National Institute for Health and Clinical Excellence

Acute Kidney Injury
Scope Consultation Table
17 May 2011 – 14 June 2011

Type	Stakeholder	Order No	Section No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
SH	Abbott Diagnostics UK	1	4.3.2 b	Availability of biomarker assays is not a limitation. CE marked assays are available for new biomarkers like NGAL and Cystatin C for majority of system solutions in the laboratory. There may be evidence from the NIHR on the utility of NGAL that can be considered as evidence by NICE in the timescale of the construction of this guideline. NIHR have already initiated a technical, clinical and health economics appraisal of commercial (CE marked for routine use) NGAL assays.	Thank you for your comment. We are unable to include biomarkers in this guideline because: 1. There is a lack of randomised control trials comparing biomarkers to standard care 2. Given the evidence base for biomarkers is evolving, an economic evaluation at this point in time is likely to be subject to significant limitations 3. The NIHR funded study is limited to patients undergoing coronary artery bypass grafting and the estimated study completion date in December 2013, after the publication of this guideline. Please note that it is possible for stakeholders to submit evidence to another area of NICE guidance development, the NICE diagnostic technologies programme. For further information please see the NICE website: http://www.nice.org.uk/aboutnice/howwework/developingnnicediagnostictechnologiesguidance/developingnicediagnostictechn

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SH	Abbott GmbH& Co KG	1	3.2 a	Current practice is based on rise in creatinine with/without fall of urine output. Creatinine is a functional and not an injury marker. Therefore precent changes of creatinine after ischemic insult are highly depending on baseline renal function (Waikar et al JASN (2009); 20: 672-79), which might not be known before. There is increasing evidence that biomarkers like urine NGAL offer clear advantages over creatinine and can contribute significantly to the current practice for diagnosis of acute kidney injury. **Creatinine Kinetics and the Definition of Acute Kidney Injury** Sushrut S. Waikar and Joseph V. Bonventre Renal Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts **ABSTRACT** Acute kidney injury (AKI) is a common and devastating medical condition, but no widely accepted definition exists. A recent classification system by the Acute Dialysis Quality Initiative (RIFLE) defines AKI largely by percentage increases in serum creatinine (SCr) over baseline. The Acute Kidney Injury Network defines the first stage by either an absolute or a percentage increase in SCr. To examine the implications of various definitions, we solved differential equations on the basis of mass balance principles. We simulated creatinine kinetics after AKI in the setting of normal baseline kidney function and stages 2, 3, and 4 chronic kidney disease (CKD). The percentage changes in SCr after severe AKI are highly dependent on baseline kidney function. Twenty-four hours after a 90% reduction in creatinine clearance, the rise in SCr was 246% with normal baseline kidney function, 174% in stage 2 CKD, 92% in stage 3 CKD, and only 47% in stage 4 CKD. By contrast, the absolute increase was nearly identical (1.8 to 2.0 mg/dl) across the spectrum of baseline kidney function. Time to reach a 50% increase in SCr was directly related to baseline kidney function: From 4 h (normal baseline) up to 27 h for stage 4 CKD. By contrast, the time to reach a 0.5-mg/dl increase in SCr was virtually identical after moderate to severe AKI (>50% reduction in creatinine clearance). We propose an alternative definition of AKI that incorporates absolute changes in SCr over a 24- to 48-h time period. *J Am Soc Nephrol* 20: 672–679, 2009. doi: 10.1681/ASN.2008070669	Thank you for your comment. We are unable to include biomarkers in this guideline because: 1. There is a lack of randomised control trials comparing biomarkers to standard care 2. Given the evidence base for biomarkers is evolving, an economic evaluation at this point in time is likely to be subject to various limitations. Please note that it is possible for stakeholders to submit evidence to another area of NICE guidance development, the NICE diagnostic technologies programme. For further information please see the NICE website: http://www.nice.org.uk/aboutnice/howwework/developingnnicediagnostictechnologiesguidance/developingnicediagnostictechnologiesguidance.jsp
SH	Abbott GmbH& Co KG	2	4.1.1	As discussed also in the stakeholder meeting the limitation of the guideline to patients > 16 years could be questioned as cause and management of AKI in children follows similar pathways	Thank you for your comment. Having considered the information provided by stakeholders, we will now be including children over the age of one month in the guideline. We have changed the scope to reflect this (section 3.1, 3.2, 4.1.1a, 4.1.2a). Some exclusions remain relevant to the paediatric population. The guideline will not cover neonates (see 4.1.2a) .The

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					guideline will not be covering IV fluid therapy (for adults or paediatrics) or the specific management of less common causes of AKI (see 4.3.2).
SH	Abbott GmbH& Co KG	3	4.3.1 b	Limitation of clinical risk assessment in the identification and ongoing assessment of AKI to Creatinine and urine output should be re-considered in light of 2 recent publication. (Haase t al, JACC (2011); 57: 1752-1761 and Singer et al, Kidney International on-line publ 16 March 2011) In the 2011 in JACC published meta analysis by Haase et al based on 2322 critically ill adult and paediatric patients NGAL testing allowed to identify a subclinical AKI in patients who did not have diagnostic increase in creatinine but a much greater risk of adverse medial outcome when compared to NGAL negative patients. Original quotes (http://www.sciencedaily.com/releases/2011/04/110418161701.htm) from AKI experts XXXX : ' We concluded that these substantial numbers of patients might reasonably be classified as having sub-clinical AKI, even though they do not fulfill current creatinine-based criteria for AKI. "Our findings dictate a need for complete reassessment of the very concept of and diagnosis of AKI. They also point to an urgent need for testing whether NGAL-based early diagnosis of AKI can lead to timelier deployment of therapies and improved outcomes' XXXX: 'Our findings suggest an important analogy between the troponin/creatine kinase relationship in acute myocardial infarction and the NGAL/creatinine relationship in AKI for the identification of previously undetected organ injury. Just as the increased diagnostic sensitivity of troponin has dramatically altered the definition, diagnosis, and management of acute myocardial infarction, similar concepts might apply to NGAL and AKI.' In a second 2011 Kidney International online published paper urinary NGAL was shown to be useful in classifying and stratifying patients with established AKI as defined by RIFLE criteria.	Thank you for your comment. We are unable to include biomarkers in this guideline because: 1. There is a lack of randomised control trials comparing biomarkers to standard care 2. Given the evidence base for biomarkers is evolving, an economic evaluation at this point in time is likely to be subject to significant limitations Please note that it is possible for stakeholders to submit evidence to another area of NICE guidance development, the NICE diagnostic technologies programme. For further information please see the NICE website: http://www.nice.org.uk/aboutnice/howwework/developingnnicediagnostictechnologiesguidance/developingnicediagnostictechnologiesguidance.jsp.

