

National Institute for Health and Care Excellence

Intravenous Fluid Therapy - Adults
Guideline Consultation Comments Table

Type	Stakeholder	Order No	Document	Section No	Page No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
SH	Association of Anaesthetists	1	Full	2.5	12 -13	to INCLUDE trauma but EXCLUDE traumatic brain injury could cause inappropriate treatment; specifically, to permit hypotonic Hartmann's for trauma when it is contra-indicated for ATBI (isotonic salt solutions recommended) poses dangers to patients.	Thank you for your comment, which refers to the hazards of isotonic volume resuscitation in ATBI. Internationally recognised trauma guidelines recommend the use of lactated Ringers solution (Na 130 mmol/L) or Hartmann's (Na 131 mmol/L) in the initial resuscitation of shocked trauma patients. It is recognised that brain injury may occur in the context of multiple injuries, although the primary disorder can usually be identified. Isotonic salt solutions may theoretically be preferable in isolated traumatic brain injury (TBI) with a risk of worsening brain swelling. However, Hartmann's is almost isotonic with blood and there is little effect on plasma osmolality after an infusion of this solution, versus 0.9% saline. The management of traumatic brain injury is outside of the scope of this guidance.
SH	Association of Anaesthetists	2	Full	3.1.2.5	20	principles of physiology and pathophysiology of intravenous fluids; surely of body fluids and their treatment. This field has been revolutionised by the work of Charles Michel and Rodney Levick, among	Thank you for your comment. However, we do not agree. In view of the lack of RCT evidence to support important aspects of our

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						others. Suggest reference a current Textbook for Medical Students/ trainee doctors such as 'An Introduction to Cardiovascular Physiology' 5th Edition. 2009.	guidance a focussed summary of the principles of fluid prescribing is required since these principles inform many of the recommendations.
SH	Association of Anaesthetists	3	Full	4	34 also 36, 71	"additional monitoring of urine sodium can help to identify whole-body sodium depletion in patients who have high-volume gastrointestinal losses, and may be useful in assessing sodium status in oedematous patients." Please explain in practical terms.	Thank you for your comment. We have expanded the text in the recommendation (see recommendation 1.2.4 in the NICE version of the guidance) and the section linking evidence to recommendations to explain the likely benefits and limitations of these measures.
SH	Association of Anaesthetists	4	Full	4.1.7	34	sodium in the range 130-154. How did you decide this range? Surely the criterion for resuscitation is an isotonic salt solution and excludes fluids like 0.9% Saline / 5% Glucose. Bolus of 500 ml; isn't that also arbitrary? Others have suggested smaller volumes as you do in bottom box of Algorithm 2).	Thank you for your comment. The rationale behind deciding on the range of sodium (130-154 mmol/L) was to include intravenous fluids that are readily available in the UK and can be used without having any adverse effect (as determined by the evidence). On your second comment regarding the volume of the bolus administered, the GDG felt 500 ml was a reasonable volume to start with. The guidance is aimed at the general ward setting and the GDG agreed that it would be safe to administer 500ml of bolus initially which could be followed up with lower volumes, if required.
SH	Association of Anaesthetists	5	Full	4.2.1	39 and 63 and 123	Algorithm 2; Evidence for advice to give high-flow oxygen? Surely automated frequent blood pressure measurement to be mandatory, and doctor to be at bedside of any patient requiring resuscitation until it is clear that patient has stabilised or is responding to	Thank you for your comment. The GDG discussed this and agreed to remove the advice to give high flow oxygen from the algorithm (see Algorithm 2).

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						treatment.	
SH	Association of Anaesthetists	6	Full	Algorithm 3	39 and 63	Algorithm 3; why 25 - 30 ml/kg/d water, 50-100 g/d glucose; why not 1.5-2.5 litres, of which 5% Glucose 1-2 litres for clarity? Nasogastric fluids? Dangers of using i.v bags on n.g tube? Are volume & electrolyte recommendations same as i.v?	Thank you for your comment. The GDG discussed and agreed that the move towards prescribing to account for body weight was safer than recommending absolute figures.
SH	Association of Anaesthetists	7	Full	4.2.3	41	pulmonary oedema; specify that this includes ARDS.	Thank you for your comment. The GDG discussed this and agreed that ARDS has many causes and it would be complicated to include this here. The table lists pulmonary oedema as a complication of fluid mismanagement and highlights its identifying features.
SH	Association of Anaesthetists	8	Full	5	43	Four Rs or Five R's? How about "Four R's plus reassessment". Drawn from B.Braun promotional literature?	Thank you for your comment. We would prefer to use the 5Rs approach and are unaware of any promotional material that previously used this.
SH	Association of Anaesthetists	9	Full	5.1.1.1	44-and others	a discourse on physiology is unnecessary. Suggested reading should be ample. Concerned that reliance should be placed on a commissioned book supplied by a fluid therapy pharmaceutical company promoting colloids. (see Appendix B p22)	Thank you for your comment. However, we do not agree. In view of the lack of RCT evidence to support important aspects of our guidance a focussed summary of the principles of fluid prescribing is required since these principles inform many of our recommendations. Although we accept that much of our text on the principles of fluid therapy is based on a book that was published with the support of a fluid therapy pharmaceutical company who produce

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							colloids, that company had no editorial input into the content of the original text which is the intellectual property right of some of our GDG members. The GDG members on this guideline, (who are also the authors of the cited book) wrote these sections of the guideline, along with input from other GDG members. If the wording and sentiment of the text is similar, it can be attributed to the GDG members' direct involvement in both pieces of work. Furthermore, several other GDG members then edited and added to the text for the purposes of this guidance and neither the background text nor our final recommendations promote colloid usage.
SH	Association of Anaesthetists	10	Full	5.1.4	52	Throughout the document it is suggested that the volume of distribution of a colloid or crystalloid is plasma, or plasma plus interstitial fluid, or whole body water (the Hillman & Twigley paradigm as interpreted by Lobo). There is no logic or evidence about this. It is correctly stated that "In hypovolaemic patients crystalloids have much better retention than these euvoalaemic volunteer studies have suggested" but then suggest that there are "actual benefits of colloids over crystalloids" are unclear. In fact, modern physiology suggests that crystalloid resuscitation is more likely to be beneficial.	Thank you for your comment. There is still a widespread belief that colloids lead to greater intravascular fluid expansion for the reasons expressed in our text but we believe that that text also made it clear that these advantages were theoretical and not necessarily borne out in practice. We feel that our text should continue to refer to this debate. However, in the light of your comments, we have made further revisions to make the uncertainty and lack of evidence clear at every point where this issue is raised. There was therefore the need to examine the evidence carefully and with that necessary background we

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						went on to examine the evidence and did not find it in favour of any benefits from colloids. We recommend the use of crystalloids for fluid resuscitation. We would also like to highlight that a recent alert issue by the MHRA also advises against the use of tetrastarches for fluid resuscitation which is in line with our recommendation which now states 'Do not use tetrastarch for fluid resuscitation.'	
SH	Association of Anaesthetists	11	Full	6.3.3.5	84	Recommendation 14; Daily chloride monitoring for patients who have received 0.9% sodium chloride. How much NaCl? 100 ml? 500 ml? 1000 ml? Surely chloride should be measured with every urea & electrolyte sample, and every patient on iv maintenance or resuscitation should have these done at least daily.	Thank you for your comment. We agree and the recommendation clearly states that any patient receiving intravenous fluids containing chloride in concentrations greater than 120mmol/L should have their chloride levels monitored daily (irrespective of the volume of fluid received).
SH	Association of Anaesthetists	12	Full	9.1.1.1		advocates colloids for patients needing "urgent resuscitation" with no logic or evidence.	Thank you for your comment. We agree and this has now been amended.
SH	Association of Anaesthetists	13	Full	10.5.1		"understanding of physiology" lacks clarity. Statement on intravascular volume is very important but contains errors, e.g. epithelial permeability, see "An Introduction to Cardiovascular Physiology"	Thank you for your comment. We have changed 'Understanding of physiology' to 'Understanding of fluid physiology and pathophysiology' and altered 'epithelial permeability' to 'capillary permeability'. We have also reworded the statement on intravascular volume.
SH	Association of Anaesthetists	14	Full	general	general	much of the Text & some diagrams taken from B.Braun promotional book. Although colloids correctly do not feature in the	Thank you for your comment. Although we accept that much of our text on the principles of fluid therapy is

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	ts					algorithms, the general tone of the text supports use of colloids by specialists without evidence.	based on a book that was published with the support of a fluid therapy pharmaceutical company who produce colloids, that company had no editorial input into the content of the original text which is the intellectual property right of some of our GDG members. Furthermore, several other GDG members then edited and added to the text for the purposes of this guidance. In the light of your comments, we have made further revisions to the text to make the uncertainty and lack of evidence clear at every point where the issue of possible colloid superiority is mentioned.
SH	Association of Anaesthetists	15	Full	general	general	For many years it has been said that colloids should not be prescribed to patients outwith ethically approved trials (most recently Cochrane), but this guidance rejects that evidence-backed position without explaining why.	Thank you for your comment. We do not understand your concern- this guidance does not recommend the use of colloids for resuscitation, unless in the context of a clinical trial and is in line with the position of the Cochrane review.
SH	Association of Anaesthetists	16	Full	general	general	appendix B; A member of the GDG withdrew citing, potential conflict of interest but continued as expert. Is this due to disagreement?. Should an expert also continue in this role, with an expressed conflict of interest?	Thank you for our comment. The scope of the guideline demanded an extension of the time span beyond that was initially allocated for development. The cited GDG member withdrew from the panel due to potential conflicts of interest and due to inability to attend the meetings for the period of extended development. The role of the expert advisor within the context of the guideline involves

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							providing advice on specific issues. However, the expert has no role in formulating or voting on the recommendations in the guideline. It was agreed that it would be beneficial for the guideline to have the cited person as an expert advisor for specific issues.
SH	Association of Anaesthetists	17	Full	general	general	no discussion of conflict between giving a lactate-containing solution while measuring venous lactate to guide resuscitation, especially in diabetics. (why not arterial lactate?)	Thank you for your comment. However, we do not agree. Lactate in Ringer's lactate/Hartmann's solution, given appropriately, is metabolised rapidly by the liver and is unlikely to cause an increase in serum lactate in the absence of other metabolic factors. Hence, routine measurement of serum lactate is not necessary, unless specifically indicated.
SH	Association of Anaesthetists	18	Full	general	general	While labouring point about chloride, no mention of lactate-induced hyperglycaemia, especially in diabetics.	Thank you for your comment. Diabetes mellitus was out of the scope of this guidance. However, the GDG did discuss this and agreed that although the lactate can be metabolised into glucose, the amount of glucose produced is relatively low and unlikely to cause hyperglycaemia
SH	Association of Clinical Biochemistry and laboratory medicine	1	Full	6.3.1.2	68	It is stated that laboratory investigation should include trends in 'urea, creatinine and electrolyte'. 'Electrolyte' is defined in the glossary and on that basis the term includes any ionised species. A more precise term is required, e.g. 'sodium, potassium and chloride'.	Thank you for your comment. We agree and have amended the wording in the glossary to reflect the specific electrolytes considered in this guidance.

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SH	Association of Clinical Biochemistry and laboratory medicine	2	Full	Algorithm 1	86	See comment 1	See response to comment 1
SH	Association of Clinical Biochemistry and laboratory medicine	3	Full	6.3.3	73-86	Given that many laboratories do not routinely measure serum chloride concentrations a statement as to whether this measurement should be made routinely available and used in the assessment and monitoring of all patients receiving intravenous fluids would be helpful.	Thank you for your comment. The GDG agreed that the evidence indicated an association of hyperchloraemia with adverse events and a risk of hyperchloraemia with the administration of solutions containing chloride levels greater than 120mmol/L. Based on this, the GDG agreed that routine measurement of serum chloride levels would be beneficial in this specific group of patients receiving intravenous fluids with chloride levels greater than 120mmmol/L.
SH	Association of Clinical Biochemistry and laboratory medicine	4	Full	10.1	153	A major issue that relates to poor fluid management does not appear to have been considered: this is the interpretation of laboratory tests, particularly measurements of sodium and potassium concentration. Thus although intuitively a low serum sodium concentration might suggest sodium deficiency, it is more frequently related to an excess of water; a high potassium concentration does not (indeed, often does not) indicate an overall excess of potassium in the body.	Thank you for your comment. We agree and a section on the interpretation of laboratory tests has now been added to the full version of the guideline. (refer section 10.1)
SH	Association of Clinical Biochemists	1	Full	general	general	This comprehensive guideline is a very useful source of information for IV fluid prescribers and it should focus attention on improving this high risk activity. The recommendation to report consequences of fluid mismanagement as critical incidents is crucial to	Thank you for your comment.

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						changing widespread ingrained poor practice.	
SH	Association of Clinical Biochemists	2	Full	4.2	36, lines 24-26	Some more information on the benefits and limitations of urine sodium measurement and the interpretation of results would be useful here.	Thank you for your comment. We have expanded the text in the recommendation and in the section linking the evidence to recommendations to provide an explanation of the likely benefits and limitations of these measures.
SH	Association of Clinical Biochemists	3	Full	5.1.4	53	Isotonic saline "...intravascular retention of sodium chloride 0.9% is likely to be better than this ... (missing word)	Thank you for your comment. Please refer to the statement preceding the line you cite' Traditionally sodium chloride 0.9% infusion has been considered to expand blood volume by only a quarter to a third of the volume infused, the remainder being sequestered in the interstitial space'. The next statement reads 'In practice, for the reasons given above, intravascular retention of sodium chloride 0.9% is likely to better than this in hypovolaemic and stressed patients.' implying that sodium chloride 0.9% expands blood volume greater than a quarter or a third of the volume infused.
SH	Association of Clinical Biochemists	4	Full	5.1.4	54	Synthetic colloids – last paragraph This needs to be altered following the MHRA Drug Safety Alert June 2013 suspending the use of HES products because of safety concerns.	Thank you for your comment. The guideline reviewed all products (including HES) commonly used in the UK for fluid resuscitation at the time of development. The issue of the drug safety alert from the MHRA coincided with the consultation period of the guideline and since the guideline

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							recommends against the use of tetrastarches, we believe it would be valuable to include the rationale and evidence base underpinning this decision in the published version of the guideline. Please note that the recommendation now states 'Do not use tetrastarch for fluid resuscitation.' and detail on the safety alert from the MHRA has also been added to the section linking the evidence to recommendations.
SH	Association of Clinical Biochemists	5	Full	8.1	128	First line – words missing “IV fluid therapy forroutine maintenance ...refers to	Thank you for your comment. We agree and this has now been amended.
SH	Association of Clinical Biochemists	6	Full	8.1.2	130	Second paragraph – incomplete sentence “Trials of IV fluid therapy for routine maintenance...”	Thank you for your comment. We agree and this has now been amended.
SH	Association of Clinical Biochemists	7	Full	8.5.1	142	Lowest box in diagram: “NG fluids or enteral feeding are preferable when maintenance needs are >3 days” It is not clear what this means	Thank you for your comment. We do not agree. The GDG felt that the statement clearly emphasises that when routine maintenance needs in a patient on intravenous fluid therapy exceed three days, nasogastric or enteral feeding may be a preferable.
SH	Association of Clinical Biochemists	8	Full	9.1.2	147	First paragraph “It is also important to correct any potassium depletion in order to maximise sodium exchange” –this statement should be referenced “when giving relatively generous amounts of potassium...”	Thank you for your comment. It is not possible to give a reference in relation to potassium sodium exchange since this is a statement from physiological principles. We have reworded the reference to diuretic usage in the context of IV fluid provision in the light of your comment.

