should not result in an increase in costs compared to current practice.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				many of these would mean that the remaining 0.1% loss of specificity would be covered in any case? As an aside, we notice that changing from the 5% to the 15% risk level would reduce the mean age of referral from 75 to 70, and wonder whether the committee might consider whether a valuable research question would be the utility of the ESKD predictions scores at different ages? One would speculate that the 5% risk group might include a large number of elderly people (50% over 75 according to the paper) for whom the competing risk of death in the presence of proteinuria and renal dysfunction is significantly greater than that of ESKD; it is difficult to infer this latter risk from the Major 2019 paper. We think this recommendation as currently drafted would have significant cost implications, and therefore merits further review. We think changing the criterion to 15% risk might significantly improve efficiencies.	
The Renal Association	Guideline	019	025	We are concerned that the removal of the recommendation to refer persons with GFR<30 ml/min may result in patients not receiving recommended treatment for anaemia and other complications of advanced CKD. Risk of progression to ESKD is certainly one consideration in the decision to refer, but complications of CKD should also be considered.	Thank you for your comment. The committee recognised that kidney function naturally reduces with age, meaning that a referral rule based on a simple eGFR cut-off will identify people who have normal age-related kidney function decline but are unlikely to reach ESRD within their lifetime. Regarding your comment about treatment for anaemia and other complications of advance CKD, the guideline includes section 1.7 on diagnosing and assessing anaemia and section 1.12 on other CKD complications where the diagnostic and treatment role of eGFR is discussed.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
The Renal Association	Guideline	022	004 - 006	We feel that the advice to target both systolic and diastolic blood pressure needs to be nuanced. In a scenario where a patient has achieved a systolic target (say, of 125mmHg), we feel that few clinicians would chase a diastolic pressure below 80 mmHg (and hence risk postural hypotension).	Thank you for your comment. We amended the rationale to highlight the importance of individualised blood pressure targets.
The Renal Association	Guideline	022	004 - 006	The blood pressure treatment targets recommended are in conflict with those recommended in the 2021 KDIGO guideline of the management of blood pressure in chronic kidney disease, which suggests a target systolic blood pressure of <120 mmHg "when tolerated" (3.1.1). This is based largely on evidence from the SPRINT trial (Cheung AK et al. J Am Soc Nephrol 28: 2812–2823, 2017) which reported a significant reduction in risk of cardiovascular events and all-cause mortality associated with the lower blood pressure target of SBP<120. This is not discussed on Page 60 where reasons for the Committee's recommendation are discussed.	Thank you for your comment. We have clarified in the rationale that a meta-analysis showed no meaningful differences in outcomes that the SPRINT trial found significant differences in when analysed separately.
The Renal Association	Guideline	022	022	We ask that the committee reconsider the statement: • *an SGLT2 inhibitor, in addition to an ACE inhibitor or an ARB, if they have type 2 diabetes, an ACR of 30 mg/mmol or more and meet the criteria in the marketing authorisation (including relevant eGFR thresholds); monitor for volume depletion and eGFR decline.* We urge that the statement is replaced with: Offer: • an SGLT2 inhibitor, in addition to an ACE inhibitor or an ARB, if they have type 2 diabetes,	Thank you for your comments. We have included a clarification to the rationale stating that eGFR monitoring should depend on people's circumstances and on the BNF advice of monitoring requirements. We have also added MHRA alerts on canagliflozin and SGLT2 inhibitors under recommendation 1.6.7.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				an ACR of 30 mg/mmol or more and meet the criteria in the marketing authorisation (including relevant eGFR thresholds). • In patients with Type 2 diabetes and adequate renal function (eGFR >45ml/min) the addition of an SGLT2i may increase the risk of hypoglycaemia if used concurrently with insulin, sulphonureas or glinides. Adjustment of the other diabetic therapies may be required to mitigate this risk. • It is not necessary to monitor eGFR more than the standard of care for diabetic patients (typically 3 monthly) as this is anticipated and is not associated with harm. • Caution should be taken when prescribing SGLT2i for people with risk factors for diabetic ketoacidosis (DKA), that is, individuals with previous DKA, pancreatic cancer/pancreatitis and patients who rapidly progressed to insulin treatment within 1 year of diagnosis. If in doubt consider referral to specialist diabetes team for guidance. • Clinicians should test for *capillary* ketones in anyone with suspected DKA (even if euglycaemic). Discontinue use if DKA is confirmed. Rationale:	

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				All published studies show no evidence of harm or increased adverse events in subjects with a reduction in eGFR >10% v those without. In those treated with SGLT2i, AKI risk was in fact decreased. Monitoring for eGFR decline following initiation of SGLT2i is unhelpful as decline is anticipated and not associated with harm. RA/ABCD guidance supports this assertion. We are concerned specifically with placing additional barriers to prescribing in primary care, which would impact the take-up of this beneficial treatment. With respect to people at risk of DKA, we feel there should be more clarity provided on who poses the greatest risk of developing DKA with flozin use. Additionally, urine ketones (acetoacetate) may be less sensitive at detecting DKA, particularly in the presence of an SGLT2i due to increased tubular ketone reabsorption.	
