National Clinical Guideline Centre

IV fluids in children

Intravenous fluid therapy in children and young people in hospital

NICE Guideline NG29

Methods, evidence and recommendations

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RCGP Royal College of General Practitioners
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Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and, where appropriate, their guardian or carer.

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1 Introduction

This guideline contains recommendations about general principles for managing intravenous (IV) fluids in children and young people under 16 years, and applies to a range of conditions and different settings. It does not include recommendations relating to specific conditions.

Recommendations on the management of intravenous fluids in adults (from their 16th birthday) in hospital settings can be found in NICE clinical guideline 174 IV fluids in adults. Healthcare professionals should use their clinical judgement when managing young people transitioning between paediatric and adult services and paediatric and adult healthcare teams should work together to provide assessment and services to young people who need IV fluids. Diagnosis and management should be reviewed throughout the transition process, and there should be clarity about who is the lead clinician to ensure continuity of care.

Correct fluid and electrolyte balance is essential to maintain normal physiological function in humans. Normally, children are able to maintain their fluid requirements through drinking. However, many children admitted to hospital may be too ill to drink and may require intravenous (IV) fluid therapy to maintain correct fluid and electrolyte balance. IV fluid therapy may also be required to restore correct fluid and electrolyte balance. Children may need IV fluids to account for losses of red blood cells, plasma, water or electrolytes, beyond the usual losses in urine, stools and sweat. These losses can occur via the loss of blood, plasma and other fluids resulting from burns, diarrhoea, vomiting or leakage of fluid from the circulation into the interstitial space. In these situations, the aim is to replace any depleted fluids and restore associated electrolyte imbalances. Other conditions can result in fluid overload, that is, an excess of fluids in the body. In these situations, the aim is to rebalance and redistribute fluids and ensure correct levels of electrolytes.

Whether IV fluid therapy is needed for fluid resuscitation, maintenance, replacement or redistribution, it is vital that the choice, volume and timing of IV fluids are correct. Different types of fluids are appropriate for different situations. Errors in prescribing or administering IV fluids can result in inadequate or excessive provision. Despite the relative complexity of estimating a patient's IV fluid needs, assessment and prescription is often delegated to healthcare professionals who have received little or no specific training on the subject. Prescribers are not always aware of the most appropriate type and volume of IV fluids to use for specific conditions. Additionally, many healthcare professionals may be unaware of the specific physiological changes associated with these conditions in children. In the past there has been little formal training and education in IV fluid management to support correct prescribing. Furthermore, failing to correct imbalances in electrolytes can lead to disturbances in intracellular or extracellular electrolyte balance in children, particularly in those with reduced liver or kidney function. Failing to deliver adequate fluid replacement can therefore have a significant impact upon morbidity and mortality.

A National Patient Safety Agency alert[31] has highlighted safety concerns in relation to the use of hypotonic IV fluids in children, as these fluids are associated with the development of hyponatraemia. Children are more at risk of developing brain swelling and neurological complications as a consequence of hyponatraemia compared to adults. There are many cases in the literature where children have died as a consequence of inappropriate hypotonic fluid therapy. Monitoring and assessment of children receiving IV fluids is of paramount importance to guide continuing therapy however, this is often difficult and challenging for healthcare professionals. In addition, blood tests required to assess and guide IV fluid therapy can be painful and distressing for the child, and difficult to repeat. As a result, assessment and monitoring is often suboptimal, with fluid and electrolyte status not being evaluated adequately. This may lead to inappropriate IV fluid prescribing.

The aim of this NICE guideline is to help prescribers understand the:

- indications for IV fluid therapy
- reasons for the choice of the various fluids available
- prevention and treatment of sodium imbalance
- principles of assessing fluid balance
- training and education needs of those prescribing IV fluids.

This guidance represents a major opportunity to improve the safety of children receiving IV fluid therapy in hospital. It applies to babies born at term, babies born prematurely whose corrected age is term or more, infants, children and young people up to 16 years. The guideline covers the general principles for managing IV fluids and applies to a range of conditions and different settings. It does not include specialised fluid prescribing needs such as those relating to specific conditions.