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Cardiac Biomarkers

The Outcome of Neutrophil Gelatinase-Associated Lipocalin-Positive Subclinical Acute Kidney Injury

A Multicenter Pooled Analysis of Prospective Studies

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Berlin and Magdeburg, Germany; Cincinnati, Ohio; Melbourne, Australia; Vicenza, Italy; New York, New York; Chicago, Illinois; Dublin, Ireland; Montreal, Quebec, Canada; Athens, Greece; Stockholm, Sweden; and Nashville, Tennessee

Objectives The aim of this study was to test the hypothesis that, without diagnostic changes in serum creatinine, increased neutrophil gelatinase-associated lipocalin (NGAL) levels identify patients with subclinical acute kidney injury (AKI) and therefore worse prognosis.

Background Neutrophil gelatinase-associated lipocalin detects subclinical AKI hours to days before increases in serum creatinine indicate manifest loss of renal function.

Methods We analyzed pooled data from 2,322 critically ill patients with predominantly cardiorenal syndrome from 10 prospective observational studies of NGAL. We used the terms NGAL(−) or NGAL(+) according to study-specific NGAL cutoff for optimal AKI prediction and the terms sCREA(−) or sCREA(+) according to consensus diagnostic increases in serum creatinine defining AKI. A priori-defined outcomes included need for renal replacement therapy (primary endpoint), hospital mortality, their combination, and duration of stay in intensive care and in-hospital.

Results Of study patients, 1,296 (55.8%) were NGAL(−)/sCREA(−), 445 (19.2%) were NGAL(+)/sCREA(−), 107 (4.6%) were NGAL(−)/sCREA(+), and 474 (20.4%) were NGAL(+)/sCREA(+). According to the 4 study groups, there was a stepwise increase in subsequent renal replacement therapy initiation—NGAL(−)/sCREA(−): 0.0015% versus NGAL(+)/sCREA(−): 2.5% (odds ratio: 16.4, 95% confidence interval: 3.6 to 76.9, $p < 0.001$), NGAL(−)/sCREA(+): 7.5%, and NGAL(+)/sCREA(+): 8.0%, respectively, hospital mortality (4.8%, 12.4%, 8.4%, 14.7%, respectively) and their combination (4-group comparisons: all $p < 0.001$). There was a similar and consistent progressive increase in median number of intensive care and in-hospital days with increasing biomarker positivity: NGAL(−)/sCREA(−): 4.2 and 8.8 days; NGAL(+)/sCREA(−): 7.1 and 17.0 days; NGAL(−)/sCREA(+): 6.5 and 17.8 days; NGAL(+)/sCREA(+): 9.0 and 21.9 days; 4-group comparisons: $p = 0.003$ and $p = 0.040$, respectively. Urine and plasma NGAL indicated a similar outcome pattern.

Conclusions In the absence of diagnostic increases in serum creatinine, NGAL detects patients with likely subclinical AKI who have an increased risk of adverse outcomes. The concept and definition of AKI might need re-assessment. (J Am Coll Cardiol 2011;57:1752–61) © 2011 by the American College of Cardiology Foundation

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				Urinary neutrophil gelatinase-associated lipocalin distinguishes pre-renal from intrinsic renal failure and predicts outcomes Eugenia Singer[1,2,4], Antje Elger[1,2], Saban Elitok[2], Ralph Kettritz[1,2], Thomas L. Nickolas[3], Jonathan Barasch[3], Friedrich C. Luft[1,2] and Kai M. Schmidt-Ott[1,2] [1]Experimental and Clinical Research Center, a joint institution of the Charité Medical Faculty and the Max-Delbrück Center for Molecular Medicine, Berlin, Germany; [2]Department of Nephrology and Hypertension, Franz-Volhard Clinic, Helios Clinics Berlin, Berlin, Germany and [3]Department of Medicine, Columbia University College of Physicians and Surgeons, New York, New York, USA	
SH	Abbott GmbH& Co KG	4	4.3.2 b	Availability of biomarker assays is not a limitation. CE marked assays are available for new biomarkers like NGAL and Cystatin C for majority of system solutions in the laboratory.	Thank you for your comment. We are unable to include biomarkers in this guideline because: 1. There is a lack of randomised control trials comparing biomarkers to standard care 2. Given the evidence base for biomarkers is evolving, an economic evaluation at this point in time is likely to be subject to significant limitations Please note that it is possible for stakeholders to submit evidence to another area of NICE guidance development, the NICE diagnostic technologies programme. For further information please see the NICE website: http://www.nice.org.uk/aboutnice/howwework/developingnnicediagnostictechnologiesguidance/developingnicediagnostictechnologiesguidance.jsp
SH	Association for Clinical Biochemistry	1	4.3.1.b	1. The use of serum creatinine in diagnosis and staging should include an evaluation of current methodologies available in routine clinical biochemistry laboratories. We should build on our knowledge of the most	Thank you for your comment. The evidence for serum creatinine is being looked at as part of the scope (4.3.1b).