The Renal Association	Guideline	023	007 - 012	For adults with CKD but without diabetes: We urge the guideline panel to include the following recommendation, after the guidance for ACEi and ARB therapy after line 12. • Offer Dapagliflozin if eGFR is ≥ 25ml/min and ≤75ml/min *and* ACR is >20mg/mmol. Offer this in addition to optimal ACEi or ARB therapy (where RAAS blockade agent is tolerated). Rationale: We are encouraged by significant study outcomes in this area, with reference to the recently published DAPA-CKD trial. We feel assured by the data that	Thank you for your comment. NICE is currently undertaking a technology appraisal of dapagliflozin for treating chronic kidney disease which will include the DAPA-CKD trial. Therefore, data from DAPA-CKD has been removed from this update. See https://www.nice.org.uk/guidance/indevelopment/gid-ta10808 for details. The NICE CKD guideline will cross refer to this technology appraisal appraising dapagliflozin when it is published. NICE are also reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Dapagliflozin has proven to be of equal benefit in non-diabetic and diabetic CKD populations, with respect to the following clinically important endpoints: • Decreased risk of kidney failure • Decreased risk of death from CV causes or hospitalisation for HF • Prolonged survival We assert that Dapagliflozin has demonstrated a good safety profile and is globally well tolerated, even at the lower end of the studied eGFR range (25-30ml/min). We understand that economic modelling is likely to support projected health system savings associated with a reduction of patients reaching RRT. Additional health system savings are forecast related to cardiovascular morbidity. These benefits are in addition to those seen in patients on ACEi/ARBs only. We suggest that excluding the non-diabetic CKD patients from the benefits of SGLT2i in the NICE guidelines will limit the confidence of integrated care systems to include them in local prescribing protocols. This has considerable implications for people living with CKD and proteinuria, at risk of eGFR decline. With the next review of these guidelines unlikely to be earlier than 3-5 years, failure to include this recommendation represents a missed opportunity for significantly improved outcomes for this cohort.	scheduled to begin on 1 September 2021, and the review will publish in November 2021.
The Renal Association	Guideline	023	007 - 012	The document does not support the use of SGLT2 inhibitors in people who have not been diagnosed with type 2 diabetes, despite evidence of reno-protection	Thank you for your comment. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				irrespective of diabetes status. This is likely to make the guideline out of date very quickly. Note that the recently published scope of the health technology appraisal for dapagliflozin is not limited to reno-protection in diabetes.	recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. NICE is also currently undertaking a technology appraisal of dapagliflozin for treating chronic kidney disease which will include the DAPA-CKD trial. Therefore, data from DAPA-CKD has been removed from this update. See https://www.nice.org.uk/guidance/indevelopment/gid-ta10808 for details. The NICE CKD guideline will cross refer to this technology appraisal appraising dapagliflozin when it is published.
The Renal Association	Guideline	024	018 - 019	We understand that the content of this guideline is not in the scope of this review. We do ask that the panel consider consolidating the key guidance below from NICE TA599 (Sodium Zirconium Cyclosilicate) within the NICE Guideline for CKD, to ensure clinicians caring for people with CKD are aware of the recommendations around the use of potassium binding agents. Sodium zirconium cyclosilicate is recommended as an option for treating hyperkalaemia in adults with CKD 3b-5 only if used: • in emergency care for acute life-threatening hyperkalaemia alongside standard care *or* • in outpatient care for people with persistent hyperkalaemia and chronic kidney disease stage 3b to 5 or heart failure, if they: – have a confirmed serum potassium level of at least 6.0 mmol/litre	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations, but we have added a new recommendation referring to the NICE technology appraisals for treating hyperkalaemia with potassium binders (sodium zirconium cyclosilicate and patiromer). We have also passed your issue on to the NICE surveillance team who will explore whether recommendation 1.6.15 (this number has been updated to 1.6.16 after consultation) needs updating in the future.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				– are not taking an optimised dosage of renin-angiotensin-aldosterone system (RAAS) inhibitor because of hyperkalaemia and – are not on dialysis.	
The Renal Association	Guideline	026	009 - 011	We are aware that this section is proposed to be out of scope for this review; however we recommend this section of the guideline is updated due to *changes in available safety data*. Apixaban can now be used to an GFR of 15ml/min. eGFR MDRD equation is also not recommended to be used to estimate renal function when dosing DOACs such as Apixaban. This is following an MHRA drug safety update. CrCl (Cockroft & Gault) is recommended. See: Direct-Acting oral anticoagulants (DOACs): reminder of bleeding risk, including availability of reversal agents (via www.gov.uk)	Thank you for your comment. We have reviewed the drug safety update and do not believe that the update suggests that the current recommendations in this area are unsafe. The current recommendation refers to an eGFR of 30-50 ml/min/1.73 m^2 and does not specify how eGFR should be estimated. Therefore, we have not made changes to this recommendation as it was not part of this guideline update and evidence was not reviewed in this area.