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						<p>"Hyperchloraemia should also be avoided as it make mobilisation of oedema more difficult by reducing renal perfusion" -this should be referenced</p> <p>"Diuretics should generally be avoided or used with great caution in order to avoid reduction in circulating blood volume and twice weekly weighing, when possible, in addition to routine daily clinical, when possible, allows examination allows oedema mobilisation to be assessed." This sentence does not make sense. It also needs to be referenced. Is GREAT CAUTION always needed? Surely diuretics can be beneficial in helping to clear oedema in some cases in addition to minimising sodium intake. The cardiologists who are asked to review overloaded patients almost invariably prescribe diuretics.</p>	<p>A reference for the statement "Hyperchloraemia should also be avoided as it make mobilisation of oedema more difficult by reducing renal perfusion" has now been added to the full guideline.</p> <p>(Reference: Chowdhury AH, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. Ann Surg. 2012 Jul;256(1):18-24.)</p>
SH	Association of Clinical Biochemists	9	Full	Glossary	186	<p>Volume depletion</p> <p>"State of vascular instability characterised by decreased sodium and water in the extracellular space "</p>	<p>Thank you for your comment. This has now been amended.</p>
SH	B Braun medical	3	Full	7.2.3.2	110	<p>Please add the gelatin solution "Gelaspan®" of B. Braun to this recommendation to the table. This is a balanced version of Gelofusine, which is widely used throughout UK hospitals.</p> <p>It should be considered that gelatin solutions are superior to HES solutions as regards their effects on coagulation (Appelman et al., 2011; Egli et al., 1997; Fries et al., 2002; Innerhofer et al., 2002; Schramko et al., 2009), while no tissue storage has been reported (Niemi et al., 2010).</p>	<p>Thank you for your comment. We cannot include references to brand names for any of products reviewed as part of the evidence in this guideline. Please note, that any such references if present, have now been removed except in the tables referring to cost. The solutions are referred to by their generic names/ sum of constituents, where appropriate.</p>

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					<p style="text-align: center;">References</p> <p>Appelman MH, van Barneveld LJ, Romijn JW, Vonk AB, Boer C. The impact of balanced hydroxyethyl starch cardiopulmonary bypass priming solution on the fibrin part of clot formation: ex vivo rotation thromboelastometry. <i>Perfusion</i> 2011; 26: 175-180.</p> <p>Egli GA, Zollinger A, Seifert B, Popovic D, Pasch T, Spahn DR. Effect of progressive haemodilution with hydroxyethyl starch, gelatin and albumin on blood coagulation. <i>Br J Anaesth</i> 1997; 78: 684-689.</p> <p>Fries D, Innerhofer P, Klingler A, Berresheim U, Mittermayr M, Calatzis A, Schobersberger W. The effect of the combined administration of colloids and lactated Ringer's solution on the coagulation system: an in vitro study using thrombelastograph coagulation analysis (ROTEG). <i>Anesth Analg</i> 2002; 94: 1280-7, table.</p> <p>Innerhofer P, Fries D, Margreiter J, Klingler A, Kuhbacher G, Wachter B, Oswald E, Salner E, Frischhut B, Schobersberger W. The effects of perioperatively administered colloids and crystalloids on primary platelet-mediated hemostasis and clot formation. <i>Anesth Analg</i> 2002; 95: 858-65, table.</p> <p>Niemi TT, Miyashita R, Yamakage M. Colloid solutions: a clinical update. <i>J Anesth</i> 2010; 24: 913-</p>	<p>With respect to gelatin, the review of the evidence base was inconclusive and did not demonstrate either benefit or harm with its use. This was with respect to all outcomes as outlined in the review protocol, which include mortality, and morbidity amongst other outcomes. Please note that coagulation was not identified <i>a priori</i> as a priority outcome by the GDG and was therefore not assessed in the evidence review.</p>
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						925. Schramko AA, Kuitunen AH, Suojaranta-Ylinen RT, Niemi TT. Role of fibrinogen-, factor VIII- and XIII-mediated clot propagation in gelatin haemodilution. Acta anaesthesiologica Scandinavica 2009; 53: 731-735.	
SH	B Braun medical Ltd	1	Full	General	General	<p>B Braun Medical Ltd welcome this review and publication of updated guidelines. We fully agree and have experienced the need for further education and understanding of fluid therapy in the clinical setting. We have provided for a number of years, free of charge, non-promotional education sessions to our customers. This package has recently been adopted the University of Wales, Cardiff and is delivered as part of their MsC course in Critical Care. We will continue to invest in clinical education and support.</p> <p>Optimal use of available technology, for example: Smart Infusion Pumps and accompanying software could ensure prevention of both under or over dosing of fluids and related complications.</p> <p>This guideline is titled "Intravenous fluid therapy – in adults in hospital". This title seems to be too general since the literature research excluded most of the patients, see chapter 2.5.. The title of the guideline should reflect which population has been addressed in the underlying literature research.</p>	<p>Thank you for your comment. The target population in the guideline was all patients in hospital receiving intravenous fluid therapy with particular emphasis on IV fluid management in general ward settings. However, the breadth of the target population meant that evidence from patients in specific settings or those with specific comorbidities was considered indirect to the entire target population. This has now been highlighted in the introduction and other relevant sections of the guideline. A pragmatic approach was taken when reviewing the evidence base and assessing indirectness for different indications of Intravenous fluid therapy. Specific populations covered in the guideline have been detailed in the introduction, relevant sections in the guidance and the review protocols (see Appendix C.)</p>
SH	B Braun medical Ltd	2	Full	4.2.18	37	One of the major issues in this draft guideline on intravenous fluid therapy is the explicit	Thank you for your comments.

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				<p>recommendation not to use HES containing solutions for resuscitation unless as part of clinical trials.</p> <p>It is conclusive and understood that the body of evidence as regards the safety and efficacy of HES is subject to ongoing and converse debate in the scientific world and therefore awaits further clarification by additional clinical trials thoroughly designed and conducted. However, this should not implicate at the same time to refrain from HES usage for initial haemodynamic stabilization of hypovolaemic patients. This is in our opinion not supported by the existing body of evidence as it was recognized within this draft. The underlying studies that have led to the recommendation not to use HES contain severe scientific limitations that were likely not adequately considered within the review process of the present draft guideline.</p> <p>Some of the major limitations are detailed hereafter:</p> <ul style="list-style-type: none"> • Disregard of SmPC of HES <ul style="list-style-type: none"> - Contra-indications (acute renal failure) - Warnings (hypervolaemia), thus inclusion of haemodynamically stable patients with no indication for a volume replacement solution: Many patients were already stabilized at baseline with crystalloids and colloids, among them HES. This initial volume resuscitation was required due to the informed consent procedure which may take hours. As patients were included several hours after the first signs of hypovolaemia and after pre-treatment 	<p>We have re-evaluated the evidence in light of your comments. We agree that the trials included in the evidence review did not meet the review protocol criteria accurately and we have downgraded the evidence for indirectness based on this (see section 7.2.2.1, tables 25 and 26- Clinical evidence profiles comparing tetrastarch with sodium chloride 0.9% and lactated Ringer's solution).</p> <ul style="list-style-type: none"> • With respect to the likelihood of the adverse events arising as a result of possible overdose, the study authors (Perner et al.) state that this was anticipated and only two patients received HES 130/0.42 in a dose higher than that recommended by the manufacturer. • The inclusion of acute kidney injury patients would not be a protocol violation (the protocol stated exclusion of patients dependent on dialysis at time of randomisation). However, the study reports that baseline data for both groups was similar with respect to presence of AKI (36% in group receiving HES and 35 % in group receiving
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				<p>with crystalloids and colloids it can be assumed that a relative overdose has led to the observed negative outcomes</p> <ul style="list-style-type: none"> • Protocol violations <ul style="list-style-type: none"> - Inclusion of ineligible patients (e.g. patients suffering from acute kidney injury, patients exceeding defined volumes/doses of pre-treatment with HES) - Not following the defined fluid resuscitation using the Surviving Sepsis Campaign Guidelines (fluid application was left to the discretion of the treating physician) • Missing data and/or incomplete documentation of essential clinical parameters <ul style="list-style-type: none"> - Missing baseline data required to follow defined fluid resuscitation (e.g. CVP) - Missing documentation of (serious) adverse events (e.g. cause of death) - Missing documentation of concomitant medication (e.g. inotropes) <p>These limitations should be considered when assessing the overall safety of HES by these recent studies. It can be concluded that there is a great likelihood that these shortcomings contribute to the negative results for HES as regards renal impairment and/or mortality.</p> <p>For the sake of completeness: New data from two so</p>	<p>lactated Ringer's solution). Also, a subgroup analysis of patients without AKI at baseline in both groups with respect to the primary outcome of death or dependence on dialysis at day 90 reports a higher relative risk (1.20, Confidence Interval 1.00-1.45) than when both groups are considered together.</p> <ul style="list-style-type: none"> • With regard to your comment on accounting for missing data and incomplete documentation of essential clinical parameters, we would like to highlight that assessment of the quality of evidence was conducted in a similar manner across all reviews in the guideline. The measurement of CVP at baseline is an invasive procedure and out of the scope of this guidance, as is the use of inotropes or other concomitant medication (see Scope, Appendix A). All-cause mortality was a pre-specified outcome of this review and has been evaluated and it was expected that the outcomes on morbidity would encompass the
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						<p>far unpublished studies (the CRYSTAL and the BaSES trial with 2857 and 241 patients respectively) has been presented during different congresses in 2012 and earlier this year. As judged from the so far available presentations these studies indicate a positive benefit-risk ratio for HES, will be published with the next months and should therefore be considered for these recommendations.</p>	<p>cause of death.</p> <ul style="list-style-type: none"> • We would like to assure you that any new unpublished data will be considered in any subsequent update of this guideline..
SH	Baxter Healthcare	1	Full	General	General	<p>Baxter welcomes the opportunity to comment on the draft IV Fluid Guidelines. We would like to congratulate NICE on highlighting the urgent need to acknowledge intravenous fluid therapy as prescription only medicines, the need for improvements in training and education of healthcare professionals in their management of IV fluids. We also agree with the call for additional relevant clinical and health economic evidence for all patient groups regarding IV fluid management.</p>	<p>Thank you for your comment.</p>
SH	Baxter Healthcare	2	Full	General	General	<p>We acknowledge the basis of the recommendation for individualised prescriptions of IV fluids based on regular monitoring, in particular when a patient has an increased potassium requirement. We would like to highlight the NPSA alert regarding the use of high strength potassium additions in ward areas. Within this alert it was identified that this is a high risk process and should not be carried out in the ward area. Therefore, the addition of potassium to IV fluids should be confined to aseptic compounding units. Please could NICE confirm that consideration has been given to the potential risks if custom admixtures need to be compounded?</p>	<p>Thank you for your comment but all practical issues concerned with the preparation and administration of IV fluids are beyond the scope of our guidance.</p>

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SH	Baxter Healthcare	3	Full	General	General	With reference to the comment 2 above, would NICE agree that individualised prescribing has the potential to limit the scope for standardisation of prescribing practice both throughout England and within individual NHS Trusts?	Thank you for your comment. We would like to highlight that the guideline aims to standardise practice in IV fluid management across the UK. As pointed out, the recommendations do take into account the need for adjusting prescription based on reassessment and monitoring. However, we do not believe that this limits the scope of standardisation, rather it is a reflection of what occurs (and what should occur) in clinical practice.
SH	Baxter Healthcare	4	Full	General	General	We agree that there is a current lack of definitive evidence to recommend or clearly differentiate between balanced and unbalanced crystalloid solutions in terms of mortality, length of stay, adverse events and quality of life. However, would NICE consider recommending balanced crystalloids, with a chloride concentration less than 120 mmol/L, in the specific patient groups identified by the literature in table 18 (page 77), specifically abdominal surgery patients (Waters, 2001, Shaw 2012) and critical care patients (Yunos 2012) to aid the prevention of electrolyte disturbances, renal insufficiency/AKI and a possible effect of mortality and morbidity? This would avoid the need for daily monitoring of serum chloride concentration.	Thank you for your comment. As correctly identified by you, there is a current lack of definitive evidence to recommend or clearly differentiate between balanced and unbalanced crystalloid solutions. Any recommendation on this topic would be based on assumption and as a result we are unable to comment on this any further. We have made a research recommendation on this topic area.
SH	Baxter Healthcare	5	Full	General	General	In light of the recent press releases published by the Royal College of Anaesthetists and the Faculty of Intensive Care Medicine (http://www.rcoa.ac.uk/news-	Thank you for your comment. In the context of fluid resuscitation, there was no evidence to show any

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						<p>and-bulletin/rcoa-news-and-statements/suspension-of-hydroxyethyl-products-the-european), and following the recent suspension of all HES licenses in the UK, would NICE consider including the Royal College's recommendation "<i>In most cases, fluid resuscitation should be undertaken with crystalloids that contain sodium in the range 130 – 154 mmol/L. Use of physiologically 'balanced' solutions such as Hartmann's solution, Ringer's lactate or Plasma-Lyte 148 may be preferred over 0.9% sodium chloride</i>"?</p>	<p>difference in outcomes with the use of sodium chloride 0.9% and other crystalloids. Therefore, we are unable to make this recommendation.</p>
SH	Baxter Healthcare	6	Full	General	General	<p>With regards to the statement referred to above from the Royal College of Anaesthetists and the MHRA's ruling on HES, would NICE also consider including Royal College of Anaesthetists following recommendation regarding the use of colloids? "<i>Clinicians who prefer to include colloids for fluid resuscitation and who have, until now, been using HES, may choose to use a gelatin solution instead. But there are only few, low-quality data showing that fluid resuscitation with gelatin is achieved with a lower volume than with crystalloid and a recent observational study shows that gelatin may be associated with acute kidney injury. Intravenous colloids cause approximately 4% of all perioperative anaphylactic reactions and the vast majority of these are caused by gelatine</i>"</p>	<p>Thank you for your comment. The recommendation to use crystalloids for fluid resuscitation was based on a clinical and cost-effectiveness review of the evidence. There was no conclusive evidence for the use of gelatin over any other type of colloid and we are unable to make a recommendation on this subject. We have however, made a research recommendation on the use of gelatin for fluid resuscitation.</p>
SH	Baxter Healthcare	7	Full	General	General	<p>IV fluid administration frequently occurs in the peri-operative period. As the scope of these guidelines includes "<i>Adults (16 years and older) in hospital receiving intravenous fluid therapy</i>", would NICE consider linking the guidelines to the British Consensus Guidelines on Intravenous Fluid Therapy</p>	<p>Thank you for your comment. In the context of fluid resuscitation, there was no evidence to show any difference in outcomes with the use of sodium chloride 0.9% and other crystalloids. Therefore, we are unable</p>

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					<p>for Adult Surgical Patients, which recommend “<i>Because of the risk of inducing hyperchloraemic acidosis in routine practice, when crystalloid resuscitation or replacement is indicated, balanced salt solutions e.g. Ringer’s lactate/acetate or Hartmann’s solution should replace 0.9% saline, except in cases of hypochloraemia e.g. from vomiting or gastric drainage.</i>”?</p>	<p>to make this recommendation.</p>
SH	Baxter Healthcare	8	Full	General	<p>An important issue that has been raised in the guideline is that of over hydration. In addition, the routine maintenance guideline section states that 1mmol/kg/day of sodium, potassium and chloride is recommended. Therefore, for an average 70kg adult, clinicians may opt to prescribe 0.18% NaCl with glucose and potassium as the preferred fluid.</p> <p>The Fife IV Fluid guidelines state that there is a risk of hyponatraemia if this fluid is administered at a rate greater than 100mls/hour.</p> <p>The guideline also emphasises the importance of accurate fluid balance measurements and documentation. We note that the economic model accounts for the burden on staff to complete fluid balance charts. The use of a volumetric pump can provide more accuracy, consistency and predictability of fluid administration. The use of gravity administration sets increases the risk of inaccurate fluid delivery and increases the administrative burden for nursing staff who must accurately record volume delivered.</p> <p>Although we are aware that route of administration for IV fluids are out of scope for this guideline, would NICE agree that a recommendation should be included to deliver fluids via a volumetric pump to minimise both the risk of over hydration and</p>	<p>Thank you for your comment. We agree with your rationale and have highlighted the risk of hyponatraemia in the recommendation and explained it in the context of the alert issued by the Medicines and Health Regulatory agency in the section linking evidence to recommendations.</p> <p>As rightly highlighted by you, the route of administration is however beyond the scope of this guidance and therefore we cannot comment on this issue.</p>

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						hyponatraemia?	
SH	Baxter Healthcare	9	Full	General	General	<p>The guideline discusses the appropriate use of Human Albumin Solution, however only 4–5% is referred to.</p> <p>As Albumin 5% contains approximately 128 mmol/L Chloride, would NICE agree that it is important to also consider the use of human albumin solution 20% which contains a lower level of Chloride?</p>	<p>Thank you for your comment.</p> <p>The GDG discussed and agreed that human albumin solution 20% was commonly used in liver disease which is out of scope of this guideline (refer Scope , Appendix A). It is not used widely in general ward settings and therefore agreed not to evaluate the evidence with respect to this solution.</p> <p>The GDG also do not agree that it contains a lower level of chloride.</p>
SH	Baxter Healthcare	10	Full	General	General	<p>Whilst we agree with the parameters outlined for routine IV fluid maintenance to be calculated by patient weight with 5 variables (volume, K, Na, Cl and Glucose) i.e. the recommendation for the initial prescription is a restriction to 25-30 ml/kg/day, approximately 1 mmol/kg/day of potassium, sodium, chloride and 50-100g glucose/day, we would like to highlight the potential high risk of an incorrect calculation. An accurate calculation depends on the patient weight being known, however this is often not the case (although it is best practice to weigh all patients). With this in mind, what do NICE view as the most important element to be accurate – mls, K, Na, Cl or glucose?</p>	<p>Thank you for your comment.</p> <p>We agree with your concerns, however, the GDG discussed and agreed that even an approximation of body weight is preferable to for prescribing fluids than prescribing with no consideration of body mass at all.</p> <p>For ease of prescription by the healthcare professional, the guideline also provides a table outlining the calculations (refer page 25 in the NICE version and section P.4, Appendix Pin the full version)</p> <p>The GDG discussed and agreed that all elements of the prescription are equally important.</p>
SH	Baxter Healthcare	11	Full	General	General	<p>We are pleased to see that NICE has recommended a fluid lead to be in post within each hospital. Would NICE consider giving further recommendations on the scope of this role, the qualifications required and time</p>	<p>Thank you for your comment.</p> <p>We would like to highlight that the guideline covers the general principles of IV fluid management and cannot</p>

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						allocated by the individual assigned to this role?	specifically recommend the details of the qualifications required and time allocated to the role of the IV fluid lead.
SH	Baxter Healthcare	12	Full	4.1.8	34	The guidelines state that the recommendation for routine maintenance IV Fluid therapy is for the initial prescription only. We do not see any guidance for fluid/electrolyte requirements on subsequent days. Would NICE be in a position to make recommendations for subsequent days to eliminate any potential for inappropriate fluid administration for routine maintenance on the subsequent days?	Thank you for your comment. We believe that the guideline provides a framework for prescribing that is quite clearly applicable to subsequent days with the need for continued appropriate prescription completely implicit within our recommendations and algorithms which emphasise the need for constant re-assessment and monitoring. Please refer to the recommendations on reassessment (1.2.3-1.2.7), specifically, recommendation 1.2.4.
SH	Baxter Healthcare	13	Full	4.1.8	34	The guidance given on initial prescription for routine maintenance is based on a healthy individual's average requirements and may not necessarily be the requirement of adults in hospital requiring IV fluid therapy, who are generally not healthy individuals. Would NICE consider making this point in the guideline and emphasising the requirement for regular reassessment?	Thank you for your comment. We believe that the guidance is clear in stating that the routine maintenance prescription must be adjusted for all other factors such as existing deficits, ongoing losses, complex distribution issues etc and already gives great emphasis to the need for re-assessment
SH	Baxter Healthcare	14	Full	Table 30	110	We notice that Baxter's Plasma-Lyte 148 is referred to as "alternate balanced solution 148 pH 7.4 in Viaflow" (note; this should be Viaflo). Please could NICE consider amending the text to Plasma-Lyte 148 for consistency, in line with the other brand names mentioned in this table and in the document as a whole? Baxter would be pleased to supply NICE with a comprehensive list of all our available intravenous	Thank you for your comment. Any references to brand names have now been removed from the document (except in the tables outlining costs). The fluids will be referred to by their generic names/sum of constituents.