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				appropriate creatinine methodology for CKD staging to determine whether the same criteria also apply to AKI diagnosis and staging. Any cost implications should also be evaluated. 2. Paralleling the use of laboratory computers to automatically calculate and report eGFR for CKD staging, their use should be explored to monitor changes in a person's serum creatinine (known in the lab as delta checking) and automatically alert a clinician to a significant increase to facilitate the early recognition of AKI and treatment/referral as appropriate, in line with the results of the NCEPOD study.	Evaluations of all current methodologies for measurement, including those for serum creatinine are beyond the scope of this guideline. For all questions included in the guideline, the economic implications (unit costs, long term costs and quality of life) will be considered.
SH	Baxter Healthcare (UK)	1	2	Would NICE consider changing the word "dialysis" and using the term "Renal Replacement Therapy" in preference as we feel it gives a more accurate reflection of the treatment and is more commonly used in clinical practice.	Thank you for your comment. The term, "dialysis" was in the original remit from the Department of health and therefore cannot be changed in this statement. However, for the purposes of the rest of this guideline the term "renal replacement therapy" was agreed as more appropriate terminology.
SH	Baxter Healthcare (UK)	2	4.1.1.b	We believe that another important group for consideration are those patients with sepsis as these patients also carry a high risk of developing AKI. Would NICE consider adding in this group and considering the evidence? ***Sepsis and Acute Kidney Injury*** ***A. Zarjou and A. Agarwal (2011) J Am Soc Nephrol 22: 999–1006.*** And ***Clinical review: Blood purification for sepsis. Rimmelé et al (2011) Critical Care 2011, 15:205***	Thank you for your comment. We have amended the scope to read "People at high risk of developing AKI such as people with CKD and urological disorders". Patients with sepsis would be covered by this. The list included in the scope is not exhaustive. The Guideline Development Group will agree the key groups for inclusion at the beginning of the guideline development process.
SH	Baxter Healthcare (UK)	3	4.3.1.a	We agree that "Clinical risk assessment in the identification and ongoing assessment of acute kidney injury" is an important area for review. Also, will NICE review the evidence relating to the impact on outcomes where there is limited availability of ultrasound and interventional radiology?	Thank you for your comment. For the questions included in the guideline, the GDG will consider all relevant clinical and cost-effectiveness evidence. Where evidence exists the Guideline

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					Development Group will consider the impact on care and make appropriate recommendations.
SH	Baxter Healthcare (UK)	4	4.3.1.d	Would NICE consider expanding this point to include prevention of AKI associated with surgery. In particular would NICE consider the evidence in prevention of AKI following cardiac surgery? ***Clinical accuracy of RIFLE and Acute Kidney Injury Network (AKIN) criteria for acute kidney injury in patients undergoing cardiac surgery. Englberger et al (2011) Critical Care, 15:R16***	Thank you for your comment. Whilst it may be possible for us to consider risk assessment (4.3.1a) for surgical patients in general we would be unable to look at cardiac surgery specifically as the guideline is aimed at the management of AKI by non-specialists.
SH	Baxter Healthcare (UK)	5	4.3.1.g	We suggest that the wording of this point could be changed to a more accurate description … Investigation and management of AKI secondary to kidney obstruction	Thank you for your comment. As it is not possible to cover all aspects of AKI within this guideline, clinical issues need to be prioritised. It was felt that the timing of relief of obstruction was the key clinical issue in this area where there was variation in practice. Ultrasound will be covered separately in 4.3.1f.
SH	Baxter Healthcare (UK)	6	4.3.1.i	We agree that this point is important but suggest that consideration is also given to criteria for ICU referral and admission with AKI	Thank you for your comment. Criteria for involvement of critical care are set out in NICE CG 50 "Acutely ill patients in hospital". This guideline will be cross referred to as appropriate during the development of this guideline.
SH	Baxter Healthcare (UK)	7	4.3.1.j	The following evidence may be useful to consider in relation to the question "At what stage should renal replacement therapy be considered?" ***Correlation between parameters at initiation of RRT and outcome in patients with acute kidney injury. Ostermann and Chang. (2009) Critical Care, 13:R175*** And ***A proposed algorithm for initiation of renal replacement therapy in adult critically ill patients Bagshaw et. Al. Critical Care 2009, 13:317 And Meta Analysis on timing of initiation of RRT Karvellas et al. (2011) Critical Care 15:R72***	Thank you for your comment and information.

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SH	Baxter Healthcare (UK)	8	4.3.2	Would NICE re-consider the inclusion of IV fluid management in the treatment of AKI? Whilst we are aware of the NICE guidelines for IV therapy in development, our understanding is that these will focus on Acute Kidney Injury patients not requiring intensive care or renal replacement therapy. There is therefore a risk that an important group of patients may be missed i.e. those in the intensive care setting who have or are at risk of AKI and who require IV therapy. There is a wealth of evidence (some examples provided below) to support the view that IV fluid management is critical in the resus phase of AKI but that the effect also carries over to the established phase. We believe that not reviewing this specifically in these guidelines could lead to poor practice and think that it is important to review the clinical importance of fluid balance assessment and resuscitation to prevent ongoing kidney injury as well as the effects of fluid balance during the pre RRT phase on later survival with AKI. ***Payen D, de Pont AC, Sakr Y et al. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. Crit Care 2008; 12: R74*** ***Bouchard J, Soroko SB, Chertow GM et al.Fluid accumulation , survival and recovery of kidney function in critically ill patients with acute kidney injury. Kidney Int 2009; 76: 422-27***	Thank you for your comment. A separate NICE guideline for IV fluid therapy is being developed alongside this one. The scope for IV fluids has recently been out for consultation (14 June - 5 July 2011). At present it reads: "Appropriate care for particular groups of patients who may be at higher risk of issues relating to intravenous fluid therapy: a. Patients with AKI, up to the point of renal replacement therapy". The ITU setting has not been excluded in the consultation version of the scope. The technical team will ensure that the information you have provided is passed to the technical team developing the guidance on IV fluid therapy.
SH	British Dietetic Association	1	general	We have circulated this consultation to our membership and we do not have any comments at this stage.	Thank you for your comment.
SH	Department of Health	1	general	The Department of Health has no substantive comments to make, regarding this consultation	Thank you for your comment.
SH	Great Western Hospitals NHS Foundation Trust	1	4.1.1	There are additional at risk groups which require additional consideration and comment: 1. Secondary care: Patients with urological disorders (who are often left with residual chronic renal failure predisposing them to acute	Thank you for your comment. 1. We agree and have changed the scope to read " People at high risk of developing AKI such as people