The Renal Association	Guideline	027	005 - 006	We are concerned by the phrase "If eGFR is below 30 ml/min/1.73 m2, think about other causes of anaemia but note that the anaemia is likely to be caused by CKD". The evidence on which this statement is made seemed to be of very low quality, and conflicted within the evidence review - most were nephrology studies of odds/risk ratios of anaemia with lower eGFRs and prone to significant confounding. I also note that the thresholds for defining anaemia varied widely, and none included a range at which renal physicians would offer intervention with ESA or iron. I am also mindful of the wide prevalence of eGFR<30 in elderly people, and wide prevalence of Hb levels of 10-12 in this and other groups which we would not intervene on.	Thank you for your comment. The third bullet point of recommendation 1.7.2 was amended replacing 'likely' by 'often'. The rationale for this recommendation has been amended to highlight that clinical judgment and people's circumstances should be considered in people with eGFR below 30 ml/min/1.73 m^2.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Therefore I fear that (1) there may not be sufficient evidence to attribute anaemia in someone with an eGFR of 29 as "likely to be caused by CKD", and (2) by putting this phrase at the beginning of the section without an acknowledgment of the poor quality of the evidence and/or that the level of anaemia being described is above the threshold at which we would intervene and/or that there are other specialists (haematologists) who are very good at managing anaemia would risk large numbers of referrals of inappropriate patients to renal specialists	
The Renal Association	Guideline	034	005	We are aware that this section is proposed to be out of scope for this review, however we recommend considering the inclusion of the following sentence after line 5: Clear documentation needed in patient's records if responsible clinician has chosen to accept the lower Hb levels so that continuity of care is maintained in all clinical settings.	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.
The Renal Association	Guideline	045	005 - 006	Can the panel clarify if they include Ca acetate/Mg binder (Osvaren) in the first line recommendation of Ca acetate? We believe this should be included as one of the first line choices available to patients.	Thank you for your comment. The committee discussed evidence on the combination of calcium acetate and magnesium carbonate which showed that results could not differentiate between this combination and the rest of interventions for serum phosphate levels at 3 months or at 6 months or for serum calcium levels at 3 months or 6 months or for discontinuation due to adverse events. Longer term outcomes and adverse events were not reported for the combination of calcium acetate and magnesium carbonate. The committee agreed to replace magnesium carbonate with calcium acetate plus magnesium carbonate in a research recommendation

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					on its effectiveness and safety in adults with stage 5 CKD who are on dialysis (minimum 12 months follow-up).
The Renal Association	Guideline	047	002	Considering that Mimpara is now off patent, would the panel consider including guidance on the appropriate use of calcimimetics where hyperparathyroidism is worsening despite intervention with vitamin D and/or phosphate binders? We suggest that this is considered even outside of its existing license. Or could the panel take this into consideration for incorporation into the CKD MBD guidance or NICE TA117 on Cinacalcet?	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations.
UK Clinical Pharmacy Association	Comments form	Q1	Q1	**Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why.** Use of SGLT2 inhibitors for indications other than diabetes, and use with lower eGFR levels. Current prescribing guidance will need to be updated. Effective communication and education will need to be provided to ensure all relevant healthcare professionals feel confident to use, are aware of the change to practice, the benefits to patients, factors to consider to ensure safe prescribing, and the restrictions on use.	Thank you for your response. Your comments will be considered by NICE where relevant support activity is being planned.
UK Clinical Pharmacy Association	Comments form	Q2	Q2	**Would implementation of any of the draft recommendations have significant cost implications?** Use of SGLT2 inhibitors in wider cohorts than current practice would result in a significant cost implication to prescribing budgets. It is important to balance this with	Thank you for your response. Your comments will be considered by NICE where relevant support activity is being planned.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				longer term cost savings and benefits including impact on quality of life.	
UK Clinical Pharmacy Association	Comments form	Q3	Q3	**What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or examples of good practice.)** Clear prescribing guidance across the interface for all prescribers. Effective communication and education will need to be provided to ensure all relevant healthcare professionals feel confident to use, are aware of the change to practice, the benefits to patients, factors to consider to ensure safe prescribing, and the restrictions on use.	Thank you for your response. Your comments will be considered by NICE where relevant support activity is being planned.
UK Clinical Pharmacy Association	Guideline	008	017	We consider that is important to mention when to screen for haematuria – at annual type 2 diabetes reviews and whenever there is a significant rise in UACR (urinary albumin creatinine ratio)	Thank you for your comment. We have clarified that haematuria should be tested in the same people as recommended in 1.1.14.