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						fluid formulations currently licensed for use in the UK via our Surecall Medical Information Service on + 44 (0) 1635 206345.	
SH	Baxter Healthcare	15	Full	8.1.2	129	The comment regarding balanced crystalloids may cause confusion “ <i>They may therefore cause less sodium and water retention than 0.9% sodium chloride as well as less hyperchloraemia and they do already contain potassium, calcium and magnesium content which may be useful to meet overall maintenance needs.</i> ” Currently balanced solutions do not contain all these ions. Hartmann’s does not contain magnesium. Plasma-Lyte 148 does not contain calcium. Would NICE consider rewording this sentence to reflect accurately the electrolyte content on currently available products? Baxter would be pleased to supply NICE with a comprehensive list of all our available intravenous fluid formulations currently licensed for use in the UK via our Surecall Medical Information Service on + 44 (0) 1635 206345.	Thank you for your comment. We would like to highlight that the statement is general to all balanced crystalloids. In light of your comment, we have now rephrased it reflect this without referring to specific electrolyte concentrations in different balanced crystalloid solutions.
SH	Baxter Healthcare	16	Full	8.1.2	129	We acknowledge that at the time of preparation of these draft guidelines there was a lack of high quality evidence regarding its burden on the patient and healthcare resources. However we would like to draw your attention to the data presented, in part at the Canadian Anesthesiologist Society Meeting, June 2010 and accepted for publication March 6, 2013 in <i>Anesthesia & Analgesia</i> . This data shows a link between hyperchloraemia and morbidity and mortality in non-cardiac surgery patients (<i>Hyperchloraemia After Noncardiac Surgery Is Independently Associated with Increased Morbidity and Mortality: A Propensity-</i>	Thank you for your comment. The publication of this study fell outside of our search dates. However, the results of the study would not affect the conclusions of the evidence review. We believe that our recommendations as they stand will reduce the use of sodium chloride 0.9%. The current evidence base does not support a stronger recommendation on this issue.

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					<p><i>Matched Cohort Study. McCluskey et al. http://www.anesthesia-analgesia.org/content/early/2013/06/11/ANE.0b013e318293d81e.full.pdf+html</i> accessed 1st July 2013).</p> <p>Routine use of 0.9% sodium chloride may lead to incidences of hyperchloraemic acidosis with subsequent renal, electrolyte, haematological, gastrointestinal consequences. Would NICE therefore agree that it would be prudent where possible, to avoid the use of 0.9% sodium chloride which can lead to iatrogenic acidosis particularly in critically ill patients with multiple co morbidities?</p>	
SH	Baxter Healthcare	17	Full	8.1.2	<p>We would like to highlight the following statement as it may lead to confusion. It appears to refer to Baxter's Plasma-Lyte M (the maintenance version of Plasma-Lyte 148).</p> <p><i>"A number of newer balanced crystalloid solutions are appearing on the market tailored better to meet the theoretical requirements for maintenance. When prescribing these fluids it is essential to specify the 'Maintenance' version where appropriate since for some there are other versions of the fluids designed for Resuscitation or Replacement."</i></p> <p>Plasma-Lyte M is also mentioned on page 39, 40 and 42 of the Appendix as one of the compared fluids in interventions and comparisons. We wish to clarify that Plasma-Lyte M is not licensed in the UK. Baxter would be pleased to supply NICE with a comprehensive list of all our available intravenous fluid formulations currently licensed for use in the UK via our SureCall Medical Information Service on + 44 (0) 1635 206345.</p>	<p>Thank you for your comment. We agree and the text has been reworded to reflect this.</p>

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SH	Baxter Healthcare	18	Full	8.1.2	130	The sentence "Trials of IV fluid therapy for routine maintenance" appears to be incomplete.	Thank you for your comment. We agree and this has now been amended.
SH	Baxter Healthcare	19	Full	4.2.1	39	The algorithms that have been produced are an excellent way to describe the decision making process for effective intravenous fluid management. Would NICE consider applying the green colour coding to all of the steps in the algorithm that recommend re-assessment?	Thank you for your comment. The four algorithms are separate and represent different pathways in IV fluid management. They have therefore been colour coded differently to highlight this.
SH	Baxter Healthcare	20	Full	5.1.4	53	In the section on balanced crystalloid solutions, no differentiation is made between the different levels of cations and anions. We are concerned that this may lead to confusion amongst inexperienced prescribers. Would NICE consider a more explicit guideline on the different levels and contents of balanced solutions?	Thank you for your comment. We agree and details of composition of different solutions (including cations and anions) are in a table in the appendix (Please refer sections P1 and P2, Appendix P)
SH	Baxter Healthcare	21	Full	10.7	162	NICE recommend formal assessment and reassessment at regular intervals to demonstrate competence in prescribing and administration. Would NICE consider specific guidance on the level of frequency of assessments and expectations for assessment methodology.	Thank you for your comment. The guideline addresses fundamental principles in the management of intravenous fluid therapy including overarching principles on how to attain higher standards of care by improving training and education in this area. The guideline provides a framework for training and assessment on which, it is expected that training schedules (with details of frequency of assessment) will be implemented by specific trusts. The NICE implementation team will also work closely in this area.
SH	Baxter Healthcare	22	Appendices	116		In the interventions section of this table, Ringers lactate has been written and it should be Ringers acetate as this is the solution used in this trial. This	Thank you for your comment. We agree and this has now been amended.

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						has been correctly identified in the patient section of this table.	
SH	Baxter Healthcare	23	NICE	2.2	22 – 23	The NICE version of the document raises the question “Are balanced crystalloids superior to...” comparing balanced crystalloids to alternatives such as gelatin or 0.9% sodium chloride. However no definition is provided on the formulation of a balanced crystalloid versus an unbalanced crystalloid. Would NICE therefore consider including a statement in the guidelines that describes the difference between a Balanced Crystalloid and an Unbalanced Crystalloid?	Thank you for your comment. The NICE version of the document is a summary of all the recommendations. For full details and explanation of all aspects of the guidance, please refer to the full version of the guideline. Balanced crystalloid solutions are defined in the full version (section 5.1.4) and the guideline also has a table detailing the composition of crystalloids reviewed as part of this guidance (section P.1, Appendix P).
SH	British Association for Parenteral and Enteral Nutrition (BAPEN)	1	NICE	Key priorities	10	Define NEWS	Thank you for your comment. We agree and this has now been defined here in addition to detail in the abbreviations section.
SH	British Association for Parenteral and Enteral Nutrition (BAPEN)	2	NICE	Algorithm	13	These algorithms have much to commend them and are kernel to the advice given. They appear to be aimed at the non-expert since “referral to expert” is advocated at several points. Many in hospitals believe themselves to be experts, but few are. There should be some attempt to define expert in the various contexts. Do we mean consultants/senior registrars in a particular specialty? Nutritional status and the response to (re-)feeding have an important effect on how the body retains sodium and potassium, and how water and electrolytes are distributed across the	Thank you for your comment. We agree and a definition of ‘expert’ has now been added to the glossary. The definition is as follows: Medium-score group: Urgent call to team with primary medical responsibility for the patient. Simultaneous call to personnel with core competencies for acute illness. These competencies can be delivered by a variety of models at a local level, such as a critical care outreach team, a

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				<p>intracellular/extracellular compartments. This is important, particularly in the post-resuscitation phase of management. For example in algorithm 1 if the patient cannot meet their fluid or electrolyte needs orally or enterally there is no further mention of a need for nutritional assessment, even though this will profoundly affect Na/K/water etc distribution. This issue probably needs greater emphasis in this guideline.</p> <p>Algorithm 2 does not tell us how fast to give the bolus of crystalloid (although this in the text). It seems to suggest that we should not seek expert help until we have infused >2000ml. This may be excessive in some patient groups, eg elderly, and perhaps there needs to be a caveat put in here to allow earlier referral if appropriate. Again, what is meant by “expert” – the on-call medical registrar, the intensivists?</p>	<p>hospital-at-night team or a specialist trainee in an acute medical or surgical specialty.</p> <p>The definition is based on the level of core competencies associated with a response to a medium score group and provides examples of how these may be achieved. This is in line with the NICE guidance for critically ill patients (refer NICE guideline CG50).</p> <p>On your second point regarding emphasis on nutritional assessment in conjunction with intravenous fluid management, we agree and have changed the recommendations to reflect this.</p> <p>See recommendations 1.2.2 (change includes accounting for malnourishment and risk of re-feeding syndrome and reference to NICE guideline CG32 on Nutrition support), 1.4.1 (change includes stating that the level of glucose will not address nutritional requirements), 1.4.3 (change includes consideration for prescribing lower levels of intravenous fluids in patients who are malnourished or at risk of re-feeding syndrome and reference to NICE guideline CG32 on Nutrition support) and 1.5.2 (change includes advice to seek expert help in patients who are malnourished or at risk of re-feeding syndrome and</p>
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							reference to NICE guideline CG32 on Nutrition support).
SH	British Association for Parenteral and Enteral Nutrition (BAPEN)	3	NICE	1.1.7	14	Presumably thirst and postural hypotension/faintness?	<p>On your third point regarding the Algorithm 2 suggesting seeking expert help only after 2000 ml of fluid has been administered- we agree that this can be erroneous and have now added a statement to seek expert help if unsure about the patient still needing fluid resuscitation in the box for reassessment.</p> <p>Thank you for your comment. We agree and recommendation 1.2.2 has now been amended to include thirst as one of the factors to be accounted for during history taking.</p> <p>Postural hypotension is already recommended as part of the assessment.</p> <p>Please refer 1.2.2, second bullet: Clinical examination should include an assessment of the patient's fluid status, including:</p> <ul style="list-style-type: none"> • pulse, blood pressure, capillary refill and jugular venous pressure • presence of pulmonary or peripheral oedema • presence of postural hypotension

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SH	British Association for Parenteral and Enteral Nutrition (BAPEN)	4	NICE	1.2.1	14	What is “passive leg raising” and what constitutes a positive result?	<p>Thank you for your comment.</p> <p>Passive leg raising is a bedside method to assess fluid responsiveness in a patient. It is best undertaken with the patient initially semi-recumbent and then tilting the entire bed through 45 degrees. Alternatively it can be done by lying the patient flat and passively raising their legs to greater than 45 degrees. If, at 30-90 seconds, the patient shows signs of haemodynamic improvement, it indicates that volume replacement may be required. If the condition of the patient deteriorates, in particular breathlessness, it indicates that the patient may be fluid overloaded</p> <p>The explanation has now also been added to the glossary in the full version of the guideline and as a footnote in the NICE version to aid understanding.</p>
SH	British Association for Parenteral and Enteral Nutrition (BAPEN)	5	NICE	1.5	18	No mention of nutrition and refeeding. These profoundly effect distribution of NA/K/water and this should be addressed in tandem with fluid/electrolyte management.	<p>Thank you for your comment.</p> <p>The algorithm does refer to the NICE guidance on Nutrition support as part of management of intravenous fluid therapy (refer Algorithm 1).</p> <p>However, in light of your comment, we have added the following references to malnourishment and re-feeding in the following recommendations:</p> <p>Recommendation 1.2.2 -change includes accounting for malnourishment and risk of re-feeding syndrome and reference to NICE</p>

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							guideline CG32 on Nutrition support. Recommendation 1.4.1- change includes stating that the level of glucose will not address nutritional requirements. Recommendation 1.4.3- change includes consideration for prescribing lower levels of intravenous fluids in patients who are malnourished or at risk of re-feeding syndrome and reference to NICE guideline CG32 on Nutrition support. Recommendation 1.5.2-change includes advice to seek expert help in patients who are malnourished or at risk of re-feeding syndrome and reference to NICE guideline CG32 on Nutrition support.
SH	British Association for Parenteral and Enteral Nutrition (BAPEN)	6	NICE	Diagram	20	Insensible losses/sweat?	Thank you for your comment. We agree that sweat does come under insensible losses, but the list is not exhaustive and only examples are provided.
SH	British Association for Parenteral and Enteral Nutrition (BAPEN)	7	NICE	General		There should be a Table in the NICE version detailing content of the commonly used crystalloids/colloids, ie similar to Table 38 in the main document	Thank you for your comment. However, we do not agree. Table 38 (in the full version) has been added as a source of useful and supporting information for the prescribing healthcare professional. The NICE version of the guidance is a summary of all the recommendations. The full version of the guidance

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						contains all the evidence and rationale underpinning the recommendations along with any supporting information (including Table 38).	
SH	British Association for Parenteral and Enteral Nutrition (BAPEN)	8	NICE	Key priorities routine maintenance	9	Mistakes are often made because of rushed/mechanical re-prescriptions of previous regimens. Always ask “does this patient need IV fluids still?” and use the algorithm afresh.	Thank you for your comment. We agree and the question on reassessment in algorithm 2 for fluid resuscitation has been rephrased to read ‘Does the patient still need fluid resuscitation?’
SH	British Association for Parenteral and Enteral Nutrition (BAPEN)	9	Full	2.5		Some of these exclusions seem very arbitrary: why not pregnancy, diabetes, inotropes, burns, head injuries. What is special about these? It is accepted that the remit of this guideline potentially is enormous and therefore trying to limit it in some ways not unreasonable. However, where there are major clinical areas entirely excluded, there should be some stated justification/explanation for this.	Thank you for your comment. We would like to highlight that this guideline is a cross cutting guideline and the recommendations are focused on general principles that apply across a range of conditions/settings rather than relating to specific conditions. The scope of the guideline was independently consulted upon prior to development and the scope was finalised taking into account the views of stakeholders. Detailed justification regarding exclusion of certain areas from the scope of the guidance was provided during stakeholder consultation on the scope.
SH	British Association for Parenteral	10	Full	3.1		Management of salt and water overload and hypo-osmolar states is important – restriction in excess	Thank you for your comment. We recognise this is a complex issue and believe that intravenous fluid management in such patients is

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	and Enteral Nutrition (BAPEN)						addressed under the section dealing with redistribution (see section 9, full version, see also algorithm 4). The guideline also recommends review of fluid management by an expert in such cases.
SH	British Association for Parenteral and Enteral Nutrition (BAPEN)	11	Full	3.1.2	19	Robust but pragmatic. I suppose the following sections explain what this means to some extent, but the term is an oxymoron	Thank you for your comment. We agree that the phrase 'robust but pragmatic' is an oxymoron. However, as rightly pointed out by you, it is appropriate to be used here and it has been explained in the sections following it.
SH	British Association for Parenteral and Enteral Nutrition (BAPEN)	12	Full	3.1.2.4	20	Exclusion of studies before 1990. NICE guidance is taken to be a gold standard for thoroughness. Nearly all the physiological studies on salt and water balance were done before then, as were the studies of the effect of feeding and glucose administration on salt and water balance. Therefore to apply a date "guillotine" of this kind weakens the evidence base. The steering group should re-consider whether key data from earlier times should be included, otherwise the document may be open to some criticism.	Thank you for your comment. We agree and this was not done across all reviews. The statement has now been modified to specify which reviews excluded studies before 1990. This was done in some cases as clinical practice with respect to intravenous fluid management in specific areas, for example, fluid resuscitation, has changed over time. Specific details are also highlighted in the appropriate review protocol (see section C.3, Appendix C)
SH	British Association for Parenteral and Enteral Nutrition	13	Full	3.3.1		Exclusion of ICU studies and of diabetes mellitus is disappointing. Why is cardiac surgery different from, say, cardiac failure? We should be able to learn from these special areas in a way that can improve general fluid management.	Thank you for your comment. The scope of the guideline was independently consulted upon prior to development and was finalised taking into account the views of stakeholders with detailed justification of the reasons

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	(BAPEN)						for exclusion of some areas. However, to answer the questions, there was a need to restrict the breadth of the work in order to make it practical. Prescribing for ITU is highly specialized with the use of inotropes and invasive monitoring making it very different from basic ward approaches, whilst fluid provision during cardiac surgery with bypass are also very atypical. Nevertheless, we did not exclude studies in any area that could indirectly inform issues within the scope of our guidance.
SH	British Association for Parenteral and Enteral Nutrition (BAPEN)	14	Full	4.1.10	34	Should this leadership exclude diabetes, intensive care, cardiac surgery, pregnancy etc? The remit sounds enormous and the data handling would verge on the impossible for an individual.	Thank you for your comment. All recommendations in this guideline pertain only to areas outlined in the scope. It is expected that the role of the IV fluids lead will be supported by a competent team.
SH	British Association for Parenteral and Enteral Nutrition (BAPEN)	15	Full	5	43	I don't think management of excess: of water or sodium or both is emphasised enough	Thank you for your comment. Such patients would qualify as patients with complex issues and our guidance makes it clear that their management requires expert input (Refer Algorithm 4: Replacement and redistribution).
SH	Croydon Health Services NHS Trust	1	Full	7.2.3.2	110	Our hospital uses Gelaspan 4% (BBraun) for fluid challenge and volume expansion in the Critical Care Unit and Operating Theatre departments. Gelaspan will be rolled out to our A & E department and all wards by the end of 2013 as the sole available colloid solution. Please add Gelaspan to your list of fluids so	Thank you for your comment. We have removed reference to all brand names in the guideline, except in the costing tables where we have now added Gelaspan 4% to the list. The evidence base for the use of

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						it accurately represents what is being used in the NHS. I consider Gelaspan to be superior to all other currently available balanced electrolyte solutions due to its use of acetate as a buffer, and the presence of magnesium and calcium in physiological concentrations.	gelatins for fluid resuscitation was inconclusive and therefore the GDG decided to make a research recommendation on the use of gelatin, particularly with reference to gelatins available in balanced electrolyte solutions.
SH	Deltex Medical	1	Full	2.5	13	Under "What this guideline does not cover" is "invasive monitoring of fluid status, for example in critical care or during surgical anaesthesia". Despite this, the draft recommendation (see 3.4, 5.2.2 and 5.2.4) then discusses and references intraoperative and postoperative fluid management studies. The draft also references the NCEPOD report (on page 9) which discusses perioperative fluid management and patient outcome.	Thank you for your comment. We agree and the scope of the guideline does not cover invasive monitoring of fluid status. The evidence base specific to invasive monitoring during intravenous fluid therapy was not reviewed during development and no specific references to invasive monitoring are mentioned in the recommendations. However, due to a lack of evidence in relation to the target population, studies from critical care settings were included as indirect evidence and the quality of evidence was downgraded for indirectness.
SH	Deltex Medical	2	Full	2.6	13	Under "Relationship between the guidance and other NICE guidance" we feel that NICE's MTG3 (CardioQ-ODM oesophageal Doppler monitor) should be referred to given the above comment (Comment #1)	Thank you for your comment. Invasive monitoring was outside of the scope of this guidance (refer Scope, Appendix A). We have now also added section in the introduction to explain this.
SH	Deltex Medical	3	Full	7.5 (#4)	126	"Several studies have shown reduced lengths of stay and reduced complications after a variety of surgical procedures when fluid therapy is optimised by targeting various haemodynamic goals (goal-directed therapy [GDT]). The most common haemodynamic	Thank you for your comment. We agree and this has now been removed.