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				injury and the use of antiobiotics such as Gentamicin in such settings which can precipitate such injury). 2. Primary Care: those on particular drugs associated with acute kidney injury in the setting of volume depletion such as diuretics, ACE / ARBs and metformin. 3. In addition, particular groups need to be pointed out as being outside the purview of "general AKI measures": such as those with hepatorenal and cardiorenal syndromes.	with CKD and urological disorders" 2. This group will be covered by the above change in wording and specifically in 4.3.1d 3. We have amended this section of the scope following consultation. However we do not agree that the groups mentioned should be excluded from consideration.
SH	Great Western Hospitals NHS Foundation Trust	2	4.3.1 a)	1. The guidelines will want to cross-reference the need for physiological monitoring as set out in NICE CG 50. 2. Guidance for the indications of urinary catheterisation in acute kidney injury and its removal during the management of such patients should be covered in this guideline. 3. The need to avoid cannulation of non-dominant forearm veins with those with chronic kidney disease is paramount in terms of the success of future vascular access and should be mentioned.	Thank you for your comments. 1 The guideline development group will cross refer to this guidance as appropriate when developing the guideline. 2 We will be looking at urinary catheterisation in 4.3.1g – timing of relief of urological obstruction. 3 Whilst we acknowledge that this is an important consideration in these patients it is beyond the scope of this guideline.
SH	Great Western Hospitals NHS Foundation Trust	3	4.3.1 b)	1. eGFR reporting for inpatients with acute kidney injury should be discouraged as this is not a valid tool for estimating renal function in such settings. 2. Primary care consultations should be cognizant of the above point with relation to assessment, as well as when liaising with secondary care about patients with potential acute kidney injury. 3. The use of urinalysis for assessment of acute kidney injury in primary care needs to be highlighted. 4. The use of centrifuged urine samples in case of suspected glomerulonephritis should be highlighted.	Thank you for your comment and these points of information. 1 & 2. This is why we are concentrating on serum creatinine and urine output in 4.3.1b 3 & 4. Urinalysis will be covered in 4.3.1c. The scope includes primary care.
SH	Great Western	4	4.3.1 f)	Estimation of measurements of renal size should be age and gender -	Thank you for your comment. The

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	Hospitals NHS Foundation Trust			referenced from published literature rather than subjective comments such as "normal sized".	Guideline Development group will consider this information when reviewing the evidence in this area.
SH	Great Western Hospitals NHS Foundation Trust	5	4.3.1 g)	1. The severity of obstructive renal findings is dependent on time course - this point needs to be highlighted in the guidelines for clinicians to consider when dealing with urinary tract obstruction. 2. The urgent management of suspected pyonephrosis deserves special mention in the guidelines and the time course of management of this condition is different from non-infective obstruction.	Thank you for your comment. 1. We agree that this would be useful information to include, however this would be most appropriate for inclusion in the guideline to ensure that the scope remains brief. 2. Whilst we recognise the importance of the management of suspected pyonephrosis, we are unable to include this as the focus is on non-specialist management of AKI and there is a need to prioritise the areas covered as part of this guideline.
SH	Great Western Hospitals NHS Foundation Trust	6	4.3.1 i)	This should include a section on the recognition of rapidly progressive glomerulonephritis (RPGN) and thrombotic microangiopathies.	Thank you for your comment. Whilst we recognise the importance of these conditions we do not consider it appropriate to include them in the guideline as the focus is on non-specialist management of AKI and there is a need to prioritise the areas covered as part of this guideline.
SH	Great Western Hospitals NHS Foundation Trust	7	4.3.1 j)	General guidance on the use of intravenous sodium bicarbonate for severe metabolic acidosis, particulary in the context of severe hyperkalaemia, while arrangements for renal replacement are being made, deserve mention.	Thank you for your comment. Whilst we recognise that intravenous sodium bicarbonate may be used in the treatment of severe metabolic acidosis we do not consider this appropriate to include in the guideline as the focus is on non-specialist management of AKI and there is a need to prioritise the areas we cover. Criteria

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					for referring to nephrology services will be included in the guideline.
SH	Kidney Alliance	1	General	The Kidney Alliance welcomes the work on Acute Kidney Injury as we see it as an important patient safety issue, crossing both primary and secondary care. Acute kidney injury is common, harmful and potentially treatable. It has a direct effect on mortality and quality of life and this is an opportunity to improve this hitherto under addressed area which needs data, leadership and comparative analysis.	Thank you for your comment.
SH	NCEPOD	1	General	This is a great piece of work and NCEPOD has nothing additional to add at this stage.	Thank you for your comment.
SH	NHS Direct	1	general	NHS Direct welcome the guideline and have no comments on the contents of the draft scope.	Thank you for your comment.
SH	Novartis Molecular Diagnostics	1	General	The scoping document for the draft scope consultation has changed little since the workshop held on 06 April 2011. Most of the discussion and comments from all relevant stakeholders seem to have been omitted and/or not taken into consideration at all. Below, please find enclosed our comments in written for NICE's consideration.	Thank you for your comments. We have responded to each comment made as part of the consultation process individually. All stakeholder comments from both the scoping workshop and the public consultation have been considered in determining the final scope. The notes from the scoping workshop are available on the NICE website for information
SH	Novartis Molecular Diagnostics	2	4.1.1.b.)	Patient with significant comorbidities need to be consider; these include (although not exhaustive) cardio-pulmonary bypass; sepsis, and ischemic heart disease.	Thank you for your comment. We have changed the scope to read "People at high risk of developing AKI such as people with CKD and urological disorders". Patients with sepsis would be covered by this. The list included in the scope is not exhaustive. The Guideline Development Group will agree the key groups for inclusion at the beginning of the guideline development process.
SH	Novartis Molecular Diagnostics	3	4.1.2	Published clinical data from paediatric studies show equal or higher incidence rate of AKI in children undergoing cardiac surgery or diagnosed	Thank you for your comment. Having considered the information provided by