UK Clinical Pharmacy Association	Guideline	019	026	We consider that those with eGFR <30 mL/min/1.73 m2 (G4 or G5) with or without diabetes should also be referred to specialist services for appropriate management.	Thank you for your comment. These criteria were tested in the model and it was discovered that using the KFRE ≥ 5% was a more cost-effective way of referring patients to secondary care. The committee also recognised that kidney function naturally reduces with age, meaning that a referral rule based on a simple eGFR cut-off will identify people who have normal age-related kidney function decline but are unlikely to reach ESRD within their lifetime. Therefore, the committee replaced the previous recommendation of those with a eGFR < 30 mL/min/1.73 m2 with a KFRE ≥ 5%.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
UK Clinical Pharmacy Association	Guideline	022		There are a number of important factors to consider when starting an SGLT-2 inhibitor linked to the side effect profile and the drug pharmacodynamics. Use of SGLT-2 inhibitors will not be appropriate for all patients meeting the criteria listed, and in some, adjustments may need to be made to existing medication. Considerations include but are not limited to hypoglycaemia (and subsequent dose adjustment of other therapies e.g insulin, sulfonylureas and glinides) and risk factors for diabetic ketoacidosis (DKA) which may prohibit use. There are also a number of MHRA alerts regarding SGLT-2 inhibitor use. Therefore we would ask that more clarity is provided around appropriate use/safe prescribing of SGLT-2 inhibitors in this group.	Thank you for your comment. The MHRA alerts on canagliflozin and SGLT2 inhibitors have been added to the guideline under recommendation 1.6.7.
UK Clinical Pharmacy Association	Guideline	022		We note no mention of sick day rules in the guideline. Due to the risk of Diabetic Ketoacidosis/euglycaemic Diabetic Ketoacidosis with SGLT-2i, we would ask that the committee consider adding guidance around sick day rules.	Thank you for your comment. We have not added additional information about sick day rules for taking SGLT2 inhibitors, as this issue is covered in the Summary of product characteristics for individual medicines (e.g. https://www.medicines.org.uk/emc/medicine/28400#gref) and applies to all people taking these treatments not just those who have CKD and diabetes.
UK Clinical Pharmacy Association	Guideline	022	020	We would suggest patients with type 1 diabetes should be reviewed in joint renal:diabetes clinics for consideration of initiation of SGLT2i (sodium glucose co-transporter 2 inhibitors). NICE TA597 (use of Dapagliflozin in Type 1 diabetes) states "treatment is started and supervised by a consultant physician specialising in endocrinology and diabetes treatment".	Thank you for your comment. SGLT2 inhibitors are not recommended for people with type 1 diabetes in this guideline. To make this clearer, recommendation 1.6.6 has been separated into 2 parts. The first part (recommendation 1.6.6) is to offer an ACE inhibitor or an ARB (titrated to the highest approved dose that is tolerated) to adults with CKD and diabetes (type 1 or type 2) if ACR is 3 mg/mmol

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					or more. The second part (recommendation 1.6.7) is to offer an SGLT2 inhibitor, in addition to an optimised dose of ACE inhibitor or an ARB, to people with type 2 diabetes, an ACR of 30 mg/mmol or more and meet the criteria in the marketing authorisation (including relevant eGFR thresholds); monitor for volume depletion and eGFR decline.
UK Clinical Pharmacy Association	Guideline	022	021 - 022	We would ask that consideration is taken to adding the words 'optimised dose of' before ACEi/ARB in line 22 'an SGLT2 inhibitor, in addition to an optimised dose of ACE inhibitor or an ARB ensuring…….'. There are a number of people who are currently taking ACEi/ARB with sub-optimal doses. In addition, one of the eligibility criteria for CREDENCE was being on a stable dose of ACEi/ARB (either the maximum labeled dose or a dose not associated with unacceptable side effects) and for DAPA-CKD a stable dose (Stable, and for the patient maximum tolerated labelled daily dose). We recognise that this is mentioned later on in the document (page 24, lines 8-10) however this should also be highlighted on page 22.	Thank you for your comment. Recommendation 1.6.6 has been separated into 2 parts. The first part (recommendation 1.6.6) is to offer an ACE inhibitor or an ARB (titrated to the highest approved dose that is tolerated) to adults with CKD and diabetes (type 1 or type 2) if ACR is 3 mg/mmol or more. The second part (recommendation 1.6.7) is to offer an SGLT2 inhibitor, in addition to an optimised dose of ACE inhibitor or an ARB, to people with type 2 diabetes, an ACR of 30 mg/mmol or more and meet the criteria in the marketing authorisation (including relevant eGFR thresholds); monitor for volume depletion and eGFR decline. Therefore, your suggestion has been added to recommendation 1.6.7.