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						<p>goal has been optimal stroke volume, as measured by oesophageal doppler or an alternative non-invasive technique (for example, LiDCO Rapid). Most studies have used colloids (hydroxyethyl starch or gelatine), although some have used crystalloid.”</p> <p>We suggest removing the “(for example LiDCOrapid)” from the above paragraph as it implies that using the LiDCOrapid for intraoperative fluid management will result in reduced lengths of stay and reduced postoperative complications. In fact, no clinical outcome studies have been published using the LiDCOrapid technology for intraoperative fluid management (four RCTs [1-4] have been published using the more accurate LiDCOplus technology with varying and inconclusive results).</p>	
SH	Deltex Medical	4	Full	General	General	<p>We caution the use of the terms ‘liberal’ and ‘restrictive’ when referring to perioperative fluid management throughout. These terms are very subjective, one clinicians liberal may be another’s restrictive. As stated by Brandstrup [5] (one of the early users of this terminology), “...we wish to abandon the term ‘restrictive’ as it has caused much confusion in the literature”.</p>	<p>Thank you for your comment. We agree with your rationale to exercise caution with the use of the terms ‘liberal’ and ‘restrictive’ and have been careful in the process of undertaking the literature reviews to categorise them appropriately by the actual volumes and content of administration.</p> <p>Please note that to avoid any misinterpretation, the recommendations are carefully and specifically worded with respect to the ml/kg body weight to be prescribed.</p>
SH	Deltex Medical	5	Full	15 (under)	36	With regard to “If patients need IV fluid resuscitation, use crystalloids that contain sodium in the range of 130-154 mmol/L, with a bolus of 500 mL over less	<p>Thank you for your comment. The guidance is aimed at general ward settings where a oesophageal Doppler</p>

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				'Resus citation')		than 15 minutes", evidence referenced in MTG3 demonstrate effective use of 200-250 mL fluid boluses with the oesophageal Doppler monitor. The precision [6] of the technology means that smaller, safer boluses can be administered with favourable outcomes.	monitor may not be routinely available. In such cases, the GDG agreed that a safe volume of bolus that can be administered is 500ml. this can be followed by further fluid therapy after reassessment of the patient, if required.
SH	Department of Health					No Comment	Thank you.
SH	Faculty of Intensive Care medicine	1	NICE	1.4.1	11	5% glucose provides minimal calorific intake (1 litre is < 20% of BMR). Emphasis of the sugar content could lead to the erroneous idea it has a nutritional role. The role is to replace free water.	Thank you for your comment. Recommendation 1.4.1 does state that the purpose of glucose in the fluid is to limit starvation ketosis. However in light of your comment, the GDG agreed to add a sentence that this does not address nutritional requirements and a reference to the NICE guideline on Nutrition support (CG32).
SH	Faculty of Intensive Care medicine	2	NICE	1.6.3	11	A lead is impractical and alone (like the algorithms) will achieve little. The emphasis must be on documentation of fluid balance and plan in the medical notes as part of the daily clinical assessment by a senior clinician. The importance of senior input is covered in full version. (10.52 p.159). It should be a key recommendation.	Thank you for your comment. It was understood that the lead would be supported by a competent team on the wards in the management of intravenous fluid therapy. The GDG discussed the importance of daily expert review of the IV fluid management plan and drafted a new recommendation to address this as follows: Recommendation 1.1.6 Patients should have an IV fluid management plan, which should include details of: •the fluid and electrolyte prescription

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							<p>over the next 24 hours</p> <ul style="list-style-type: none"> •the assessment and monitoring plan. <p>Initially, the IV fluid management plan should be reviewed by an expert daily. IV fluid management plans for patients on longer-term IV fluid therapy whose condition is stable may be reviewed less frequently.</p> <p>This recommendation is also a key priority for implementation.</p>
SH	Faculty of Intensive Care medicine	3	NICE	1.1.4	13	Suggest present algorithms as 4 separate charts	<p>Thank you for your comment.</p> <p>The four algorithms have presented separately as four separate charts in each of the relevant sections in the full guideline.</p>
SH	Faculty of Intensive Care medicine	4	NICE	1.4.4	17	This regime risks hyponatraemia at volumes less than 2.5 litres per day, particularly in sick patients with raised ADH. The risks of hypotonic fluids and hyponatraemia should be emphasised more	<p>Thank you for your comment.</p> <p>The risk of hyponatraemia was discussed at several GDG meetings as we share your concerns about this complication of IV fluid therapy. The recommendation is for the initial 24 hours “routine maintenance” prescription only and this is stressed in the full guideline. Further prescriptions should be guided by monitoring to allow for the individual hormonal changes that patients develop in response to their illness. In addition we have altered the recommendation to a reduced initial volume in groups at a potentially higher risk of hyponatraemia such as the older and</p>

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							frail. Our interpretation of available evidence and experience of GDG members suggest the risk of hyponatraemia is highest when volumes of greater than 2.5 litres of water per day are used persistently.
SH	Faculty of Intensive Care medicine	5	NICE	Diagram	20	Large ranges so figure unhelpful. Large losses from these sites require estimation of electrolyte content	Thank you for your comment. Unfortunately the large ranges of electrolyte content are a reality and at least the figures cited should trigger careful consideration of these aspects as well as furthering interpretation of the results from biochemical monitoring. We agree that measurement of actual electrolyte composition can be helpful in the case of large losses (although not always practical) and we have added a note to this effect.
SH	Faculty of Intensive Care medicine	6	NICE	1.2.2	15	There is no mention of the use of invasive and non invasive measures of fluid requirements both. These may be for the specialist, but they are becoming increasingly frequent, with more widespread US machines and courses (FICE, FATE and FEEL). It is likely that their use will become an increasingly integral part of patient bedside assessment. This true of US of the IVC and lung USS to assess lung water, as well as echocardiography	Thank you for your comment. Invasive monitoring was not considered as it was out of the scope of this guidance (refer Scope, Appendix A). However, to state this upfront, we have also added a section in the introduction to the guidance to explain this.
SH	Faculty of Intensive Care medicine	7	NICE	1.2.1	14	The Assessment part of the algorithm should consider whether the likely differential diagnosis, specifically cardiac conditions.	Thank you for your comment. The algorithms are intended to be a framework for management of intravenous fluid therapy. It is hoped that clinical judgment and consideration of differential diagnoses

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							should guide management in any clinical scenario.
SH	Faculty of Intensive Care medicine	8	NICE	1.4.4	17	Maintenance fluids should only be prescribed at the daily senior ward round. They are never urgent, and can often be supplemented by oral intake. Their repeated prescription by juniors causes excessive fluids to be given and increased cost	<p>Thank you for your comment.</p> <p>The GDG discussed the issue of daily expert review of intravenous fluid prescriptions to address the issue identified in the comment and drafted a new recommendation which reads as follows:</p> <p>Recommendation 1.1.6</p> <p>Patients should have an IV fluid management plan, which should include details of:</p> <ul style="list-style-type: none"> •the fluid and electrolyte prescription over the next 24 hours •monitoring plan <p>Initially, the management plan should be subject to expert review daily. Plans for patients on longer-term IV fluid therapy whose condition is stable may be reviewed less frequently.</p>
SH	Faculty of Intensive Care medicine	9	NICE	1.6.1	18	Many patients requiring intravenous fluids in hospital will be surgical patients, the critically ill, those with high GI outputs and therefore any training should probably focus more on illness states than “normal” physiology, which has long been a failing of medical teaching of fluid management.	<p>Thank you for your comment.</p> <p>We believe that the guideline does address the management of intravenous fluid therapy of all populations of patients as outlined in the scope (refer Appendix A). This includes patients with ‘normal’ physiology and ‘abnormal’ pathophysiology.</p>
SH	Faculty of Intensive Care medicine	10	Full	9.5	150	Typos; fkuids requireemnts .	<p>Thank you for your comment.</p> <p>We agree and this has now been amended.</p>

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SH	Fresenius Kabi Ltd	1	Full	general	general	<p>The guidance document intends to cover general areas of hospital practice where fluids are indicated. This may include the surgical setting as well as patients in the Intensive Care Unit (ICU). In this context, the selection of Randomised Controlled Trials (RCTs) and/or reviews for the assessment of fluids is very important, and one would expect that this selection represents the wide variation of fluid use in clinical practice. On the other hand, if the assessment of a particular fluid excludes a specific setting, no general recommendation should be provided, but limitations as a result of a particular selection of RCTs should be clearly addressed in the document (e.g. in sections 2.4 and 2.5 of the Full Version).</p> <p>Therefore, patients undergoing elective surgery should either be excluded from the conclusions of this guideline, or Tetrastarch studies in perioperative settings should be included in the evaluation, which may then allow valid conclusions on these populations for these products.</p> <p>Moreover, it is scientifically not justified to extrapolate data from one setting to another, for example, data gained in RCTs involving large numbers of sepsis patients to e.g. elective surgery. However, this has been done in the case of the assessment of Tetrastarches.</p> <p>We also suggest to clearly separate between the results obtained with different, not bioequivalent Tetrastarch products (e.g. Voluven and Tetraspan). This may be of high importance as in contrast to the 6S trial [Perner et al. 2012]; the CHEST study [Myburgh et al. 2012] did not find statistically</p>	<p>Thank you for your comment. The guideline is primarily aimed at intravenous fluid management in general ward settings and does not address fluid resuscitation in intra-operative settings. The scope states that groups that will be covered include surgical patients (pre- and postoperative patients) and excludes patients undergoing invasive monitoring of fluid status, for example in critical care or during surgical anaesthesia (refer Scope, appendix A). Please also refer to the scope in Appendix A. We have now also added a section in the introduction to the guideline to state that critically ill patients and patients under surgical anaesthesia are not covered in the scope if this guidance.</p> <p>Due to paucity of evidence/if no evidence was identified in the target population for fluid resuscitation, evidence from intra-operative settings was considered as indirect evidence and was appropriately downgraded. The recommendations are not aimed at intra-operative patients. Peri-operative fluid management has been broadly covered by the sections on replacement and redistribution.</p> <p>On your point regarding the extrapolation of data from sepsis patients to all areas of hospital</p>
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				<p>significant differences in 90-day mortality.</p> <p>The recommendation in the draft NICE Guideline to use Tetrastarches only in research settings seems to be mainly based on the mortality data from the 6S trial, not taking differences between Tetrastarches or the limited applicability of data from this setting to other medical fields into account.</p> <p>Other patient relevant outcomes such as “blood loss” and “transfusion requirements” and, consequently, further RCTs should also be considered with regard to the assessment of fluids. Furthermore, these patient relevant outcomes also play an important role in the economic assessment of fluids.</p>	<p>practice, it was the GDG’s opinion that the majority of patients who need IV fluids for fluid resuscitation are critically ill and have some degree of underlying sepsis. To account for this we have also downgraded the evidence for indirectness. Please note that the evidence from sepsis patients has been extrapolated to the target population of the review which is patients requiring intravenous fluids for resuscitation and not to intra-operative patients. This is explicitly detailed in the review protocol. However, we have now added more detail in the relevant sections (see sections 3.1.2.1, and 7.2, full version) regarding this.</p> <p>A decision to review all tetrastarches as a single class, irrespective of their source, was taken a priori at the start of the review process based on the GDG’s expert opinion and consensus.</p> <p>The GDG discussed the outcomes in order of priority at the stage of formulating the protocols for the evidence reviews.</p> <p>Due to the limited time span of development, seven key outcomes were prioritised for each review question and these are listed in the relevant protocols. We agree that outcomes such as blood loss and transfusion requirements are important outcomes. However, these were not</p>
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						prioritised a priori by the GDG in preference to the outcomes extracted.
SH	Fresenius Kabi Ltd	2	Full version	2.5	13	<p>As long as the draft NICE Guidelines take into consideration the evaluation of certain products (e.g. Tetrastarches) and mainly data from ICU and sepsis patients, we suggest adding under 2.5 that patients undergoing elective surgery are not covered or are only covered with limitations.</p> <p>For example, the “review for types of fluid for resuscitation” includes perioperative patients in the evaluation of gelatins and albumin, but not for Tetrastarches (for details refer also to Appendices, section C.3), although surgical trials are available. Moreover, this review generally excluded intraoperative cardiac surgery (CABG, where fluid is used to prime the pump) which becomes clear only in the appendices of the draft NICE Guideline on page 37 but is so far not mentioned under section 2.5 of the Full version. Besides bypass priming, fluids play in general an important role in this clinical setting, and in many clinical trials in cardiac surgery investigational fluids were used both for priming and perioperative fluid therapy. Therefore it should be reconsidered whether to include this setting in the scope of the Guideline.</p> <p>Nevertheless, if being excluded, section 2.5 should indicate the exclusion of cardiac surgery as even patients with burns, traumatic brain injury or patients needing neurosurgery have been explicitly mentioned as being excluded in this section.</p> <p>From a logical point of view, no conclusions should be made for settings excluded from the evaluation.</p>

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					<p>A general extrapolation of data gained in RCTs involving large numbers of sepsis patients (as it is the case for the assessment of Tetrastarches) to elective surgery is not justifiable. Therefore we suggest excluding elective surgery from the guideline or, alternatively to include Tetrastarch publications in perioperative settings in the evaluation, which may then allow valid conclusions on this population for these products.</p> <p>With regard to waxy-maize based HES 130/0.4, a positive benefit/ risk ratio can in particular be assumed for surgical patients. The safe/efficacious use of HES 130/0.4 in the perioperative setting has been reconfirmed by a variety of published clinical studies, reviews, and meta-analyses:</p> <ul style="list-style-type: none"> - Hamaji et al. Volume replacement therapy during hip arthroplasty using hydroxyethyl starch (130/0.4) compared to lactated Ringer decreases allogeneic blood transfusion and postoperative infection; Rev Bras Anestesiol. 2013;63(1):27-44 - Feldheiser et al. Balanced crystalloid versus balanced colloid solution using goal-directed haemodynamic algorithm. Br J Anaesth 2013;110(2):231-40 - Van der Linden et al. Safety of Modern Starches Used During Surgery. Anesth Analg 2013;116(1):35-48 - Martin et al. Effect of waxy maize-derived hydroxyethyl starch 130/0.4 on renal function in surgical patients. Anesthesiology 2013;118(2):387-94 - Lee et al. Effect of hydroxyethyl starch 130/0.4 on blood loss and coagulation in patients with recent 	<ul style="list-style-type: none"> - Hamaji et al 2013 was excluded as fluid given for pre-loading. - Feldheiser et al 2013 was excluded due to use of goal directed therapy in resuscitation - Van der Linden 2013 et al. was excluded as it was a review - Lee et al. 2011 was excluded as it was in the wrong population (intraoperative cardiac surgery) - Yang et al. 2011 was excluded as the population was out of the scope (severe liver disease patients) - Wu et al. 2010 was excluded as the population was out of the scope (kidney transplant patients) - Muralidhar et al. 2010 was excluded as it was in the wrong population (intraoperative cardiac surgery) - Mukhtar et al. 2009 was excluded as it was in the wrong population (liver transplant patients) - Godet et al. 2008 has been included in the comparison for gelatin vs. tetrastarches (see section 7.2.1, full guideline, page 100) - Niemi et al. 2008 was excluded as
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					<p>exposure to dual antiplatelet therapy undergoing off-pump coronary artery bypass graft surgery. <i>Circ J</i> 2011;75:2397–402</p> <ul style="list-style-type: none"> – Yang et al. Alternatives to albumin administration in hepatocellular carcinoma patients undergoing hepatectomy: an open, randomized clinical trial of efficacy and safety. <i>Chin Med J</i> 2011;124:1458–64 – Wu et al. Effects of the novel 6% hydroxyethyl starch 130/0.4 on renal function of recipients in living-related kidney transplantation. <i>Chin Med J</i> 2010;123:3079–83 – Muralidhar et al. Influence of colloid infusion on coagulation during off-pump coronary artery bypass grafting. <i>Indian J Anaesth</i> 2010;54(2):147–53 – Mukhtar et al. The safety of modern hydroxyethyl starch in living donor liver transplantation: A comparison with human albumin. <i>Anesth Analg</i> 2009;109(30):924–30 – Godet et al. Safety of HES 130/0.4 (Voluven®) in patients with preoperative renal dysfunction undergoing abdominal aortic surgery: a prospective, randomized, controlled, parallel-group multicentre trial. <i>Eur J Anaesthesiol</i> 2008;25:986–94 – Niemi et al. Hemodynamics and acid-base equilibrium after cardiac surgery: comparison of rapidly degradable hydroxyethyl starch solutions and albumin. <i>Scandinavian Journal of Surgery</i> 2008;97:259–265 – Mahmood et al. Randomized clinical trial comparing the effects on renal function of hydroxyethyl starch or gelatine during aortic 	<p>it was in the wrong population (cardio-pulmonary bypass surgery)</p> <ul style="list-style-type: none"> - Mahmood et al. has been included in the review comparing gelatin with tetrastraches (see section 7.2.1, full guideline, page 100) - Ellger et al. 2006 was excluded as it was in the wrong intervention (compared dual vs. single agent (HES200/0.5 + gelatin vs HES130/0.4). - Van der Linden et al. 2005 was excluded as it was in the wrong population (intraoperative cardiac surgery) <p>Please also see the list of excluded studies, section H.3. Appendix H.</p>
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					<ul style="list-style-type: none"> - aneurysm surgery. Br J Surg 2007;94:427–33 - Ellger et al. High-dose volume replacement using HES 130/0.4 during major surgery: Impact on coagulation and incidence of postoperative itching. Ned Tijdschr Anesth 2006;19(3):63-8 - Van der Linden et al. Hydroxyethyl starch 130/0.4 versus modified fluid gelatin for volume expansion in cardiac surgery patients: the effects on perioperative bleeding and transfusion needs. Anesth Analg 2005;101(3):629-34 		
SH	Fresenius Kabi Ltd	3	Full	3	General	<p>Other patient relevant outcomes such as “blood loss” and “transfusion requirements” and, consequently, further recently performed clinical fluid trials should be considered with regard to the assessment of fluids for resuscitation. Furthermore these patient relevant outcomes play an important role in the economic assessment of fluids. Clinical studies demonstrated a significant increase in the usage of fresh frozen plasma [Feldheiser et al. 2013] and red blood transfusion [Hamaji et al. 2013] in patients treated with crystalloids compared to Tetrastarches (HES 130/0.4). The additional costs for blood products should be considered in the economic assessment, too.</p> <p>In addition, if important paediatric trials in surgery [e.g. Hanart et al. Perioperative volume replacement in children undergoing cardiac surgery: albumin versus hydroxyethyl starch 130/0.4. Crit Care Med. 2009;37(2):696-701] are excluded, no conclusions should be drawn for paediatric patients. In our view, paediatric patients are especially sensitive, and inclusion of those data should be considered.</p>	<p>Thank you for your comment. The GDG discussed the outcomes in order of priority at the stage of formulating the protocols for the evidence reviews.</p> <p>Due to the limited time span of development, seven key outcomes were prioritised for each review question and these are listed in the relevant protocols. We agree that outcomes such as blood loss and transfusion requirements are important outcomes. However, these were not prioritised a priori by the GDG in preference to the outcomes extracted.</p> <p>The scope of the guideline is specific to intravenous fluid therapy in adult patients in hospital and the recommendations are not applicable to the paediatric patients. A separate guideline is in development for the management of intravenous fluid therapy in children and this has now been added to the list of related NICE</p>