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				with sepsis. As such this population is very relevant for the decision problem to be addressed by the guideline. See for example references PMID 20978799, PMID: 21300375, PMID 18070344	stakeholders, we will now be including children over the age of one month in the guideline. We have changed the scope to reflect this (section 3.1, 3.2, 4.1.1a, 4.1.2a). Some exclusions remain relevant to the paediatric population. The guideline will not cover neonates (see 4.1.2a) .The guideline will not be covering IV fluid therapy (for adults or paediatrics) or the specific management of less common causes of AKI (see 4.3.2).
SH	Novartis Molecular Diagnostics	4	4.3.1	The clinical impact of an early diagnosis of AKI versus a late diagnosis of AKI should be considered as key clinical issue. For instance, what does it mean in terms of prevention, detection and time to intervention of downstream effects such as chronic kidney disease?	Thank you for your comment. We are planning to look at this area in 4.3.1 (a) "Clinical risk assessment in the identification and ongoing assessment of acute kidney injury".
	Novartis Molecular Diagnostics	5	4.3.1 a)	The utility and limitations of using clinical scores for assessing the patient's risk for AKI might be discussed in this section, including a comparison of different scoring methods. This is of special importance when considering serum creatinine a biomarker that reflects an established damage to the kidney structure with implications for early detection and prevention of downstream consequences (see comment 5 above)	Thank you for your comment. The utility and limitations of using clinical scores for assessing the patient's risk for AKI would be most appropriate for discussion in the guideline so that the scope remains brief. The guideline Development Group will consider this information when developing the guideline.
SH	Novartis Molecular Diagnostics	6	4.3.1. b)	Limitations and advantages of different scoring systems of AKI should be discussed in this section, e.g. using RIFLE versus AKIN criteria (see comments 5 and 6 above)	Thank you for your comment. We agree that this would be useful information to include, however this would be most appropriate for inclusion in the guideline to ensure that the scope remains brief.
SH	Novartis Molecular Diagnostics	7	4.3.2. b)	The use of biomarkers as auxiliary tools to diagnose AKI should be considered. There is currently not yet enough literature to support the use of biomarkers as stand-alone tools to detect AKI, but the use of biomarkers as auxiliary tools on top of SCr and urine output might be justified by the time this guideline will be published. See for example	Thank you for your comment. We are unable to include biomarkers in this guideline because: 1. There is a lack of randomised control trials comparing

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				references PMID 20935115, PMID 20363104, PMID 20173352, PMID 19956925, PMID 19956924	biomarkers to standard care 2. Given the evidence base for biomarkers is evolving, an economic evaluation at this point in time is likely to be subject to significant limitations Please note that it is possible for stakeholders to submit evidence to another area of NICE guidance development, the NICE diagnostic technologies programme. For further information please see the NICE website: http://www.nice.org.uk/aboutnice/howwework/developingnnicediagnostictechnologiesguidance/developingnicediagnostictechnologiesguidance.jsp
SH	Novartis Molecular Diagnostics	8	4.3.2. c)	It is appreciated that another guideline is been developed for intravenous fluid management; however, as it is critical part of current management of patients with AKI and/or CKD, at least a summary which addresses its overall effect on AKI need to be considered (see comment 6 above)	Thank you for your comment and suggestions. A separate NICE guideline for IV fluid therapy is being developed alongside this one. "Acute Kidney Injury patients not requiring renal replacement therapy" has been identified as a group that will be covered. The two guidelines are being developed in parallel and there has already been work across the scoping phases of guideline development. This will continue throughout guideline development to ensure consistency of approach and the input of relevant professional groups .
SH	Novartis Molecular Diagnostics	9	4.4	A sustained loss of kidney function / or a sustained increase of serum creatinine at discharge should be considered as clinical outcome. In many hospital databases and medical records a long-term outcome of chronic kidney disease is not recorded, as CKD can only be diagnosed after	Thank you for this information. The outcomes listed are examples suggested for questions that we expect the guideline to answer. The list is not exhaustive and

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				several months. However, a sustained increase of serum creatinine demonstrates non-recovered loss of renal function and can be considered a surrogate of CKD.	will be tailored to each evidence review. The guideline development group will finalise the list and we will include your suggestions in the options that we will consider.
SH	Novartis Molecular Diagnostics	10	4.4	Chronic Kidney Disease should be considered as outcome, in particular as this has a significant impact on patients quality of life and a represents a substantial cost for the NHS.	Thank you for your comment. The outcomes listed are examples suggested for questions that we expect the guideline to answer. The list is not exhaustive and will be tailored to each evidence review. The guideline development group will finalise the list and we will include your suggestion in the options that we will consider.
SH	Novartis Molecular Diagnostics	11	4.4.c)	As part of length of stay, it would be also critical to record the type of hospitalisation associated to it (e.g. A&E, ward, ICU)	Thank you for your comment. The outcomes listed are examples suggested for questions that we expect the guideline to answer. The list is not exhaustive and will be tailored to each evidence review. The guideline development group will finalise the list and we will include your suggestion in the options that we will consider.
SH	Novartis Molecular Diagnostics	12	4.5	Detailed resource utilisation and additional cost of AKI complications to the hospital per patient should be described	Thank you for your comment. 1. A review of economic literature will be carried out on every question and detailed resource utilisation and additional cost of AKI complications will be considered in the analysis where appropriate.

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					2. Where there is limited or no cost effectiveness literature and an area is prioritized for economic evaluation by the guideline development group, original economic modeling will be undertaken.
SH	Novartis Molecular Diagnostics	13	4.5	Hospital day costs pre and post should be measured, and assessed within a cost-effectiveness framework	Thank you for your comment. 1. A review of economic literature will be carried out on every question and hospital day costs will be considered in the analysis where appropriate. 2. Where there is limited or no cost effectiveness literature and an area is prioritized for economic evaluation by the guideline development group, original economic modeling will be undertaken.
SH	Novartis Molecular Diagnostics	14	4.5	The economic aspects of the guideline are too vague. For instance, it might be obvious that the risk of developing CKD after an AKI episode and the associated costs for CKD need to be considered, as episodes of AKI increase significantly the risk of developing CKD; however, it would be useful to lay out the 'basics' of the cost-effectiveness framework.	Thank you for your comment. Exact details of which resource use components are to be included in the health economics analyses will be determined as the development of the guideline progresses. The Guideline Development Group will