UK Clinical Pharmacy Association	Guideline	023	007	There is evidence suggesting the beneficial use of SGLT2i (sodium glucose co-transporter 2 inhibitors) regardless of diabetes status. In DAPA-CKD (Heerspink et al, 2020) consistency was noted in the primary and secondary composites in both populations (with or without type 2 diabetes). There is need to review this guidance with imminent new trials which have included non-diabetes population. We are concerned that the recommendation for the use only in chronic kidney disease and diabetes may deprive patients from the best evidence-based treatments.	Thank you for your comment. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. NICE is also currently undertaking a technology appraisal of dapagliflozin for treating chronic kidney disease which will include the DAPA-CKD trial. Therefore, data from DAPA-CKD has been removed from this update. See

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					https://www.nice.org.uk/guidance/indevelopment/gid-ta10808 for details. The NICE CKD guideline will cross refer to this technology appraisal appraising dapagliflozin when it is published.
UK Clinical Pharmacy Association	Guideline	063	009	There is evidence suggesting the beneficial use of SGLT2i (sodium glucose co-transporter 2 inhibitors) regardless of diabetes status. In DAPA-CKD (Heerspink et al, 2020) consistency was noted in the primary and secondary composite in both populations (with or without type 2 diabetes). There is need to review this guidance with imminent new trials which have included non-diabetes population. We are concerned that the recommendation for the use only in chronic kidney disease and diabetes may deprive patients from the best evidence-based treatments.	Thank you for your comment. NICE are reviewing the evidence on SGLT2 inhibitors in people with CKD and type 2 diabetes, and we may update recommendation 1.6.7 as a result of this. The consultation on this review is scheduled to begin on 1 September 2021, and the review will publish in November 2021. NICE is also currently undertaking a technology appraisal of dapagliflozin for treating chronic kidney disease which will include the DAPA-CKD trial. Therefore, data from DAPA-CKD has been removed from this update. See https://www.nice.org.uk/guidance/indevelopment/gid-ta10808 for details. The NICE CKD guideline will cross refer to this technology appraisal appraising dapagliflozin when it is published.
University of Oxford Clinical Trial Service Unit	Guideline	General	General	We fully support the positive step in this revised guideline recommending use of SGLT-2 inhibitors in people with type 2 diabetes and proteinuric diabetic kidney disease, in line with marketing authorisations. It is noteworthy (and not mentioned in the document) that there is an ongoing (and almost fully recruited) EMPA-KIDNEY trial of 6000 people with chronic kidney disease, which has recruited people with non-albuminuria diabetic kidney disease and people with non-diabetic causes of kidney disease (www.empakidney.org)	Thank you for your comment. We will pass the information about the ongoing trial to the NICE surveillance team which monitors guidelines to ensure that they are up to date.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
University of Oxford Clinical Trial Service Unit	Guideline	023	002	1. The new SGLT-2 recommendation for use in proteinuric diabetic kidney disease comes with a recommendation to monitor for volume depletion and eGFR decline. Is there any good rationale for increasing monitoring beyond what is appropriate for the stage of CKD already? Our opinion is that there is no indication to create an extra new routine of additional patient monitoring on commencement of SGLT-2 inhibition beyond standard clinical follow-up, as any acute decline in eGFR is a marker of effect not harm, and there is no additional risk of acute kidney injury or hyperkalaemia in the randomized trials. In fact, the totality of the evidence is suggesting relative reductions of 20-30% in risk of acute kidney injury serious adverse events, and that the clinical benefits of SGLT-2 inhibition are similar in size in those with and without an eGFR dip (see reference below in Kidney International using EMPA-REG OUTCOME data). A universal recommendation for additional monitoring could reduce uptake of this important intervention, result in physicians inappropriately stopping SGLT-2 inhibition due to misunderstanding the expected decline in eGFR, and the recommendation causes additional burden on patients and healthcare resources. We suggest that is monitoring is suggested, it is done only in those who the treating physician considers to be at risk of significant risk of volume depletion (e.g. due to co-medication). Reference: Characterization and implications of the initial estimated glomerular filtration rate dip upon sodium-glucose cotransporter-2 inhibition with empagliflozin in	Thank you for your comment. We have included a clarification to the rationale stating that eGFR monitoring should depend on people's circumstances and on the BNF advice of monitoring requirements for people using SGLT2 inhibitors.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				the EMPA-REG OUTCOME trial. Kidney International (2021) https://doi.org/10.1016/ j.kint.2020.10.031 https://www.kidney-international.org/action/showPdf?pii=S0085-2538%2820%2931277-1	