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						guidance in development.	
						<p>With reference to the specific studies cited in your comment, Feldheiser et al 2013 was excluded due to the use of goal directed therapy and Hamaji et al. 2013 was excluded as fluid was given for pre-load (please also refer the excluded studies list section H.3, Appendix H).</p> <p>Hanart et al has been excluded as the study was conducted in children (population out of the scope of this guidance).</p>	
SH	Fresenius Kabi Ltd	4	Full version	4.2	37	<p>The recommendation in the draft NICE Guideline to use Tetrastarches only in research settings seems to be mainly based on the evidence of an increase in mortality at 90 days in septic patients observed in only a single study (6S study). In this study a specific Tetrastarch specification (Tetraspan) has been used. The CHEST study, performed with a different Tetrastarch specification (Voluven), did not show a statistical difference in mortality between groups overall, and in none of the pre-defined subgroups.</p> <p>Furthermore, due to the major differences in the pathophysiology of patients with sepsis and non-septic patients, an extrapolation of the sepsis data to other areas of hospital practice is questionable.</p> <p>In the case that the final NICE Guideline will include surgical patients, advantages of Tetrastarches in surgical settings (see references) should be acknowledged and reflected accordingly.</p>	<p>Thank you for your comments.</p> <p>A decision to review all tetrastarches as a single class was taken <i>a priori</i> at the start of the review process based on the GDG's expert opinion and consensus.</p> <p>We would also like to highlight that since the time of consultation on the draft guideline, the Medicines and Health Regulatory Authority (MHRA), UK has issued a Class 2 drug alert on the use of all hydroxyethyl starches.</p> <p>On your point regarding the extrapolation of data from sepsis patients to all areas of hospital practice, it was the GDG's opinion that the majority of patients who need IV</p>

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				<p>References :</p> <ul style="list-style-type: none"> - Feldheiser et al. Balanced crystalloid versus balanced colloid solution using goal-directed haemodynamic algorithm. <i>Br J Anaesth</i> 2013;110(2):231-40 - Yang et al. Alternatives to albumin administration in hepatocellular carcinoma patients undergoing hepatectomy: an open, randomized clinical trial of efficacy and safety. <i>Chin Med J</i> 2011;124:1458-64 - Muralidhar et al. Influence of colloid infusion on coagulation during off-pump coronary artery bypass grafting. <i>Indian J Anaesth</i> 2010;54(2):147-53 - Niemi et al. Hemodynamics and acid-base equilibrium after cardiac surgery: comparison of rapidly degradable hydroxyethyl starch solutions and albumin. <i>Scandinavian Journal of Surgery</i> 2008;97:259–265 - Mahmood et al. Randomized clinical trial comparing the effects on renal function of hydroxyethyl starch or gelatine during aortic aneurysm surgery. <i>Br J Surg</i> 2007;94:427–33 <p>The recommendation for albumin (page 37, line 2, no. 17) seems to be based mainly on a single study only where mortality at 28 days reached borderline statistical significance in a subgroup-analysis of septic patients treated with albumin.</p>	<p>fluids for fluid resuscitation are critically ill and have some degree of underlying sepsis. Nevertheless, to account for this we have downgraded the evidence for indirectness.</p> <p>We would like to clarify that the guidance is aimed at intravenous fluid management in general ward settings. The recommendations are not targeted at intra-operative patients. Evidence from intra-operative settings was only used as indirect evidence for fluid resuscitation and has been appropriately downgraded. Peri-operative fluid management has been broadly covered by the sections on replacement and redistribution.</p> <p>Although the recommendation for the use of albumin in patients with severe sepsis was based on evidence from a single study, we would like to highlight that:</p> <ul style="list-style-type: none"> • the subgroup was pre-specified in the study and had approximately 1200 patients • the difference in mortality was considered to be clinically important by the GDG based on an absolute risk difference of 46 fewer per 1000 (from 92
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							fewer to 7 more)
SH	Fresenius Kabi Ltd	5	Full	5.1.4	54 (line 25-27)	On page 54, line 26, one trade name (Gelofusine) of a succinylated gelatin has been mentioned in brackets, suggesting that only one succinylated gelatin may be available in the UK which would be not correct. Besides Gelofusin, a further succinylated gelatin, named Geloplasma, is available in the UK as well. Therefore, we suggest listing both trade names of the different succinylated gelatins (consistent with table 30 on page 110 where both trade names are already mentioned), or alternatively not to mention any brand name in this section.	Thank you for your comment. We agree and all brand names have now been replaced with generic names in the guideline except in costing and economic modelling.
SH	Fresenius Kabi Ltd	6	Full	7.2.1.1	92	Table 21 on top of page 92 lists seven studies comparing Gelatin with Tetrastarch, which is not consistent with the provided number in section 7.2.1.1. Here, there are six RCTs cited comparing Gelatin with Tetrastarches. However, of the six RCTs included, reference 121 belongs to a study by Wu et al. 2001, which compared Gelatines to lactated Ringer's solutions. As there seem to be some mismatches in this section we suggest revising this section.	Thank you for your comment. We agree and the table has now been revised to be consistent with the text. Seven studies were identified overall for all comparisons involving gelatin. Of these five studies compared gelatin with tetrastarch, three compared gelatin with lactated Ringer's solution and one study compared gelatin with sodium chloride 0.9%.
SH	Fresenius Kabi Ltd	7	Full	7.2.2.1	97	For the assessment of Tetrastarches, the majority of studies was performed in septic patients or patients admitted to ICU. A general extrapolation of data gained in RCTs involving large numbers of sepsis patients to elective surgery is not justifiable as there are major differences in the pathophysiology of patients with sepsis and patients undergoing a standard elective surgery Moreover and in view of the few selected studies, it is	Thank you for your comment. We would like to clarify that the guidance is targeted at generalised ward settings. Studies in intra-operative patients were included only due to a lack of evidence in the target population and the evidence from these studies has been appropriately downgraded for indirectness.

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				<p>highly relevant to note that the studies used different Tetrastarch specifications. Results obtained with potato-derived HES 130/0.42 (e.g. Tetraspan) cannot be extrapolated to waxy maize starch-based products HES 130/0.4 (e.g. Voluven).</p> <p>In the draft Guideline it is stated that 6% hydroxyethylstarch 130/0.4 has been compared in one study to Ringer's acetate (see page 97, line 16/ 17). In fact, the product used in the 6S-study (Cited study 80, Perner et al.) was HES 130/0.42 (Tetraspan) and not HES 130/0.4. The latter has meanwhile been corrected in the publication and we, therefore, suggest revising this in the final NICE Guidelines accordingly.</p> <p>The differentiation is of importance as waxy maize-based Voluven (HES 130/0.4) and the potato-based Tetraspan (HES130/0.42) are different products. Both exhibit different physico-chemical properties [Sommermeyer et al.;Transfus Altern Transfus Med 2007;9(3):27-33] and are based furthermore on different carrier solutions.</p> <p>Most important, clinical studies support the lack of bioequivalence of the two HES specifications and that the clinical effects of the products differ. Lehmann et al. [Drugs R D 2007;8(4):229-40] showed that HES 130/0.4 derived from waxy maize starch and HES 130/0.42 derived from potato starch are not bioequivalent. Furthermore, a retrospective cohort trial with more than 4000 ICU patients [Vandeweghe et al., Abstract book 25th ESICM Annual Congress, 2012;48(A-0154)] reported that acute kidney injury (AKI) occurred significantly more often in patients treated with potato based HES 130/0.42 compared to</p>	<p>The GDG did discuss the different types of tetrastarches and it was agreed <i>a priori</i> that these would be considered as a single class when evaluating the evidence, irrespective of their source.</p> <p>We agree however, that there was an error and we have now clarified that 6% hydroxyethyl starch 130/0.42 was compared to Ringer's acetate solution in the study by Perner et al.</p> <p>We would also like to highlight that since the time of consultation on the draft guideline, the Medicines and Health Regulatory Authority (MHRA), UK has issued a Class 2 drug alert on the use of all hydroxyethyl starches.</p> <p>With reference to your comment regarding the exclusion of patients admitted to the ICU following cardiac surgery, for the treatment of burns or following liver transplantation surgery, we would like to clarify that these populations were out of the scope of this guidance and would not be reviewed even if admitted to ICU (see Scope, Appendix A).</p> <p>On your comment regarding the inclusion of surgical trials for the review on gelatin, we would like to clarify that</p>
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				<p>waxy maize based HES 130/0.4 (Day 3: 15.6% vs. 20.7%, p=0.02, Day 5: 12.5% vs. 22.0%, p<0.001). Most recently, Langanke et al. [Eur J Anaesthesiol 2013;30:1-7] reported that “pulmonary inflammation in sepsis is differentially influenced by Tetrastarches produced from the different raw materials”.</p> <p>The fact that synthetic colloids vary considerably has been touched in the draft NICE Guideline so far under 7.1.1 on page 90 but not stressing the lacking bioequivalence between certain Tetrastarches.</p> <p>Overall it is important to note that there are no studies showing that the use of waxy maize-derived HES 130/0.4 is associated with a significant increase in overall mortality.</p> <p>In conclusion, we suggest differentiating between waxy maize-derived HES 130/0.4 and potato-derived HES 130/0.42 in the final NICE Guidelines.</p> <p>The CHEST study (Cited study no. 66 in the draft NICE Guideline) didn't include “all patients admitted to intensive care units”. In the CHEST study patients admitted to the ICU following cardiac surgery, for the treatment of burns or following liver transplantation surgery have been excluded according to the published exclusion criteria (see table S1B of the appendix of the CHEST publication). We therefore suggest revising on page 97, under 7.2.2.1, line 12-13 the statement …”and one study was conducted in all patients admitted to intensive care units…”.</p> <p>Furthermore, we would like to suggest to also include clinical trials in surgery, as this was done for the</p>	<p>these have been included as indirect evidence in the review on fluid resuscitation (as with other reviews) and have been appropriately downgraded.</p>
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						<p>assessment of gelatin (e.g. trials on gelatin versus hydroxyethyl starches might apply also for the assessment of Tetrastarches) or alternatively explain why they have not been considered.</p> <p>In conclusion, the extrapolation of data from non-identical products and critically ill patients (and here mainly sepsis patients) to other patient populations is scientifically not justified. We would suggest including further studies performed in surgical settings into the evaluation of Tetrastarches. This may only be necessary if elective surgery patients are not explicitly excluded from the scope and conclusions of the final NICE Guideline.</p>	
SH	Fresenius Kabi Ltd	8	Full	7.2.2.3	103	<p>In our view it is important to note that there are no studies showing that the use of waxy maize-derived HES 130/0.4 is associated with a significant increase in overall mortality. In the two studies used in the draft NICE Guidelines and where no significant difference in mortality has been seen, Voluven (HES 130/0.4) has been used. In contrast, in the 6S-study [Perner et al. 2012] with the potato starch-based HES 130/0.42 (Tetraspan), a significant higher mortality at day 90 has been reported. We therefore suggest to clearly separate between the results obtained with different, non bioequivalent Tetrastarch products in the final NICE Guideline.</p> <p>There is evidence from two further clinical studies performed in this setting which are assumed to be published soon. Preliminary results have already been presented and provide opposite conclusions which might be relevant for the guideline:</p> <p>The CRISTAL trial (ClinicalTrials.gov identifier:</p>	<p>Thank you for your comment.</p> <p>The GDG did discuss the different types of tetrastarches and it was agreed <i>a priori</i> that these would be considered as a single class when evaluating the evidence, irrespective of their source.</p> <p>Any new and relevant evidence from high quality randomised controlled trial settings in the target populations will be considered in the update of the guideline. On a preliminary review of the protocol of the CRISTAL trial, we identified this was an open label trial which may contribute to risk of bias when assessing certain outcomes.</p> <p>The guidance is aimed at management of intravenous fluid therapy in general</p>

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				<p>NCT00318942) was a multi-centre, multi-national investigator-initiated study in about 3000 intensive care unit patients (including sepsis) and was presented in January 2013 at the 41st International Congress of the Société de Réanimation de Langue Française (SRLF) in Paris (Session “Fluid Loading”). Colloid and crystalloid resuscitation were compared by a randomised, open-label design. Diverse colloids including Tetrastarches were used in approximately half of the patients. In this study, 90-day mortality was significantly reduced in the colloid group. There were no significant differences in renal function or the need for RRT.</p> <p>The BaSES trial [ClinicalTrials.gov identifier: NCT00273728] was a single-centre, investigator-initiated study performed in Basel, Switzerland, and first presented at the European Society of Anaesthesiology (ESA) conference in June 2012. This double-blind, randomised study included about 241 patients with severe sepsis and septic shock treated with Voluven (HES 130/0.4) or crystalloid. Both groups received additional infusion of Ringer's lactate solution. Mortality among ICU patients, hospital mortality, as well as renal function parameters did not differ between groups. However, there was a significantly reduced hospital length of stay in favour of Voluven.</p> <p>The preliminary results of both studies, CRISTAL and BaSES, suggest different conclusions than those obtained from the 6-S trial and should be considered.</p> <p>Moreover, as long as elective surgery patients are not explicitly excluded from the scope of the final NICE</p>	<p>ward settings. With reference to patients undergoing elective surgery, this includes peri-operative care (these patients have been considered in sections of the guidance relating to replacement and redistribution). Evidence from intra-operative patients was not directly applicable to the target population, and whilst it has been included as indirect evidence for the review on fluid resuscitation, it has been appropriately downgraded.</p>
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						Guideline, any evidence statement should reflect in addition the data obtained from this patient population.	
SH	Fresenius Kabi Ltd	9	Full	7.4	121	<p>The recommendation in the draft NICE Guideline to use Tetrastarches only in research settings seems to be mainly based on the evidence of an increase in mortality at 90 days in septic patients, observed only in a single study (6S-study), which has been performed furthermore with a specific Tetrastarch product (Tetraspan). In the 6S-study a potato-based HES130/0.42 in a balanced carrier solution has been used. In contrast to the 6S-trial, the CHEST study [Myburgh et al. 2012] did not find a statistically significant difference in 90-day mortality and has been performed with a different Tetrastarch specification (waxy maize-based HES130/0.4 in 0.9% NaCl; Voluven). Both Tetraspan and Voluven differ in view of raw material and carrier solutions. We therefore suggest revising the recommendation for the final NICE Guidelines as there are different results obtained with the different Tetrastarches and as waxy maize-based HES130/0.4 and potato-based HES130/0.42 are not bioequivalent.</p> <p>Besides, an extrapolation of sepsis data to “all patients receiving fluid resuscitation” is not directly possible due to several reasons:</p> <ol style="list-style-type: none"> 1. There are major differences in the pathophysiology of patients with sepsis and patients undergoing standard elective surgery. 2. There is no strong rationale for the Guideline Development Group assumption that the majority of patients receiving fluid resuscitation may have underlying sepsis. Vogel et al. 	<p>Thank you for your comment. A decision to review all tetrastarches as a single class, irrespective of their source, was taken <i>a priori</i> at the start of the review process based on the GDG's expert opinion and consensus.</p> <p>We would also like to highlight that since the time of consultation on the draft guideline, the Medicines and Health Regulatory Authority (MHRA), UK has issued a Class 2 drug alert on the use of all hydroxyethyl starches.</p> <p>On your point regarding the extrapolation of data from sepsis patients to all areas of hospital practice, it was the GDG's opinion that the majority of patients who need IV fluids for fluid resuscitation are critically ill and have some degree of underlying sepsis. Nevertheless, to account for this we have downgraded the evidence for indirectness.</p> <p>We would like to clarify that the guidance is aimed at intravenous fluid management in general ward settings. The recommendations are not aimed at intra-operative patients. Evidence from intra-operative settings was only used as indirect evidence for fluid resuscitation and has been</p>