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					consider your suggestions on the risk and associated costs of CKD in any analysis that is carried out.
SH	Royal College of Nursing	1	General	The Royal College of Nursing welcomes proposals to develop this guideline. It is very timely and hopefully will draw from the recent publication on Acute Kidney Injury failings by NCEPOD. The draft scope is comprehensive.	Thank you for your comment.
SH	Royal College of Nursing	2	3.1 b)	b) We would recommend to add the AKIN definition similar to what has been added for RIFLE – proposal needs to delineate the link / differences in use of both RIFLE & AKIN	Thank you for your comment. We agree that this would be useful information to include, however this level of detail would be most appropriate for the guideline introduction. The scope is a brief overview document.
SH	Royal College of Nursing	3	3.1. d)	d) There also needs to be some reference to AKI mortality in those patients not requiring renal replacement therapy - Lafrance et (2010) work has identified a high mortality in patients who did not require dialysis in most sever forms of AKI. Reference: Lafrance PJ, and Miller R D. (2010) Acute Kidney Injury Associates with Increased Long-Term Mortality. *J Am Soc Nephrol* 21: 345-352	Thank you for your comment. We have added this information into the scope (3.1.c)
SH	Royal College of Nursing	4	4.1.2 a)	As children under 16 have been excluded from this guideline (once again) are we to assume that a separate one will be done for children in the future?	Thank you for your comment. Having considered the information provided by stakeholders, we will now be including children over the age of one month in the guideline. We have changed the scope to reflect this (section 3.1, 3.2, 4.1.1a, 4.1.2a). Some exclusions remain relevant to the paediatric population. The guideline will not cover neonates (see 4.1.2a) .The guideline will not be covering IV fluid therapy (for adults or paediatrics) or the specific management of less common causes of AKI (see 4.3.2).

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SH	Royal College of Nursing	5	4.2	Should the 'Health care setting 'include all settings rather than just the NHS. We acknowledge that NICE guidelines are for use in the NHS but consider that these guidelines must cover all providers so that a high and consistent standard can be adhered to.	Thank you for your comment. NICE guidance is commissioned for the NHS, but people providing healthcare in other settings, such as private settings, may find the guidance relevant.
SH	Royal College of Nursing	6	4.3.1 b)	b) eGFR should be included here so that the sentence reads: b) eGFR, serum creatinine and urine output in diagnosis and staging.	Thank you for your comment. Having discussed this at the stakeholder workshop, we do not think that eGFR should be prioritised as a question as it is only valid when renal function is stable and is not used in the AKIN criteria for AKI.
SH	Royal College of Paediatrics and Child Health	1	4.1.1 a	The causes and consequences of AKI in children are in fact similar to those in adults and there is commonality in management strategy. As in many areas, the evidence base on which to inform guidelines for the management of children with AKI is small and it is consequently helpful to draw upon the evidence base for adults. This approach has been successfully used for NICE guidance on peritoneal dialysis and anaemia. At the recent NICE workshop on AKI there was unanimous support for including children in the guidance, and there is support for this approach from both the British Association for Paediatric Nephrology and from the Royal College of Paediatrics and Child Health. It would be greatly regrettable if children are not included in this guidance, missing an opportunity to enhance the care of critically ill children destined to have significant morbidity and mortality.	Thank you for your comment. Having considered the information provided by stakeholders, we will now be including children over the age of one month in the guideline. We have changed the scope to reflect this (section 3.1, 3.2, 4.1.1a, 4.1.2a). Some exclusions remain relevant to the paediatric population. The guideline will not cover neonates (see 4.1.2a) .The guideline will not be covering IV fluid therapy (for adults or paediatrics) or the specific management of less common causes of AKI (see 4.3.2).
SH	Royal College of Paediatrics and Child Health	2	4.1.1 a	The age range should be widened to include children for these reasons. The experience related to AKI in young people aged 16 to 18 will often be included in the paediatric literature and not in the adult literature and you will have inadequate information if you do not include paediatric searches. The mechanism of kidney injury to produce AKI in children are exactly the	Thank you for your comment. Having considered the information provided by stakeholders, we will now be including children over the age of one month in the guideline. We have changed the scope to reflect this (section 3.1, 3.2, 4.1.1a, 4.1.2a). Some exclusions remain relevant

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				same as for adults; in other words sepsis, asphyxia, systemic illness, iatrogenic through drug therapies with nephrotoxic side effects and not from primary disease. *SL Goldstein, P Devarajan. Acute Kidney Injury in childhood: should we be worried about progression to CKD? Pediatric Nephrology. 26/4 (April 2011):509-522.*	to the paediatric population. The guideline will not cover neonates (see 4.1.2a) .The guideline will not be covering IV fluid therapy (for adults or paediatrics) or the specific management of less common causes of AKI (see 4.3.2).
SH	Royal College of Paediatrics and Child Health	3	4.1.2.a	"with a different spectrum of causes": This statement is **incorrect**; paediatric AKI is seen, as in adults, with the same mechanisms (see earlier comment) "disease progression": The factors in disease progression of the younger end of the spectrum of the proposed scope (16 years of age onwards) are going to be different to what will be found in the oldest patients but **the same** as in the younger children. "This group has a much lower incidence of acute kidney injury": This is another reason for asking for children to be included in this guideline as a specific AKI paediatric guideline will not have priority within the wider paediatrics topics.	Thank you for your comment. Having considered the information provided by stakeholders, we will now be including children over the age of one month in the guideline. We have changed the scope to reflect this (section 3.1, 3.2, 4.1.1a, 4.1.2a). Some exclusions remain relevant to the paediatric population. The guideline will not cover neonates (see 4.1.2a) .The guideline will not be covering IV fluid therapy (for adults or paediatrics) or the specific management of less common causes of AKI (see 4.3.2).
SH	Royal College of Paediatrics and Child Health	4	3.1 a	"It is mainly seen in acutely unwell patients, so about 90% of cases occur in hospital inpatients." We note that this is also the case in children, where most of the AKI occurs in hospitalised children.	Thank you for your comment. Having considered the information provided by stakeholders, we will now be including children over the age of one month in the guideline. We have changed the scope to reflect this (section 3.1, 3.2, 4.1.1a, 4.1.2a). Some exclusions remain relevant to the paediatric population. The guideline will not cover neonates (see 4.1.2a) .The guideline will not be covering IV fluid therapy (for adults or paediatrics) or the specific management of less common causes of AKI (see 4.3.2).
SH	Royal College of Paediatrics and	5	3.1 b	RIFLE and AKIN have also been adopted in paediatrics.	Thank you for your comment. Having considered the information provided by