University of Oxford Clinical Trial Service Unit	Guideline	062	Final sentences on page	It is stated that the committee were "confident that these drugs would still be effective for blood glucose control in people with diabetes and CKD, and would therefore provide similar benefits for diabetes 2 control as in people without CKD." However this is demonstrably incorrect and the reason for historical contraindications to use of this class of drug in CKD. The glucose lowering effect is very substantially attenuated as kidney function declines. See clear demonstrations on this in the following summary of trials using empagliflozin trial data. DZI Cherney et al.: Empagliflozin: effect of renal function on outcomes. Kidney International (2018) 93, 231–244 https://www.kidney-international.org/article/S0085-2538(17)30477-5/abstract However, the committee can have some confidence that the relative clinical benefits on renal progression outcomes may not be attenuated to the same degree in people with CKD, and that benefits may remain at lower eGFRs among those with albuminuria (see CREDENCE main publication). The indication for use of SGLT-2 inhibition in CKD should be based on modifying renal (and heart failure) risk and clinicians should not expect these agents to have important effects on lowering HbA1c in CKD.	Thank you for your comment. We have amended the rationale to note that the benefits are not expected to be the same for blood glucose control in people with diabetes and CKD as in people with diabetes but without CKD. The committee were confident that the overall clinical benefit in people with diabetic kidney disease would be as large as the benefits estimated in the technology appraisals for people with diabetes but without CKD.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
University of Oxford Clinical Trial Service Unit	Guideline	062	014	It is stated there is a lack of cost-effectiveness studies, but the committee should be made aware that there is a recently published simulation based cost-effective analysis of canagliflozin using CREDENCE data suggesting cost-savings as well as benefits on quality of life when used in proteinuria diabetic kidney disease (using UK costings). Cost-Effectiveness of Canagliflozin Added to Standard of Care for Treating Diabetic Kidney Disease (DKD) in Patients with Type 2 Diabetes Mellitus (T2DM) in England: Estimates Using the CREDEM-DKD Model https://link.springer.com/article/10.1007/s13300-020-00968-x *Diabetes Therapy* (2020)	Thank you for your comment. This paper was published after the searches for this guideline were completed. However, this was presented to the committee at the post-consultation meeting and is now included in the evidence review, and the agreed that the paper further supports the recommendations on SGLT2 inhibitors made in the guideline.
Vifor Pharma UK Limited	Guideline	043	025	Consider adding PTH, vitamin D and serum calcium to this list as per KDIGO recommendation (KDIGO 2019).	Thank you for your comment. The section of phosphate binders within this guideline is intended for renal physicians. In clinical practice, renal physicians assess bone biochemistry before offering phosphate binders to people with chronic kidney disease. This has been clarified in the rationale of these recommendations.
Vifor Pharma UK Limited	Guideline	044	013	Consider adding the statement: In June 2021, this was an off-label use of calcium-based phosphate binders in people not on dialysis. See NICE's information on prescribing medicines.	Thank you for your comment. Recommendation 1.11.8 (this number has been updated to 1.11.9 after consultation) has been amended to include your suggestion.
Vifor Pharma UK Limited	Guideline	067	013	The Committee recommended after reviewing the evidence that the best treatment strategy is to start with calcium acetate, and switch to sevelamer carbonate if the person gets hypercalcaemia. However, there is no mention of restricting the dose of the Ca-based treatments.	Thank you for your comment. We have added to the rationale that renal physicians should consider pre-existing vascular calcification on binder choice.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				There is evidence that calcium in Ca-based phosphate-binders (Ca-carbonate; Ca-acetate) may be absorbed and can contribute to vascular and extravascular calcification. KDIGO recommend restricting the dose of calcium-based phosphate binders in adult patients with CKD stages 3-5D receiving phosphate-lowering treatment (KDIGO 2019).	
Vifor Pharma UK Limited	Evidence review L	General	General	We understand the literature search for the clinical evidence review for children and young people only captured published studies up until July 2019. However, we would like to draw the committee's attention to a recent prospective, randomised Phase 3 study that evaluated the safety and efficacy of sucroferric oxyhydroxide in 85 paediatric patients (aged 2–18 years) with CKD and hyperphosphatemia (Greenbaum LA et al. Pediatr Nephrol. 2020). This trial demonstrated that sucroferric oxyhydroxide was well tolerated by paediatric patients and effectively controlled serum phosphorus levels. Based on the data from this study, the European Medicines Agency granted an extension to the therapeutic indication of sucroferric oxyhydroxide to include control of serum phosphorus levels in children aged ≥2 years with stage 4 or 5 CKD or with those with CKD on dialysis (full details available here). Given the lack of data from prospective clinical trials of phosphate binders in paediatric CKD patients, the committee may also wish to consider the data from this Phase 3 sucroferric oxyhydroxide paediatric study for the current guideline update.	Thank you for your comment. We have added the trial by Greenbaum and colleagues to evidence review L on the use of phosphate binders. The committee discussed the results of the trial and agreed that the evidence was not strong enough to support a recommendation for sucroferric oxyhydroxide for children and young people with CKD and hyperphosphataemia.