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				<p>evaluated the incidence of postoperative sepsis after elective procedures in the US. Results: "A total of 6,512,921 weighted elective surgical cases met the inclusion criteria and 78,669 cases (1.21%) developed postoperative sepsis" [Vogel et al. 2010; Postoperative Sepsis in the United States; Annals of Surgery. 252(6):1065-1071]. Fowler et al. analysed 331,429 coronary artery bypass grafting cases and reported that "major infection occurred in 11,636 patients (3.51%)" [Fowler et al. 2005; Clinical Predictors of Major Infections After Cardiac Surgery; Circulation 30;112(9 Suppl):I358-65].</p> <p>3. There is not sufficient plausible scientific data justifying an extrapolation of data from different Tetrastarch products in critically ill patients to other patient populations, such as surgical patients.</p> <p>In the draft NICE Guideline this point has been acknowledged for the main studies used for the Tetrastarch evaluations. On page 101 it has been stated "<i>Study (Myburgh 2012) conducted in patients in ICU and may not be generalisable to other patients receiving resuscitation outside of ICU. Other studies were conducted in patients with sepsis Guidet2012) or trauma (James 2011) and may not be generalisable to all patients receiving fluids resuscitation.</i>"</p> <p>On page 102 it has been stated "<i>Study (Perner 2012) was conducted in patients with severe sepsis and findings may not be generalisable to all patients receiving intravenous fluids for resuscitation.</i>"</p>	<p>appropriately downgraded. Peri-operative fluid management has been broadly covered by the sections on replacement and redistribution. The GDG discussed and agreed that evidence from patients undergoing intra-operative cardiac surgery however, was too indirect to the target population of patients receiving intravenous fluids for resuscitation and no evidence from this population has been considered in the review of the evidence. This is explicitly detailed in the review protocol. However, we have now added more detail in the relevant sections (see sections 3.1.2.1, and 7.2, full version) regarding this.</p> <p>With respect to the list of clinical studies cited in your comment, we believe, these were excluded primarily for the above reasons and these are detailed in the excluded studies list (see section H.3, Appendix H).</p> <p>We have now also added a section in the introduction to the guideline to state that critically ill patients and patients under surgical anaesthesia are not covered in the scope of this guidance. Please also refer to the scope in Appendix A.</p>
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					<p>4. The safe/efficacious use of Tetrastarches in the perioperative setting has been reconfirmed by a variety of published clinical studies, reviews, and meta-analyses:</p> <ul style="list-style-type: none"> – Hamaji et al. Volume replacement therapy during hip arthroplasty using hydroxyethyl starch (130/0.4) compared to lactated Ringer decreases allogeneic blood transfusion and postoperative infection; <i>Rev Bras Anestesiol</i>. 2013;63(1):27-44 – Feldheiser et al. Balanced crystalloid versus balanced colloid solution using goal-directed haemodynamic algorithm. <i>Br J Anaesth</i> 2013;110(2):231-40 – Van der Linden et al. Safety of Modern Starches Used During Surgery. <i>Anesth Analg</i> 2013;116(1):35-48 – Martin et al. Effect of waxy maize-derived hydroxyethyl starch 130/0.4 on renal function in surgical patients. <i>Anesthesiology</i> 2013;118(2):387-94 – Lee et al. Effect of hydroxyethyl starch 130/0.4 on blood loss and coagulation in patients with recent exposure to dual antiplatelet therapy undergoing off-pump coronary artery bypass graft surgery. <i>Circ J</i> 2011;75:2397–402 – Yang et al. Alternatives to albumin administration in hepatocellular carcinoma patients undergoing hepatectomy: an open, randomized clinical trial of efficacy and safety. <i>Chin Med J</i> 2011;124:1458–64 – Wu et al. Effects of the novel 6% hydroxyethyl 	
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					<p>starch 130/0.4 on renal function of recipients in living-related kidney transplantation. Chin Med J 2010;123:3079–83</p> <ul style="list-style-type: none"> – Muralidhar et al. Influence of colloid infusion on coagulation during off-pump coronary artery bypass grafting. Indian J Anaesth 2010;54(2):147–53 – Mukhtar et al. The safety of modern hydroxyethyl starch in living donor liver transplantation: A comparison with human albumin. Anesth Analg 2009;109(30):924–30 – Godet et al. Safety of HES 130/0.4 (Voluven®) in patients with preoperative renal dysfunction undergoing abdominal aortic surgery: a prospective, randomized, controlled, parallel-group multicentre trial. Eur J Anaesthesiol 2008;25:986–94 – Niemi et al. Hemodynamics and acid-base equilibrium after cardiac surgery: comparison of rapidly degradable hydroxyethyl starch solutions and albumin. Scandinavian Journal of Surgery 2008;97:259–265 – Mahmood et al. Randomized clinical trial comparing the effects on renal function of hydroxyethyl starch or gelatine during aortic aneurysm surgery. Br J Surg 2007;94:427–33 – Ellger et al. High-dose volume replacement using HES 130/0.4 during major surgery: Impact on coagulation and incidence of postoperative itching. Ned Tijdschr Anesth 2006;19(3):63–8 – Van der Linden et al. Hydroxyethyl starch 130/0.4 versus modified fluid gelatin for volume expansion in cardiac surgery patients: the effects on perioperative bleeding and transfusion 	
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						needs. Anesth Analg 2005;101(3):629-34	
SH	Fresenius Kabi Ltd	10	Full	4	126 (referring to question 4, last paragraph)	In spite of knowing that the Feldheiser et al. study can probably not answer all questions touched in the last paragraph on page 126 ("There is evidence showing benefit of physiological (or balanced) fluids compared with saline-based fluids; therefore, it would seem appropriate to undertake a blinded, randomised controlled trial of colloid in balanced solution compared with a balanced crystalloid solution for perioperative GDT."), we would like to refer to the results of this double-blind pilot study as it may be important for the considerations made. In the study 6% HES 130/0.4 in a balanced electrolyte carrier solution (Volulyte) has been compared to a balanced crystalloid solution in patients with primary ovarian cancer undergoing cytoreductive surgery, using a goal-directed haemodynamic algorithm. Results showed that the Tetrastarch group required less study fluid with longer intravascular effect and a reduced need for transfusion of fresh frozen plasma during surgery. This was associated with better hemodynamic stability, higher stroke volume, cardiac index, and corrected flow time and lower systemic vascular resistance. No intergroup difference could be found concerning ICU- and hospital length of stay as well as peri- and postoperative renal function.	Thank you for your comment. We agree with your rationale and the Feldheiser et al. study was discussed by the GDG as part of the development process. However, as you have rightly pointed out, the study does not meet the criteria of the review protocol and therefore the findings were not considered relevant to this review. The GDG have drafted a research recommendation on this topic area.
SH	Fresenius Kabi Ltd	11	Appendices	3.1.1; 3.1.2	9	Since patients/population with intraoperative cardiac surgery (CABG, where fluid is used to the prime pump) are currently not included in the assessment of types of fluid for resuscitation (refer also to page 37, section C.3), this patient group should be mentioned in section "Groups that will not be covered", and no general conclusions including this patient group should be made.	Thank you for your comment. Studies in intra-operative patients were included in the review on fluid resuscitation. However, it was acknowledged that this evidence was indirect to the target population and therefore it was appropriately downgraded for indirectness. When

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						discussing the review protocols, the GDG agreed that studies involving intra-operative cardiac surgery patients were however too indirect to be considered applicable as evidence for this review. This was noted specifically as an exclusion in the review protocol for fluid resuscitation (please refer section C. 3, Appendix C).
SH	Fresenius Kabi Ltd	12	Appendices	C3	37	<p>The “population” excludes neurosurgical and brain trauma patients as well as intraoperative cardiac surgery (CABG, where fluid is used to prime the pump). In cardiac surgery, however, fluids play an important role not only in the context of priming, but also for perioperative fluid therapy, thus, the exclusion seems not justified. Furthermore, other patient relevant outcomes such as blood loss, and transfusion requirements should be taken into account for an assessment of the types of fluid for resuscitation.</p>

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							relevant protocols. We agree that outcomes such as blood loss and transfusion requirements are important outcomes. However, these were not prioritised <i>a priori</i> by the GDG in preference to the outcomes extracted.
SH	Fresenius Kabi Ltd	13	Appendices	E3.2	general	We would like to suggest to also include clinical trials in surgery, as this was done for the assessment of gelatin (e.g. trials on gelatin versus hydroxyethyl starches might apply also for the assessment of Trestarches) and Albumin, or alternatively explain why they have not been considered.	Thank you for your comment. Clinical trials in surgical patients have been considered for all comparisons, including those comparing gelatin with hydroxyethylstarch for the review on fluid resuscitation.
SH	Infection Prevention Society	1	Full NICE	General	General	<p>It would be helpful to draw to the attention of those who would use this guideline the following:</p> <p>Intravenous fluid administration, including intravenous drug therapy, poses a significant infection risk to the patient. Therefore all infusion related procedures must involve an aseptic technique. Additionally monitoring of patients receiving intravenous fluids needs to include:</p> <ul style="list-style-type: none"> • monitoring of insertion site for phlebitis or infection • monitoring of the patient for catheter-related blood stream infections <p>If signs of infection are present effective actions to investigate and remove infected catheters to prevent life-threatening infections should be instigated without delay.</p> <p>Adherence to safe intravenous protocols must be maintained for all procedures. This includes the correct catheter choice and removal of catheters as</p>	<p>Thank you for your comment. We agree with your observations. However, the scope of this guidance does not include routes of administration of IV fluids (see scope in appendix A) and any complications occurring as a result of lack of asepsis during administration and infection at insertion site.</p>

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						soon as clinically indicated.	
SH	Masimo	1	Full	6.2.1	65	<p>Traditional static parameters including CVP, Blood Pressure, Pulse Pressure, Pulmonary Capillary Occlusion (Wedge) Pressure and Cardiac Output do not reliably predict whether a patient will respond to additional fluid administration with an increase in cardiac output and tissue perfusion (i.e. they do not predict ‘fluid responsiveness’).</p> <p>Dynamic parameters such as pulse pressure variation, stroke volume variation, systolic pressure variation and Pleth Variability Index (PVI) all have a high sensitivity and specificity for determining if a patient will respond to additional fluid administration with an increase in cardiac output (i.e. they are effective in predicting ‘fluid responsiveness’). Pulse pressure variation and stroke volume variation are invasive and are appropriate for patients at high risk. Pleth Variability Index (PVI) is non-invasive and predicts fluid responsiveness with a specificity and sensitivity equivalent to invasive measurements. PVI is appropriate (low cost and low risk) for patients at low to moderate risk.</p>	<p>Thank you for your comment. The guidance is aimed at intravenous fluid management in general ward settings in the UK. Currently, the Pleth-Variability Index (PVI) is not available in such settings and the GDG felt that they could not recommend its use. In light of your comment, the GDG discussed that this topic will be considered in any subsequent update of this guideline.</p>
SH	Masimo	2	Full	10.2	154	<p>Static parameters are invasive and do not reliably predict fluid responsiveness.</p> <p>While invasive methods such as pulse pressure variation and stroke volume variation are reliable predictors of whether a patient will respond to fluid administration, they are expensive and are associated with the risk of intravascular catheters including infection and other line complications. Pleth Variability Index (PVI) is completely non-invasive (and therefore</p>	<p>Thank you for your comment. The guidance is aimed at intravenous fluid management in general ward settings in the UK. Currently, the Pleth-Variability Index (PVI) is not routinely available in such settings and the GDG felt that they could not recommend its use.</p> <p>The GDG discussed the possibility of this being a topic to be revisited in the</p>

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						low risk) and does not require additional cost (it is measured with the pulse oximeter probe).	update of this guidance.
SH	Medicines and Healthcare products Regulatory Agency	1	Full	General	General	<p>The benefit-risk balance of hydroxyethyl starch products for fluid replacement is being reviewed at a European level. The final European position will not be reached until at least Autumn 2013. Within the UK the MHRA, acting on advice from its independent expert group, the Commission on Human Medicines (CHM), has suspended the licences of hydroxyethyl starch and issued a recall of these products. The decision to suspend the licences for these products was taken on the basis that:</p> <ul style="list-style-type: none"> i) Evidence from randomised controlled clinical trials shows that the use of hydroxyethyl starch, when compared to crystalloids, is associated with an increased risk of mortality and renal replacement therapy or renal failure in patients with sepsis and in the critically ill. ii) There is a lack of evidence to provide reassurance that these risks are not present in other clinical settings such as surgery, trauma and burns patients. iii) There is little evidence that hydroxyethyl starch provides any clinically relevant benefit over crystalloids in any setting. <p>The suspension in the UK will last until a definitive position is reached in Europe. At that point the EU decision will be binding on all member states.</p> <p>Further details can be found in the Drug Safety Update (DSU) bulletin on the MHRA's website: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON286974</p>	<p>Thank you for your comment. We agree and evidence and recommendations in this guideline support the position of the MHRA.</p> <p>We would like to highlight that the new recommendation now states 'Do not use tetrastarch for fluid resuscitation.'</p>

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SH	Medicines and Healthcare products Regulatory Agency	2	NICE	1.3.2	17	Section 1.3.2 of the guideline states "Do not use tetrastarch for resuscitation, unless as part of a clinical trial." See our general comments above about the suspension of use of hydroxyethyl starch. Clinical trials using hydroxyethyl starch in the UK have been stopped.	Thank you for your comment. We agree and would like to bring your attention to the new recommendation which now states 'Do not use tetrastarch for fluid resuscitation.' The evidence base and rationale leading on to this decision has been detailed in the section linking the evidence to the recommendation which now also includes a note on the alert issued by the MHRA.
SH	NHS England	1.	Full	1.2.2		What about thirst as part of assessment of fluid balance?	Thank you for your comment. We agree and 'thirst' has now been added as a criteria for the assessment of fluid balance (refer recommendation 1.2.2 and Algorithm 1. Assessment. Box 2).
SH	NHS England	2.	Full	1.2.2		Weighing twice a week is good, may need note about calibration of weighing scales and standardisation within a hospital	Thank you for your comment. We agree and believe that all scales used in clinical settings are subject to calibration protocols. This has now also been added to the section linking the evidence to recommendations.
SH	NHS England	3.	Full	1.4.2		The adjustment of IV fluid prescription for obesity is less well known than much of the rest of the content – may need more prominence (ideally build in to a management protocol for obese patients)	Thank you for your comment. We agree, and therefore the GDG made a specific recommendation (Recommendation 1.4.2) regarding adjustments in the IV fluid prescription for obese patients.
SH	NHS	4.	Full	1.6.3		The statement about "hospitals should have an IV	Thank you for your comment.

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	England					fluids lead..." may need some clarification. Previous NICE recommendations along these lines have not always had the desired effect. Its important the responsibilities for training, clin gov, audit and review of prescribing are shared between all relevant senior staff, not assigned to a single individual	We agree and believe that the IV fluids lead will invariably be supported by a competent team.
SH	NHS England	5.	Full	Diagram of ongoing losses		This is a great diagram, although a couple of potential excess losses, such as burns, are missing.	Thank you for your comment. The scope of the guideline does not include burns as it was felt that IV fluid management in these patients would need special consideration. The diagram aims to illustrate the nature and content of common abnormal losses.
SH	Resuscitation Council	1	NICE	KPI	10	Weight measurement only twice per week will fail to detect important fluid accumulation in some patients, particularly those at risk of congestive heart failure.	Thank you for your comment. We agree and believe that the recommendation that patients receiving IV fluid therapy to address replacement or redistribution problems may need more frequent monitoring (includes weight measurement) addresses this issue. The recommendations are a guide for management of intravenous fluid therapy and it is hoped that this will not replace clinical judgement to weigh patients more frequently if the need arises.
SH	Resuscitation Council	2	NICE	general	general	There is no reference that I can see to the additional risk of IV fluid therapy in terms of infection risk, and the crucial importance of examining cannula entry sites at least daily, and changing cannulae with	Thank you for your comment. The scope of the guideline does not include access of administration of IV fluids and any associated adverse

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						appropriate frequency.	events. We have now added a section to the introduction of the guideline to explain this upfront. Please also refer Scope, Appendix A.
SH	Resuscitation Council	3	NICE	Algorithm 1	13 First green box	Beware. All the indicators listed except leg raise test (which many people will not use) will be present in a person with congestive heart failure who should NOT receive IV fluid. Absence of signs of fluid overload should be stated as a requirement before IV fluid prescription. This may seem obvious but some people will follow this guideline in a “blinkered” way if it is not stated explicitly. See note 7 below.	Thank you for your comment. The GDG agree and hence the words ‘indicators that a patient may need fluid resuscitation include’ precede the list of indicators. The GDG discussed the assessment of fluid resuscitation in the algorithm in conjunction with the recommendation (refer recommendation 1.2.1). The GDG agreed that assessment of hypovolaemia was key to this assessment of fluid resuscitation as some patients may still require fluids for resuscitation inspite of having clinical signs of fluid overload. The algorithm has also been reworded to reflect this.
SH	Resuscitation Council	4	NICE	Algorithm 2	Heading	This would be better changed to “Urgent/emergency fluid replacement” or if absolutely necessary “Fluid resuscitation” to minimise any confusion with cardiopulmonary resuscitation.	Thank you for your comment. We agree and the document now refers to the heading of Algorithm 2 as ‘Fluid resuscitation’
SH	Resuscitation Council	5	NICE	Algorithm 2	First lilac box	Is there good evidence to recommend high-flow oxygen in all cases? Does this not generate potential conflict with BTS guidelines on use of oxygen therapy?	Thank you for your comment. The algorithm has now been amended to not include any reference to the use of high flow oxygen. It is hoped that the use of oxygen for resuscitation will be undertaken taking into account clinical