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	Child Health				stakeholders, we will now be including children over the age of one month in the guideline. We have changed the scope to reflect this (section 3.1, 3.2, 4.1.1a, 4.1.2a). Some exclusions remain relevant to the paediatric population. The guideline will not cover neonates (see 4.1.2a) .The guideline will not be covering IV fluid therapy (for adults or paediatrics) or the specific management of less common causes of AKI (see 4.3.2).
SH	Royal College of Paediatrics and Child Health	6	3.1 c	"There is evidence that even small deteriorations in renal function are associated with increased mortality." This is also the case in children where mortality from their illness increases in those who have had AKI, and as in the adult population. Modest drops as in AKIN also used in children.	Thank you for your comment. Having considered the information provided by stakeholders, we will now be including children over the age of one month in the guideline. We have changed the scope to reflect this (section 3.1, 3.2, 4.1.1a, 4.1.2a). Some exclusions remain relevant to the paediatric population. The guideline will not cover neonates (see 4.1.2a) .The guideline will not be covering IV fluid therapy (for adults or paediatrics) or the specific management of less common causes of AKI (see 4.3.2).
SH	Royal College of Paediatrics and Child Health	7	3.2 c	Similarly, in children the majority of these patients are admitted to general paediatric units or under the oncologists, surgeons, intensive care for non renal related conditions.	Thank you for your comment. Having considered the information provided by stakeholders, we will now be including children over the age of one month in the guideline. We have changed the scope to reflect this (section 3.1, 3.2, 4.1.1a, 4.1.2a). Some exclusions remain relevant to the paediatric population. The guideline will not cover neonates (see 4.1.2a) .The guideline will not be covering IV fluid

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					therapy (for adults or paediatrics) or the specific management of less common causes of AKI (see 4.3.2).
SH	Royal College of Paediatrics and Child Health	8	4.3.1	We think it should include follow up as there will be specific advice regarding monitoring, safety of drugs in compromised renal function, etc. The guideline title should include "follow up".	Thank you for your comment. We are unable to change the remit that is given to us by the Department of Health. Advice to patients and carers is covered by 4.3.1(k) "Information and support for patients and carers."
SH	Royal College of Paediatrics and Child Health	9	General	Although paediatrics is specifically excluded, the scope otherwise looks quite good.	Thank you for your comment.
SH	Royal College of Pathologists	1	4.3.1 b.	Consider serum creatinine methodology as many laboratories use methods which are subject to interference, for example from bilirubin. This may lead to cases of hepato-renal failure being missed if serum creatinine is the key biochemical parameter.	Thank you for your comment. We will only be considering the value of the measure of serum creatinine in the diagnosis and staging of AKI. Evaluation of methodology is beyond the scope of this guideline
SH	Sheffield Teaching Hospital NHS Foundation Trust	1	4.3.1 (a)	Suggest careful consideration of the criteria used for defining of AKI. Junior doctors find AKIN criteria difficult to remember/ apply. In our local policy, we are working on a simplified version, to achieve better engagement. Also there should be some guidance on identifying those at risk of AKI prior to onset. The need for provision of learning resources for junior doctors/ nursing staff could be specifically mentioned.	Thank you for your comments. The Guideline Development Group will consider these points when developing the guideline.
SH	Sheffield Teaching Hospital NHS Foundation Trust	2	4.3.1 (h)	No concrete evidence for the use of either. If used, specialist input (nephrology/critical care) should be sought. Therefore, does not need be included in guidelines that are mainly aimed at non-specialists	Thank you for your comment. Feedback at the scoping workshop indicated that these drugs were still being used incorrectly by non-specialists in some areas and that therefore this issue needs to addressed to allow the guideline development group to make appropriate recommendations for care.
SH	Sheffield Teaching	3	4.3.1 (j)	Whereas the indications for renal replacement therapy should be clearly	Thank you for your comment. We will be

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	Hospital NHS Foundation Trust			stated, the timing of initiation of RRT in those with no absolute indication is a specialist area, and the guidelines are by-and-large aimed at non-nephrologists. As above, I do not think there is a need for prescriptive guidance on timing of RRT.	considering the indications for RRT when reviewing stage at which RRT should be started.
SH	Sheffield Teaching Hospital NHS Foundation Trust	4	4.3.1 (i)	As well as criteria for involvement of renal services, criteria for involvement of critical care, should also be included, especially in the settings of: i) single organ failure but unsafe to transfer due to severe hyperkalaemia or acidaemia. Some critical care departments are reluctant to accept those patients. ii) hypotension Safety for transfer is an area that merits some guidance	Thank you for your comment. Criteria for involvement of critical care are set out in NICE CG 50 "Acutely ill patients in hospital" and these will be cross referred to as appropriate as part of the guideline development process.
SH	Sheffield Teaching Hospital NHS Foundation Trust	5	4.4	Rate of hospital acquired AKI should be an outcome measure (the implementation of the guidelines should reduce rates of avoidable AKI/ worsening from mild to severe stages of AKI). Data could be obtained from critical care units, renal departments and laboratory reporting systems.	Thank you for this information. The outcomes listed are examples suggested for questions that we expect the guideline to answer. The list is not exhaustive and will be tailored to each evidence review. The guideline development group will finalise the list and we will include your suggestion in the options that we will consider.
SH	South Wales Critical Care Network	1	General	I've sought comments from my colleagues in the South Wales Critical Care Network and received nothing but assent and agreement with what is proposed. I would be grateful if it could be noted that the Network is fully supportive of the scope.	Thank you for your comment and support for this guideline.
SH	The Royal College of Physicians/The Renal Association	1	1	I'm very pleased that prevention detection and management will be covered. It is essential that prevention is part of this guideline as it is an area where there is potential to make a significant difference	Thank you for your comment.
SH	The Royal College of Physicians/The Renal Association	2	3.1 b	The KDIGO AKI guidelines will be published in August edition of Kidney International	Thank you for your comment and information.
SH	The Royal College of Physicians/The	3	4.1.1 b	There needs to be consideration for what stage of chronic kidney disease	Thank you for your comment. We agree. However this would be most appropriate