Vifor Pharma UK Limited	Evidence review L	072	014 − 021	The guideline recommends considering sucroferric oxyhydroxide in dialysis patients if a non-calcium agent is required and sevelamer carbonate is not suitable. This	Thank you for your comment. The recommendation was based on the economic evidence which showed that sucroferric oxyhydroxide was an effective and

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				recommendation was based on the analysis of adverse events data showing that sucroferric oxyhydroxide is associated with a higher risk of diarrhoea, compared with sevelamer hydrochloride. However, we do not agree with rationale for this recommendation. Firstly, the comparison between sucroferric oxyhydroxide and sevelamer hydrochloride does not seem appropriate, given that sevelamer hydrochloride is not specifically recommended as a first- or second-line treatment by the guideline. Furthermore, the network meta-analysis results (Table 23, pages 55–57) did not appear to show a clinically important difference in the risk of diarrhoea between sucroferric oxyhydroxide and the two agents recommended as first- and second-line options, calcium acetate and sevelamer carbonate. Although diarrhoea is a common adverse event with sucroferric oxyhydroxide, clinical trials and post-marketing surveillance studies have shown it is usually transient and mild-to-moderate in severity. In the Evidence Review, the committee also note sucroferric oxyhydroxide has a clinically significant effect by reducing the risk of constipation compared with calcium acetate and sevelamer carbonate. Many dialysis patients suffer from constipation due to multiple causes including fluid restriction, low dietary fibre intake and concomitant medications (including phosphate binders). Consequently, it is possible that sucroferric oxyhydroxide treatment may even help to alleviate constipation in some of these patients.	cost-effective next option for people in whom sevelamer carbonate is not suitable.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				We believe it is misleading to suggest that sevelamer carbonate and calcium acetate should be the preferred options over sucroferric oxyhydroxide for clinical reasons. As mentioned in the Evidence Review, every phosphate binder is different and patients may prefer one binder over another based on its characteristics (e.g., tablet burden, formulation, taste and palatability) and adverse event profile. Based on this, we believe sucroferric oxyhydroxide is likely to be a more appropriate treatment option for some dialysis patients than sevelamer carbonate or calcium acetate, and vice versa.	
Vifor Pharma UK Limited	Guideline	025	003	We recognise this section (1.6.17) was not within the scope of the current update but would like to note that recommending to stop renin-angiotensin system antagonists if serum potassium is 6 mmol/L or more is not aligned with the current recommended use of next-generation potassium binders (refer to TA599 and TA623): *"for people with persistent hyperkalaemia and stages 3b to 5 chronic kidney disease or heart failure, if they:* *-have a confirmed serum potassium level of at least 6.0 mmol/litre and* *-are not taking, or are taking a reduced dosage of, a renin-angiotensin-aldosterone system (RAAS) inhibitor because of hyperkalaemia and* *-are not on dialysis."*	Thank you for your comment. Recommendations in greyed out areas of the consultation guideline were outside of the scope of the current update, and evidence on these areas has not been reviewed. Therefore, we cannot make substantive changes to these recommendations, but we have added a new recommendation referring to the NICE technology appraisals for treating hyperkalaemia with potassium binders (sodium zirconium cyclosilicate and patiromer). We have also passed your issue on to the NICE surveillance team who will explore whether recommendation 1.6.17 (this number has been updated to 1.6.18 after consultation) needs updating in the future.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Vifor Pharma UK Limited	Guideline	026	025	We would recommend clarification on 'other causes of anaemia', the committee mentions GI bleeding and certain cancers, is this an exhaustive list? What does the Committee mean by 'anaemia caused by CKD' in recommendation 1.7.2? The pathogenesis of anaemia in CKD is multifactorial (Babitt et al JASN 2012), with the main causes listed below. Are these causes all included in the guideline as 'anaemia caused by CKD'? The main cause of anaemia in CKD are: - EPO deficiency (Artnunc et al Nephrol Dial Transplant 2007) - Suppression of erythropoiesis due to accumulated toxins and inflammation - Shortened red blood cell lifespan caused by inflammation - Functional iron deficiency caused by: inflammation and decreased hepcidin excretion, both lead to high serum hepcidin; or by ESA treatment, the iron supply cannot be mobilised rapidly enough to meet the requirements of increased erythropoiesis - Absolute iron deficiency caused by: blood loss (1-3 g per year in HD), diet with low iron content, and decreased iron absorption (due to high hepcidin as the disease progresses Zarisky et al Clin J Am Soc Nephrol 2009, 2010) With the deterioration of kidney function, CKD patients are at increased risk of iron-restricted erythropoiesis	Thank you for your comment. The purpose of this recommendation is to remind clinicians that there are multiple causes of anaemia and they should investigate the cause. The rationale and impact says "such as" GI bleeding and certain cancers, making clear that these are examples and that it is not an exhaustive list. 'Anaemia caused by CKD' means that anaemia is a complication caused by CKD. There is evidence from population studies suggesting an increasing prevalence of anaemia with decreasing GFR level. Additionally, the prevalence of anaemia associated with CKD increases progressively with category of GFR, especially when the person reaches GFR categories G4 or G5.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				leading to anaemia, due to absolute and/or functional iron deficiency. It is notably challenging to diagnose iron deficiency in the context of CKD since there are no thresholds of laboratory parameters validated to diagnose iron deficiency in populations with functional iron deficiency. It has long been recognised that there is lack of concordance between body iron content and ferritin levels in patients with CKD, with patients showing no evidence of iron in bone marrow biopsy specimens, indicative of severe iron deficiency, despite apparently normal blood ferritin levels (Gotloib et al J Nephrol. 2006).	