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						co-morbidities of the patient.
SH	Resuscitation Council	6	NICE	Algorithm 4	General, especially Third pink box left column	<p>There is a major focus on some predominantly surgical conditions but no mention of one of the most common and hazardous medical emergencies requiring emergency IV fluid therapy, namely diabetic ketoacidosis. This should at least be mentioned.</p>
SH	Resuscitation Council	7	NICE	1.2.1	14	<p>See note 3 above. This could be reworded for clarity as "Assess whether the patient is hypovolaemic and needs IV fluid resuscitation. In the absence of evidence of fluid overload, indicators for urgent fluid resuscitation include:..."</p>

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							<ul style="list-style-type: none"> •capillary refill time is more than 2 seconds or peripheries are cold to touch •respiratory rate is more than 20 breaths per minute •National Early Warning Score (NEWS) is 5 or more •passive leg raising suggests fluid responsiveness.
SH	Resuscitation Council	8	NICE	1.2.4	16	As note 1 above. Weight measurement only twice per week will fail to detect important fluid accumulation in some patients, particularly those at risk of congestive heart failure. The need for more frequent weight measurement in many people, especially those at risk of CHF, should be emphasised.	<p>Thank you for your comment. We agree and believe that the recommendation does address this issue.</p> <p>Please refer first bullet point of recommendation 1.2.4:</p> <ul style="list-style-type: none"> •patients receiving IV fluid therapy to address replacement or redistribution problems may need more frequent monitoring.
SH	Resuscitation Council	9	NICE	1.3	16	See previous comment. Potential confusion with this wording. Either use "Fluid resuscitation" or preferably avoid the use of the word "resuscitation" in this context.	<p>Thank you for your comment. We agree and this has now been reworded to 'fluid resuscitation' throughout the guidance.</p>
SH	Resuscitation Council	10	NICE	1.3.2	17	See previous comment. Potential confusion with this wording. Either use "Fluid resuscitation" or preferably avoid the use of the word "resuscitation" in this context.	<p>Thank you for your comment. This has now been reworded to 'fluid resuscitation'.</p>
SH	Resuscitation Council	11	NICE	1.3.3	17	See previous comment. Potential confusion with this wording. Either use "Fluid resuscitation" or preferably avoid the use of the word "resuscitation" in this context.	<p>Thank you for your comment. This has now been reworded to 'fluid resuscitation'.</p>
SH	Resuscitation Council	12	NICE	1.4.5	18	I think what is meant here is "consider AVOIDING delivery of routine maintenance fluids during the night", when monitoring may be less easy or less	<p>Thank you for your comment. We agree and this has now been reworded to make the meaning clearer.</p>

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						intense.	The new recommendation reads as follows: Recommendation 1.4.5 Consider delivering IV fluids for routine maintenance during daytime hours to promote sleep and well-being.
SH	Resuscitation Council	13	NICE	1.5.2	18	the term “gross oedema” is open to very subjective interpretation.	Thank you for your comment. We agree that the term ‘gross oedema’ is broad. However, the GDG agreed that although not easy to define, it was a widely recognised and understood term.
SH	Resuscitation Council	14	NICE	Table	21	Hypokalaemia due to continued use of diuretic therapy whilst administering IV fluids should itself be reported as a critical incident.	Thank you for your comment. The administration of concomitant medication such as diuretics and inotropes during intravenous fluid therapy was not included in the scope of the guideline and so we are unable to comment on this.
SH	Resuscitation Council	15	NICE	GENERAL	GENERAL	Following on from the above note, I cannot find anywhere in this guideline a clear recommendation that if a person requires IV fluids it is very rarely appropriate for them to receive a diuretic at the same time, so the use of IV fluids should be accompanied by careful and repeated review of other medication.	Thank you for your comment. The use of concomitant medication, including diuretics and inotropes, during intravenous fluid therapy was excluded from the scope of this guidance. As a result we are unable to comment on this issue. However, it is understood that clinical practice will always consider the judicious use of concomitant medications when prescribing intravenous fluids. In light of your comment however, we have added in our recommendation that history taking should include ‘current medications’ which we hope will

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							address your concerns (see recommendation 1.2.2, NICE version)
SH	Resuscitation Council	16	NICE	2.1	22	Again there is use of the term “resuscitation” in a confusing setting. Do they mean “fluid resuscitation”, better called “emergency fluid replacement” or something similar, or do they mean CPR?	Thank you for your comment. We agree and this has now been changed to ‘fluid resuscitation’ throughout the document.
SH	Resuscitation Council	17	NICE	2.2	22	And again there is use of the term “resuscitation” in a confusing setting. They actually mean “emergency treatment” of patients with acute HYPOVOLAEMIC shock. I suggest rewording of this to avoid confusion. Patients with acute cardiogenic shock do not usually require IV fluids, often the opposite is true.	Thank you for your comment. We agree and this has now been changed to ‘acute hypovolaemic shock’.
SH	Resuscitation Council	18	NICE	2.2	23	And again there is use of the term “resuscitation” in a confusing setting. They actually mean “emergency treatment” of patients with acute HYPOVOLAEMIC shock. I suggest rewording of this to avoid confusion. Patients with acute cardiogenic shock do not usually require IV fluids, often the opposite is true.	Thank you for your comment. We agree and these have now been changed to ‘fluid resuscitation’ and ‘acute hypovolaemic shock’.
SH	Resuscitation Council	19	NICE	General Comment	General	The document does not define ‘resuscitation’, which is used clinically for a variety of scenarios ranging from a brief and gentle pre-operative circulatory ‘smartening up’ through to full-blown CPR. Perhaps the use of the term ‘resuscitation’ should now be reserved for CPR, with an alternative term being used for all fluid administration, i.e., “intravenous fluid therapy”. This could be refined by using the following specific terms <ul style="list-style-type: none"> • ‘rapid circulatory replenishment’ • ‘routine maintenance’ • ‘replacement and redistribution’ 	Thank you for your comment. The term ‘resuscitation’ has been used in the context of fluid resuscitation and this has been explained in different sections of the guideline where appropriate including a detailed explanation in section 7.1. However, we agree that the term ‘resuscitation’ may not accurately convey the desired meaning and thus this has now been replaced by ‘fluid resuscitation’ across the guidance. We believe that ‘fluid resuscitation’ is widely recognised as a term indicating the urgent management of circulatory failure with intravenous fluid therapy.

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SH	Resuscitation Council	20	NICE		Page 35 line 15 Page 35, line 37 Page 65, line 29 Page 123, algorithm 2	<p>There are several instances where the document implies that a NEWS value of 5 is an “indicator of urgent resuscitation” [i.e., the term resuscitation being used in the sense as outlined in page 36, line 15]. This is not necessarily correct. There are several combinations of abnormal physiological measurements that would produce a NEWS value of 5 that are not necessarily indicators for fluid therapy (e.g., febrile pneumonia with low SpO₂ and ongoing oxygen therapy). There is also inconsistency in the use of NEWS >5 and NEWS.5/6 (the latter is clearly incorrect)</p>	
SH	Resuscitation Council	22	NICE	7.1	89	<p>Intravenous fluid for resuscitation. It states ' Haemorrhagic shock has been described in 4 stages based on symptoms and signs. Although based on blood loss, the same principles will apply to hypovolaemia from any cause.' The 'evidence' for this statement is the ATLS manual. The ATLS 'evidence' comes from animal work done 50 years ago, based on penetrating trauma, it is no longer supported by the current evidence. Firstly, in Europe, 95% of trauma is blunt; this elicits a very different cardiovascular response to penetrating trauma. This is clearly demonstrated in the papers by Guly HR et al (Resuscitation 2010;81:1142, 2011;82:556) and more recently Mutschler M et al (Resuscitation 2013;84:309) which show that trauma patients do not behave as described by ATLS. Furthermore, the European Trauma Course has</p>	<p>Thank you for your comment. We have corrected the value to NEWS >5. We agree that a NEWS >5 can arise in several clinical situations not always requiring fluid resuscitation. In the guideline the NEWS score is highlighted as one of several indicators that may lead to a decision of fluid resuscitation. The need for volume assessment is stressed at the beginning of the recommendation. The recommendation now reads “Assess whether the patient is hypovolaemic. Indicators that a patient may need urgent fluid resuscitation include ...”</p> <p>Thank you for your comment. Your points are well made and, on reflection, the reference to the ATLS 4 stages of haemorrhagic shock adds little to this section - it has been deleted'.</p>

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						completely abandoned this artificial classification because of the evidence against it. I would also take issue with the claim that the same principles apply to hypovolaemia from any cause; are we really suggesting that sick, septic patients behave in this way, or indeed patients with anaphylactic shock? Finally, what about confounding issues such as concurrent medications, pregnancy, pre-existing diseases processes e.g. diabetes?	
SH	Resuscitation Council	23	NICE	General	General	Starches are no longer available so any reference to these needs to be removed or appropriately downplayed in the document.	<p>Thank you for your comment.</p> <p>We agree and would like to highlight that the recommendation now states 'Do not use tetra starch for fluid resuscitation.'</p> <p>This is based on a clinical and cost-effectiveness review of the evidence. We acknowledge that an alert has been issued by the Medicines and Health Regulatory Authority (MHRA) during consultation on the draft guideline. A reference to this alert has now been added onto the section linking evidence to recommendations which outlines the rationale for this recommendation.</p> <p>We believe that our recommendation is supported by the position of the MHRA.</p>
SH	Resuscitation Council	24	NICE	General	General	Gelatins are still over-emphasised in this guidance considering that they have have no benefit and several actual or possible adverse features. The UK is	<p>Thank you for your comment.</p> <p>Could you please clarify the areas in the guideline where you feel gelatins</p>

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						<p>one of the few countries that use a large amount of gelatins, more by fashion, and individual bias, than any real clinical indication or evidence.</p> <p>They are not available in the US. The fact that they are associated with anaphylaxis, albeit rare, can effect coagulation, and in some observational studies also had a harmful effect on renal function in ICU patients, means that without any evidence of benefit, and evidence of potential harm, their use should be discouraged.</p> <p>In addition the cost of gelatins is clearly higher e.g. in my hospital the cost of a gelatin is 6-10 times the cost of the same volume of Hartmann's or 0.9% sodium chloride. The myth that smaller volumes of gelatin are needed for volume expansion no longer holds true. It would be hard for any economic analysis to justify gelatin use.</p> <p>NICE should take a lead on this issue, as in some settings it is still common to substitute a gelatine for emergency volume expansion for hypovolaemia when a suitable crystalloid is already being infused. This requires a time resource, extra prescribing, and delays fluid resuscitation with crystalloids.</p> <p>NICE should actively discourage use of gelatins in its guidance, apart from research and further evaluation purposes. The extra risks albeit small, and significant cost need to be justified.</p>	<p>have been over-emphasised? The evidence with respect to gelatin was inconclusive and, based on this, the GDG were unable to make a recommendation on gelatin. The GDG have made a research recommendation on the use of gelatin and it is hoped that this will result in high quality trials being carried out in future which will offer conclusive evidence on the use of gelatin.</p>
SH	Royal College of Anaesthetists	1	NICE	1.4.1	17	<p>Routine maintenance of 25-30ml/kg/day will be difficult to interpret into clinical situations for some doctors and nurses. We would suggest the additional comments in brackets such as $1\text{ml}/\text{kg}/\text{hour} = 70\text{mls} / \text{hour}$ for a</p>	<p>Thank you for your comment. We agree and the guideline does include a table to calculate the volume of fluid to be prescribed for ease of</p>

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						70kg man. This will avoid poor prescribing due to mathematical errors and is a figure that Foundation Doctors will recall and be able to prescribe to.	administration (refer section P.4, Appendix P)
SH	Royal College of Anaesthetists	2	NICE	1.4.2	17	For obese patients it may be worth recommending a higher limit of safe prescription such as 80ml/hour or 100ml/hour with regular assessment – otherwise this could lead to continuous fluid rates of 200mls/hour (30ml/kg/day) prescribed by inexperienced doctors for patients weighing 150kg.	Thank you for your comment. We believe that recommendation 1.4.2 as it stands, does address this issue. The recommendation does highlight that prescribers should seek expert help for patients with BMI greater than 40 kg/m ² . The recommendation also states that patients rarely need more than 3 litres of fluid per day
SH	Royal College of Anaesthetists	3	NICE	general		Most patients in hospital receive antibiotics and other drugs (such as intravenous paracetamol, metronidazole each of which is 100mls 3-4 times a day) all of which contribute to fluid and sodium load. These volumes are rarely charted in fluid prescription charts and over several days can lead to significant volumes. It may be worth considering recommending the lower end of fluid volume prescription so that these additions do not have this impact. It is easy to give more fluid, much harder to take it away.	Thank you for your comment. We agree and the guideline therefore recommends taking in to account all sources of fluid intake (including fluids administered as part of antibiotics and other medication). Refer recommendation 1.1.7 When prescribing IV fluids and electrolytes, take into account all other sources of fluid and electrolyte intake, including any oral or enteral intake, and intake from drugs, IV nutrition, blood and blood products.
SH	Royal College of Anaesthetists	4	NICE	1.4.5	17	The delivery of IV fluids during day time with the routine of stopping IV fluids unless there is clinical indication could have several major impacts for the NHS: 1) Reduced IV fluid use with cost saving 2) Less inappropriate IV fluid prescribing – the doctors will need a clinical indication to restart	Thank you for your comment. We agree with your rationale and these were factors that the GDG did consider when discussing this recommendation. More details on this have now been added to the LETR section of this recommendation.

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						<p>the fluids</p> <p>3) Reduced work for nurses at night</p> <p>4) Better night time sleep for patients not being woken by alarming pumps</p> <p>5) Improved patient mobility (important to reduce other complications) due to not being tied to a drip</p> <p>Could this point be expanded – particularly for patients who have been on IV fluids for more than 48 hours without ongoing losses / fluid shifts.</p>	<p>However, on further discussion, the GDG felt that the recommendation need to reworded slightly to make its objective clearer.</p> <p>The new recommendation now reads as follows:</p> <p>Recommendation 1.4.5</p> <p>Consider delivering IV fluids for routine maintenance during daytime hours to promote sleep and well-being.</p>
SH	Royal College of Anaesthetists	5	Full	general	general	<p>The document as a whole is of extremely high quality</p> <p>Importantly the evidence base has been reviewed from a new start in the light of some evidence for colloids being subject to questionable research.</p>	Thank you for your comment.
SH	Royal College of Anaesthetists	6	Full	9.5.1	151	<p>This algorithm, although good, does not read clearly in all areas due to the layout.</p> <p>Can there be bulleted points in the green boxes as there are in the orange boxes below.</p>	<p>Thank you for your comment.</p> <p>We have tried to make the algorithm as comprehensive as possible in addition to make it fit on one side of an A4 page/or a poster, so that it can be printed off if need be. The GDG felt that it was useful to have all the algorithms on the same page as this helps the reader to have a clearer picture of how the algorithms link with one another. We realise that this results in the text being closely spaced in some areas, but we hope this will be overseen in the context of its effective use. For clarity of reading, we have now also added the separate algorithms as links to the NICE version of the guideline.</p>

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SH	Royal College of Anaesthetists	7	NICE	general	general	Some downloadable PDFs that could be printed by hospitals and put up in relevant areas (like the advanced life support guidelines) would be useful in helping fluid prescribing on the wards	Thank you for your comment. We would like to highlight that there is a downloadable algorithm included in the NICE guideline. The NICE implementation team produce materials to support the implementation of the guideline and this will follow along with and after the publication of this guideline.
SH	Royal College of Anaesthetists	8	Full	10.7	162	The box states that hospitals have a responsibility to ensure all healthcare professional are trained on the principles covered in the guidelines. This may suggest a requirement for formalised testing and the timing of such testing should not impact on the F1 foundation year. This should not impact on hospital workload but may be considered for medical school delivery, via a standardised undergraduate course.	Thank you for your comment. We agree with your observations and believe that in the medium to longer term the training should be primarily through undergraduate training. In the short-term there may be a requirement for bringing current staff up to speed with formalised training (for example, a training module) and testing. We do not anticipate that this will impact on any hospital duties.
SH	Royal College of Anaesthetists	9	NICE	general	general	Could a chart be standardised for initial fluid balance assessment when the patient arrives in hospital - with deficit /ongoing losses / maintenance with fluid prescribing built in?	Thank you for your comment. We agree and believe that this may be addressed by the work of the NICE implementation team who produce materials to support the implementation of the guideline. This will follow along with and after the publication of this guideline.
SH	Royal	10	Full	8.5.1	142	Could the wording in the boxes be bulleted / some	
						Thank you for your comment.	