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	Renal Association				for discussion in the guideline so that the scope remains brief.
SH	The Royal College of Physicians/The Renal Association	4	4.3.1 e	I would recommend using the terminology contrast induced acute kidney injury rather than contrast induced nephropathy	Thank you for your comment. The technical team will use both terminologies when searching for evidence. As there is no widely used terminology for this, the GDG will then consider which terminology is most appropriate to use when writing the full guideline.
SH	The Royal College of Physicians/The Renal Association	5	4.3.1 i	It will be important to give advice regarding timely referral to renal services	Thank you for your comment.
SH	The Royal College of Physicians/The Renal Association	6	4.3.1 j	I would not specifically cover this point, but concentrate on timely referral to renal services which may occur at different stages of acute kidney	Thank you for your comment. Referral to renal services will be covered by 4.3.1 (i) "Criteria for involving nephrology services".
SH	The Royal College of Physicians/The Renal Association	7	4.3.1 k	I think it is essential to improve the information provided to patients and carers with respect to AKI	Thank you for your comment. This is included in section 4.3.1.k of the draft scope.
SH	The Royal College of Physicians/The Renal Association	8	4.3.2 b	We're starting to see the introduction of biomarkers of acute kidney in the within the NHS. It is definitely an area that NICE needs to keep an eye on at a time when finances are very strict.	Thank you for your comment. We are unable to include biomarkers in this guideline because: 1. There is a lack of randomised control trials comparing biomarkers to standard care 2. Given the evidence base for biomarkers is evolving, an economic evaluation at this point in time is likely to be subject to significant limitations Please note that it is possible for stakeholders to submit evidence to another area of NICE guidance development, the NICE diagnostic

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					technologies programme. For further information please see the NICE website: http://www.nice.org.uk/aboutnice/howwework/developingnnicediagnostictechnologiesguidance/developingnicediagnostictechnologiesguidance.jsp
SH	The Royal College of Physicians/The Renal Association	9	4.3.2c	I have some concerns with intravenous fluid management not being within the guideline. The use of intravenous fluids is essential in the prevention and treatment of acute kidney injury. It is one of the few therapeutic manoeuvres that is available to prevent and treat the condition. I would suggest that the two groups work together on this and the advice is available in both guidelines. My concern is that if it is not in the AKI its importance will be dismissed.	Thank you for your comment and suggestions. A separate NICE guideline for IV fluid therapy is being developed alongside this one. "Acute Kidney Injury patients not requiring renal replacement therapy" is identified in the scope consultation as a group that will be covered. The two guidelines are being developed in parallel and there has already been work across the scoping phases of guideline development. This will continue throughout guideline development
SH	The Royal College of Physicians/The Renal Association	10	4.4	I would strongly recommend also including the following outcome measures: recovery of kidney function, degree of kidney function following the episode of AKI-i.e. the degree of chronic kidney disease, appropriate referral to GP or renal services following an episode of AKI	Thank you for your comment. The outcomes listed are examples suggested for questions that we expect the guideline to answer. The list is not exhaustive and will be tailored to each evidence review. The guideline development group will finalise the list and we will include your suggestions in the options that we will consider.
SH	The Society and College of Radiographers	1	General	We would welcome these guidelines as the evidence included shows poor survival rates and poor management of these patients.	Thank you for your comment.
SH	The Society and College of Radiographers	2	4.1.1 and 4.1.2	The groups identified in 4.1.1 and 4.1.2 seem acceptable as there are significant differences in the way renal failure occurs	Thank you for your comment.

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SH	The Society and College of Radiographers	3	4.3.1 C	We do not feel that urinalysis alone should be the only clinical testing offered. Potassium levels are important as are others that need to be analysed via a blood test	Thank you for your comment. We will consider tests important for risk assessment in 4.3.1a.
SH	The Society and College of Radiographers	4	4.3.2 B	Biomarkers do show potential and therefore we do not feel they should be dismissed.	Thank you for your comment. We are unable to include biomarkers in this guideline because: 1. There is a lack of randomised control trials comparing biomarkers to standard care 2. Given the evidence base for biomarkers is evolving, an economic evaluation at this point in time is likely to be subject to significant limitations Please note that it is possible for stakeholders to submit evidence to another area of NICE guidance development, the NICE diagnostic technologies programme. For further information please see the NICE website: http://www.nice.org.uk/aboutnice/howwework/developingnnicediagnostictechnologiesguidance/developingnicediagnostictechnologiesguidance.jsp
SH	The Society and College of Radiographers	5	4.4	We are not clear what the outcomes mean? There would seem to be more priority issues than 'length of stay in hospital' for example.	Thank you for your comment. The outcomes listed are examples suggested for questions that we expect the guideline to answer. The list is not exhaustive and will be tailored to each evidence review.

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					The guideline development group will finalise the list that we will consider.
SH	The Society and College of Radiographers	6	4.5	This comes across as a cost cutting exercise, which is concerning.	Thank you for your comment. Due to the limited resources available in the NHS, it is necessary to prioritize the interventions. This is done by using cost effectiveness analysis. This type of analysis considers both costs and outcomes to determine which interventions achieve the highest health gain per pound spent. This is done in the guideline in two ways: 1. A review of economic literature will be carried out on every question and this data will be considered in the analysis along with unit costs and longer-term costs and quality of life. 2. Where there is limited or no cost effectiveness literature and an area is prioritized for economic evaluation by the guideline development group, original economic modeling will be undertaken. The aim of the health economic analysis is not to cut costs but to ensure the sustainability of the NHS, through

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					ensuring the cost effectiveness of the interventions it recommends.
SH	The Vascular Society	1	4.3.1	One presumes that nephrotoxic contrast agents will be covered within the drugs section but this needs to be highlighted. One of the most significant reasons for AKI on vascular units in contrast nephrotoxicity. It would be useful for the guidelines to discuss the evidence and give appropriate guidelines on pre-procedural fluid replacement therapy and/or N-Acetylcysteine, cessation of ACE inhibitors etc.	Thank you for your comment. This is covered by 4.3.1(e) in the scope "Acetylcysteine and/or intravenous fluids to prevent contrast-induced nephropathy".
SH	The Vascular Society	2	4.3.1	In addition, section.4.3.1 (j) of the draft document states that they will look into the stage at which renal replacement therapy is introduced, should they also look at what criteria that are used to initiate RRT and whether this has any bearing on outcome and survival.	Thank you for your comment. We will be considering the criteria used to initiate RRT when reviewing the stage at which RRT should be started. The relevant outcomes will be tailored to each evidence review.
SH	The Vascular Society	3	General	A well written scope and fully supported by the Vascular Society.	Thank you for your comment and support for this guideline..
SH	UK Renal Pharmacy Group	1	general	The UK Renal Pharmacy Group supports the scope of the AKI guideline development.	Thank you for your comment.