Vifor Pharma UK Limited	Guideline	036	009	Recommendation 1.9.18 is that "Offer a high-dose intravenous iron regimen to adults, children and young people with stage 5 CKD on in-centre (hospital or satellite unit) haemodialysis, if they have iron deficiency (see recommendation 1.7.3)." The TSAT and ferritin thresholds recommended to define iron deficiency generally in CKD as in 1.7.3 (i.e. TSAT<20% and serum ferritin<100 mcg/L) are not consistent with the inclusion criteria for iron deficiency used in the PIVOTAL study, namely TSAT<30% and ferritin<400 mcg/L, which apply to the specific population in the study- patients with CKD stage 5D on ESA therapy. PIVOTAL is the largest study demonstrating an impact on patient outcomes and used to support recommendation 1.9.18. Limiting this recommendation to only those patients with TSAT<20% and serum	Thank you for your comment. This difference was discussed by the committee and documented in evidence review K. The discussion has been added to the rationale as well. In this discussion, the committee noted that the inclusion criteria from the trial (transferrin saturation <30%, serum ferritin 400 micrograms/litre) differed from the criteria for diagnosing iron deficiency in this NICE guideline (transferrin saturation <20%, serum ferritin <100 micrograms/litre). The committee agreed that the regimen was still appropriate when using the NICE diagnostic criteria.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				ferritin<100 mcg/L (levels representative of absolute iron deficiency in this population), means that many patients with 'functional iron deficiency' will be excluded and could have benefited from treatment as demonstrated in the PIVOTAL study. We suggest that the text in the recommendation is changed to: "Offer a high-dose intravenous iron regimen to adults, children and young people with stage 5 CKD on in-centre (hospital or satellite unit) haemodialysis, if they have iron deficiency defined as TSAT<30% and ferritin<400 mcg/L."	
Vifor Pharma UK Limited	Guideline	036	012	The guideline shows in Table 3 an example of a high-dose intravenous iron regimen for adults taken from the evidence (PIVOTAL study) but it also gives the option to 'use a bioequivalent dose of iron'. However, the Guideline does not provide a recommendation on how to determine a 'bioequivalent dose of iron'. We suggest replacing the 'bioequivalence' term in the statement to: *"See table 3 for an example of a high-dose intravenous iron regimen for adults or use the equivalent dose of iron from another product that supports the same therapeutic benefit (for example same ferritin increase and same ESA dosage)."* Bioequivalence of IV iron complexes is not straightforward and the EMA recommends the use of a	Thank you for your comments. The committee acknowledged the difficulty of bioequivalence in iron products. Therefore, the rationale now includes more detail about this difficulty and that a pharmacist should be consulted for bioequivalent doses when considering iron preparations. The rationale also states that the committee agreed that the type of intravenous iron was not relevant and that there was no reason to recommend a specific preparation. Table 3 provides an example from the PIVOTAL trial, but other bioequivalent doses might be used based on local availability and policies.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				proportional 'weight of evidence' step-wise approach to demonstrate bioequivalence (EMA, 2015). Data from a clinical study in 75 haemodialysis patients have shown that substitution with an iron sucrose similar, can differ substantially from the originator iron sucrose product in their efficacy, resulting in significant reduction of hemoglobin (Hb) levels (Rottembourg et al., 2011). In this study, switching from IV iron sucrose originator (Venofer®) to an iron sucrose similar was associated with an average increase of 34.6% in the required IV iron dose and a 13.8% increase in the ESA dosage to reach Hb levels similar to those previously achieved with the originator product in haemodialysis patients (Rottembourg et al., 2011). Similar findings were reported in another study where 342 stable patients on haemodialysis were switched from a follow-on IV iron sucrose product to its originator, which enabled dose reductions in both the IV iron dose (34.3%) and the ESA dose (12.5%) whilst maintaining Hb levels (Agüera et al 2015). The above two studies did not form part of the evidence reviewed for the Committee to reach the conclusion that the type of intravenous iron was not relevant and that there was no reason to recommend a specific preparation.	
Vifor Pharma UK Limited	Guideline	036	019	Table 3: it should be clear in the table that the doses in the IV Iron Sucrose column are milligrams of iron (i.e. 600 mg Fe, 200 mg Fe) and not milligrams of 'iron sucrose'.	Thank you for your comment. We have checked the table and are confident that it is accurate.

Chronic kidney disease: assessment and management

Consultation on draft guideline - Stakeholder comments table
21st January 2021 – 19th March 2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Vifor Pharma UK Limited	Guideline	046	019	Consider adding serum calcium.	Thank you for your comment. Serum calcium has been added to recommendation 1.11.18.

**None of the stakeholders who comments on this clinical guideline have declared any links to the tobacco industry.*