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	College of Anaesthetists					other format - to make it easier to read?	We have tried to make the algorithm as comprehensive as possible in addition to make it fit on one side of an A4 page/or a poster, so that it can be printed off if need be. The GDG felt that it was useful to have all the algorithms on the same page as this helps the reader to have a clearer picture of how the algorithms link with one another. We realise that this results in the text being closely spaced in some areas, but we hope this will be overseen in the context of its effective use.
SH	Royal College of Anaesthetists	11	Full	22	140	Can this be expressed as ml/kg/hour as well.	Thank you for your comment. The GDG discussed the recommendation in light of your comment and agreed that it was best to express it in ml/kg/day.
SH	Royal College of Anaesthetists	12	NICE	general	general	A summary PDF of all the recommendations would be very useful.	Thank you for your comment. The NICE version of the guideline is a summary of all the recommendations, research recommendations and key priorities for implementation. It can be viewed/used in the pdf format.
SH	Royal College of Anaesthetists	13	NICE	general	general	Small pocket sized summary cards with guidelines for fluid therapy would be very useful for foundation trainees.	Thank you for your comment. We would like to highlight that it is not possible to produce pocket size summary cards with the guidelines for IV fluid therapy. However, PDF versions of the algorithms will be available for printing. The NICE implementation team

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							produce materials to support the implementation of the guideline and this will follow along with and after the publication of this guideline.
SH	Royal College of Anaesthetists	14	Full	general	general	The analysis of the RCTs has been done extremely well and we are in agreement with the evidence base, conclusions and recommendations made.	Thank you for your comment.
SH	Royal College of Anaesthetists	15	NICE	Algorithm	13	There is no mention of blood loss. We realise that these guidelines cannot cover everything but some patients in hospital requiring IV fluid resuscitation may have covert bleeding (post-operative, into the gut, retroperitoneal) This should be put into the resuscitation algorithm somewhere e.g. consider blood loss. Most patients requiring 2000mls of fluid resuscitation on the ward will be either bleeding or be septic. This could be added at the point 'seek expert help'.	Thank you for your comment. We agree and believe that the algorithm does refer to this when it says 'Identify cause of deficit and respond'
SH	Royal College of Anaesthetists	16	NICE & FULL	general	general	Peri-operative fluid management. The management of perioperative fluids can be generalised for many operations but major surgery poses many challenges. There are patient specific and operation specific issues which affect fluid therapy requirements. Post operatively these are also affected by blood loss, SIRS response and Sepsis. There is an excellent overview in the DoH ER Manual – could parts of this be included into a section on peri-operative care? Emphasis should be placed on protocolised fluid therapy as part of the Enhanced Recovery pathway with fluid management being under the daily review of senior doctors who can effect change from the pathway. A target day for enteral feeding with protocolised	Thank you for your comment. The aim of the guideline was to primarily guide management of intravenous fluid therapy in general ward settings. We have reviewed the evidence from intra-operative settings but this has been downgraded for indirectness. With regard to peri-operative care, the guidance on the management of intravenous fluid therapy during the peri-operative period is broadly covered by the sections on replacement and redistribution (see algorithm 4). We agree with your observations and believe that the recommendations do

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					taking down of the IVI may reduce the incidence of fluid overload.	emphasise the importance of enteral feeding as soon as possible (See recommendation 1.1.1 The assessment and management of patients' fluid and electrolyte needs is fundamental to good patient care, and should be part of every ward review. Provide intravenous (IV) fluid therapy only for patients whose needs cannot be met by oral or enteral routes, and stop as soon as possible. Also Algorithm 1- Assessment assesses if patients can meet their fluid and electrolyte needs by oral or enteral routes.) We believe that continuous reassessment of patients should elicit the time of cessation of IV fluid therapy at the earliest.
SH	Royal College of Anaesthetists	17	NICE FULL	general	Perioperative fluid management. Goal directed fluid therapy has been shown to reduce complications, Length of hospital stay and mortality. Many of the studies used gelatins for bolus, which despite having a risk of anaphylaxis have very different properties to those of starches. There is considerable debate currently ongoing around colloids, gelatins and starches and NICE is advised to hold intravenous fluid therapy guidance back until current research and debate completes its deliberations.	Thank you for your comment. We acknowledge that there is considerable research and debate currently ongoing around the use of gelatins and starches for fluid resuscitation. However, the scope of this guidance encompasses much more than the choice of fluids available for resuscitation and the GDG felt that the guidance was long overdue. The guidance makes definitive recommendations only in those areas where the evidence base is conclusive. In areas where the evidence was inconclusive (for e.g., gelatins), the

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							guideline recommends further research. NICE guidelines are re-evaluated and updated in due course or if there are significant changes to the evidence base.
SH	Royal College of Anaesthetists	18	NICE FULL	General	General	This NICE Guideline could not be more timely. Inappropriate intravenous fluid therapy is possibly one of the leading cause of iatrogenic/adverse events in hospital and often left to the most Junior Doctors to prescribe. With the development of Enhanced Recovery Programmes there is the perfect opportunity to integrate standardised fluid therapy into standard care pathways and reduce this.	Thank you for your comment.
SH	Royal College of Anaesthetists	19	NICE FULL	General	General	There could be more specific guides for anaesthetists – particularly for fluid bolusing in the operating theatre environment.	Thank you for your comment. The intention of the guideline was to aid prescribing and management of IV fluids in general ward settings. While we have reviewed the evidence from intra-operative settings as evidence for fluid resuscitation, this has been downgraded for indirectness.
SH	Royal College of Anaesthetists	20	Full	6.3.3.1	73	New Cochrane systematic review available Burdett E, Dushianthan A, Bennett-Guerrero E, Cro S, Gan TJ, Grocott MP, James MF, Mythen MG, O'Malley CM, Roche AM, Rowan K. Perioperative buffered versus non-buffered fluid administration for surgery in adults. Cochrane Database Syst Rev. 2012;12:CD004089. doi: 10.1002/14651858.CD004089.pub2. PMID: 23235602	Thank you for your comment. We have reviewed the evidence outlined in your comment. The protocol of the Cochrane review is different from that of the review protocol outlined in this guideline (see review protocol in C3, Appendix C). We have added a note to explain the differences in detail in the full version of the guideline (refer section 7.2.4.1) Further, on rechecking the studies in

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							the Cochrane review that assessed outcomes of interest to this review protocol, we found that they do not meet the inclusion criteria of this review and the reasons have been listed in the excluded studies list (refer H3, Appendix H).
SH	Royal College of Nursing				No Comment		Thank you.
SH	Royal College of Physicians	1	Full /NICE	General	The RCP is grateful for the opportunity to comment on the draft guideline. We have had sight of and wish to endorse the response submitted by the Faculty of Intensive Care Medicine. We would also like to make the following comments.		Thank you for your comment.
SH	Royal College of Physicians	2	Full /NICE	General	We are aware that The Renal Association will be commenting on the guideline. We would draw the development groups attention to comments they will be making with regard to: <ul style="list-style-type: none"> • The NICE guideline uses the term 'dehydration' when it should say 'hypovolaemia'. Many experts suggest avoiding the term dehydration unless it is meant to mean water depletion. The guidelines does use the word hypovolaemia in other places. • The lack of specific reference to the role of IV fluids in Acute Kidney Injury (AKI), particularly the risks in oliguric AKI. 		Thank you for your comment. We agree with your first point and the term 'dehydration' has now been replaced with 'hypovolaemia' across the text of the guideline. The GDG discussed the merits of using "hypovolemia and/or dehydration" and agreed that hypovolemia is the appropriate terminology for this guideline. On the second point regarding reference to Acute Kidney Injury (AKI), the guideline did consider the role of IV fluids in Acute Kidney Injury. The review protocols outline patients presenting with AKI as a specific subgroup and AKI was also considered as one of the important outcomes for many of the clinical evidence reviews

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						(refer protocols for fluid resuscitation, routine maintenance and replacement and redistribution in section C.3-C.6, Appendix C). The group further benefited from having two consultant nephrologists (one as GDG member and one as expert advisor. The expert advisor to the group is also a GDG member on the NICE guidance on Acute Kidney Injury which is due to be published in June 2013). However, the evidence reviews did not reveal any conclusive evidence for the use of a particular type of iv fluid in patients with AKI.
SH	Royal College of Physicians	3	Full /NICE	General	General	Many experts feel that the monitoring of daily bloods is extremely burdensome (and unnecessary).
SH	Royal College of Physicians	4	Full /NICE	General	General	The evidence behind measuring daily serum chloride, and then acting on high/low values, is unclear. Indeed, many labs do not offer chloride as a routine, and measuring bicarbonate is probably more useful.

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						understood. We therefore undertook a review which showed an association between hyperchloraemia and adverse events. The evidence also showed that hyperchloraemia occurs in populations receiving solutions containing high chloride levels (greater than 120 mmol/L) and therefore, the GDG agreed that this specific group of patients would benefit from daily monitoring of serum chloride levels. Furthermore, we understand that the testing of serum chloride can be done routinely as part of standard testing and would incur minimal extra costs. The GDG also discussed the testing of bicarbonate levels routinely when discussing possible review questions but agreed that they were generally used appropriately. Hence this was not prioritised as a review question.
SH	Royal College of Physicians	5	Full /NICE	General	At times the guidelines would benefit from a redraft. For example, the recommendations on monitoring carry the rider 'patients on longer-term IV fluid therapy whose condition is stable may be monitored less frequently;' although this comes after the injunction for universal daily monitoring; and 'longer-term' is undefined. Also 'Consider human albumin solution 4–5% only for resuscitation in patients with severe sepsis.' is ambiguous; We believe this means 'Only consider HAS if you are resuscitating a pt with severe sepsis;' but are not sure.	Thank you for your comment. The recommendations are intended to be a guide to aid good clinical practice and achieve higher standards in IV fluids management. With respect to monitoring, this would include the daily reassessment of fluid and electrolyte status. However, patients who are stable and receiving IV fluids for routine maintenance for longer periods may be monitored less frequently. The GDG discussed the recommendation in light of your comment and agreed

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							that an example of 'longer term' had been outlined in the algorithm as greater than three days (see Algorithm 3, Routine maintenance). On your second comment, we agree and the recommendation has now been changed to read as follows: changed to Recommendation 1.3.3 Consider human albumin solution 4–5% for fluid resuscitation only in patients with severe sepsis.
SH	Royal Liverpool and Broadgreen University Hospitals NHS Trust	1	Full	7.2.3.2	110	Please be aware that Royal Liverpool University Hospital Trust are using Gelaspan 4% as their balanced gelatin and this is not listed in Table 30 (fluids for resuscitation). Please could you consider adding Gelaspan to the table so that it accurately represents products available and currently being used in the NHS.	Thank you for your comment. The table is not meant to be all inclusive and also the costs are only indicative, since prices vary between Trusts. We have now included Gelaspan 4% for completeness. The commercial medicines unit inform us that the price is the same as gelofusine. Please note that we have removed reference to all brand names in the guideline, except in the costing tables. where we have now added Gelaspan 4% to the list. The evidence base for the use of gelatins for fluid resuscitation was inconclusive and therefore the GDG decided to make a research recommendation on the use of gelatin, particularly with reference to gelatins available in balanced electrolyte solutions.

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SH	Stockport NHS Foundation Trust	1	Full	3.1.1	19	'That' written twice in first sentence	Thank you for your comment. We agree and this has now been amended.
SH	Stockport NHS Foundation Trust	2	Full	3.1.2.5	20	'That' written twice in first sentence	Thank you for your comment. We agree and this has now been amended.
SH	Stockport NHS Foundation Trust	3	Full	10	general	This section refers to junior medical staff and junior doctors who prescribe fluids. What about non-medical prescribers?	Thank you for your comment. The recommendations and text in this section of the guideline relate to training and education of all health care professionals involved in the prescription and management of intravenous fluids in hospital.
SH	Vidacare BV	1	Full	4.2.1 And 7.4.1	39 123	Although Vidacare appreciate that route of administration is not covered in these guidelines the Algorithm 2 Resuscitation : Initiate Treatment; states "secure large bore IV access". As the European Resuscitation Council Guidelines and Resuscitation Council Guidelines UK both NICE endorsed now state Intraosseous access is the route of choice if IV access is not possible or associated with delay in the first two minutes, we feel the Algorithm 2 should reflect this. Stating secure IV/IO access.	Thank you for your comment. We agree. However, as pointed out, the scope of the guidance does not cover access of administration of IV fluids and we are not able to comment on intraosseous access. (Please refer scope, Appendix A), We have also added a section in the introduction to the guideline to explain this.

Registered stakeholders that were invited to comment and did not do so

3M Health Care UK

Aintree University Hospital NHS Foundation Trust

Airedale NHS Trust

Alder Hey Children's NHS Foundation Trust

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Allocate Software PLC
Association of British Healthcare Industries
Association of British Insurers
Association of Clinical Pathologists
Association of Surgeons in Primary Care
Association of Surgeons of Great Britain and Ireland
Associazione Infermieristica per lo Studio delle Lesioni Cutanee
Bard Limited
Barnsley Hospital NHS Foundation Trust
Blackpool, Fylde and Wyre Hospitals NHS Foundation Trust
Bradford District Care Trust
Breakspear Medical Group Ltd
British Association for Immediate Care
British Association For Paediatric Nephrology
British Association of Critical Care Nurses
British Association of Day Surgery
British Association of Paediatric Nephrology
British Dietetic Association
British Infection Association
British Medical Association
British Medical Journal
British National Formulary
British Nuclear Cardiology Society
British Pharmaceutical Nutrition Group
British Psychological Society
British Society for Immunology
British Society of Paediatric Gastroenterology Hepatology and Nutrition

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BSPGHAN
Burton Hospitals NHS Trust
C. R. Bard, Inc.
Cambridge University Hospitals NHS Foundation Trust
Camden Link
Capsulation PPS
Care Quality Commission (CQC)
Clatterbridge Centre for Oncology

College of Emergency Medicine
Cystic Fibrosis Trust
Department for Communities and Local Government
Department of Health, Social Services and Public Safety - Northern Ireland
Dorset Primary Care Trust
East and North Hertfordshire NHS Trust
East Kent Hospitals University NHS Foundation Trust
East Midland Ambulance Services NHS
East Midlands Ambulance Service NHS
Economic and Social Research Council
Edwards Lifesciences
Faculty of Sport and Exercise Medicine
Five Boroughs Partnership NHS Trust
G&N Medical Ltd
George Eliot Hospital NHS Trust
Gloucestershire Hospitals NHS Foundation Trust
Gloucestershire LINK
Great Western Hospitals NHS Foundation Trust

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Guy's and St Thomas' NHS Foundation Trust
Hammersmith and Fulham Primary Care Trust
Health Protection Agency
Health Quality Improvement Partnership
Healthcare Improvement Scotland
Heart of England NHS Foundation Trust
Herts Valleys Clinical Commissioning Group
Hindu Council UK
Humber NHS Foundation Trust
Imperial College Healthcare NHS Trust
Independent Healthcare Advisory Services
Infection Control Nurses Association
ITP Support Association, The
Lancashire Care NHS Foundation Trust
Lancashire Teaching Hospitals NHS Trust
Leeds Community Healthcare NHS Trust
Leeds Teaching Hospitals NHS Trust
Letterkenny General Hospital
Liverpool Primary Care Trust
London Ambulance Service NHS Trust
Luton and Dunstable Hospital NHS Trust

MacoPharma
Meningitis Research Foundation
Mid Cheshire Hospitals NHS Trust
Ministry of Defence
National Association of Primary Care
National Clinical Guideline Centre

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National Collaborating Centre for Cancer
National Collaborating Centre for Mental Health
National Collaborating Centre for Women's and Children's Health
National Institute for Health Research Health Technology Assessment Programme
National Patient Safety Agency
National Public Health Service for Wales
National Treatment Agency for Substance Misuse
Neonatal & Paediatric Pharmacists Group
NHS Clinical Knowledge Summaries
NHS Connecting for Health
NHS Direct
NHS Kidney Care
NHS Plus
NHS Sheffield
NHS Sickle Cell & Thalassaemia Screening Programme
NHS South of England
NHS Warwickshire North CCG
NICE technical lead
NOrF
North of England Critical Care Network
North Tees and Hartlepool NHS Foundation Trust
North West Ambulance Service NHS Trust
North West London Perinatal Network
Nottingham City Council
Nottingham City Hospital
Oxford Health NHS Foundation Trust
Papworth Hospital NHS Foundation Trust

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Parenteral and Enteral Nutrition Group
Patient Liaison Committee
Pfizer
Pharmacosmos
Primary Care Pharmacists Association
Public Health England
Public Health Wales NHS Trust
Queen Elizabeth Hospital King's Lynn NHS Trust
Rarer Cancers Foundation
Renal Association
Royal Berkshire NHS Foundation Trust
Royal Brompton Hospital & Harefield NHS Trust
Royal College of General Practitioners
Royal College of General Practitioners in Wales
Royal College of Midwives
Royal College of Obstetricians and Gynaecologists
Royal College of Paediatrics and Child Health
Royal College of Paediatrics and Child Health , Gastroenterology, Hepatology and Nutrition
Royal College of Pathologists
Royal College of Psychiatrists
Royal College of Radiologists
Royal College of Surgeons of England
Royal Free Hospital NHS Foundation Trust
Royal Free London NHS Foundation Trust
Royal Pharmaceutical Society
Royal Society of Medicine

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Scottish Intercollegiate Guidelines Network
Sheffield Childrens Hospital
Sheffield Teaching Hospitals NHS Foundation Trust
Smiths Medical International
Social Care Institute for Excellence
Society for Acute Medicine
South Asian Health Foundation
South London & Maudsley NHS Trust
South London Cardiac and Stroke Network
South West Yorkshire Partnership NHS Foundation Trust
South Western Ambulance Service NHS Foundation Trust
Southport and Ormskirk Hospital NHS Trust
St John Ambulance
St Mary's Hospital
Staffordshire and Stoke-on-trent NHS Partnerships
Teva UK
The Association for Clinical Biochemistry & Laboratory Medicine
The Association of safe Aseptic practice
The Haemophilia Society
The Intensive Care Society
The Patients Association
The Rotherham NHS Foundation Trust
The University of Glamorgan
Trauma Audit & Research Network
UK Clinical Pharmacy Association
UK Lung Cancer Coalition
UK Multiple Sclerosis Specialist Nurse Association

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United Kingdom National External Quality Assessment Service
University Hospital Birmingham NHS Foundation Trust
University Hospitals Birmingham
Vifor Pharma UK Ltd
ViroPharma Ltd
VYGON
Walsall Local Involvement Network
Warwickshire County Council
Welsh Government
Western Cheshire Primary Care Trust
Western Sussex Hospitals NHS Trust
Wirral University Teaching Hospital NHS Foundation Trust
Worcestershire Acute Hospitals Trust
Wrightington, Wigan and Leigh NHS Foundation Trust
York Hospitals NHS Foundation Trust

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