2 Development of the guideline

2.1 What is a NICE clinical guideline?

NICE clinical guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. We base our clinical guidelines on the best available research evidence, with the aim of improving the quality of healthcare. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific review questions.

NICE clinical guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional.

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- Guideline topic is referred to NICE from the Department of Health.
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the National Clinical Guideline Centre (NCGC).
- The NCGC establishes a Guideline Development Group.
- A draft guideline is produced after the group assesses the available evidence and makes recommendations.
- There is a consultation on the draft guideline.
- The final guideline is produced.

The NCGC and NICE produce a number of versions of this guideline:

- the 'full guideline' contains all the recommendations, plus details of the methods used and the underpinning evidence
- the 'NICE guideline' lists the recommendations
- 'information for the public' is written using suitable language for people without specialist medical knowledge
- NICE Pathways brings together all connected NICE guidance.

This version is the full version. The other versions can be downloaded from NICE at www.nice.org.uk.

2.2 Remit

NICE received the remit for this guideline from the Department of Health. They commissioned the NCGC to produce the guideline.

The remit for this guideline is:

'to develop a clinical guideline on IV fluid therapy in children and young people in hospital'.

2.3 Who developed this guideline?

A multidisciplinary Guideline Development Group (GDG) comprising health professionals and researchers as well as lay members developed this guideline (see the list of Guideline Development Group members and the acknowledgements).

The National Institute for Health and Care Excellence (NICE) funds the National Clinical Guideline Centre (NCGC) and thus supported the development of this guideline. The GDG was convened by the NCGC and chaired by Dr Peter Crean in accordance with guidance from NICE.

The group met approximately every 6 weeks during the development of the guideline. At the start of the guideline development process all GDG members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest.

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix B.

Staff from the NCGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers, health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate and drafted the guideline in collaboration with the GDG.

2.3.1 What this guideline covers

The guideline will contain recommendations about general principles for managing IV fluids in babies born at term, children and young people and applies to a range of conditions and different hospital settings.

The guideline will cover the assessment, monitoring and reassessment of fluid and electrolyte status, IV fluid therapy for resuscitation, maintenance and replacement and redistribution, the management of hyponatraemia and hypernatraemia developing during IV fluid administration and the skills needed for adequate training and education of healthcare professionals.

For further details please refer to the scope in Appendix A and the review questions in Section 3.1.

2.3.2 What this guideline does not cover

The guideline does not provide recommendations for adults aged 16 or over, or for babies born prematurely whose corrected age is less than term.

The guideline does not cover routes of administration of IV fluid therapy, how to deliver IV fluids, the use of blood and blood products, prescribing and monitoring of electrolytes, minerals and trace elements, other than sodium, potassium and chloride provision, the use of inotropes to support people with circulatory failure, invasive monitoring of fluid status, parenteral nutrition, labelling, preparation and storage of products, ethical issues or patient and carer information needs specific to IV fluids.

2.3.3 Relationships between the guideline and other NICE guidance

Related NICE Technology appraisals:

- Pre-hospital initiation of fluid replacement therapy in trauma (2004) NICE technical appraisal guidance TA74

Related NICE Clinical guidelines:

- Diabetes (type 1 and type 2) in children and young people (2015) NICE guideline NG18
- Bronchiolitis in children (2015) NICE guideline NG9
- Medicines optimisation (2015) NICE guideline NG5
- Medicines adherence (2009) NICE guideline CG76
- Intravenous fluid therapy in adults in hospital (2013) NICE guideline CG174
- Acute kidney injury (2013) NICE guideline CG169
- Feverish illness in children (2013) NICE guideline CG160
- Neutropenic sepsis (2012) NICE guideline CG151
- Sedation in children and young people (2010) NICE guideline CG112
- Bacterial meningitis and meningococcal septicaemia (2010) NICE guideline CG102
- Diarrhoea and vomiting in children (2009) NICE guideline CG84
- Urinary tract infection in children (2007) NICE guideline CG54

Related NICE guidance currently in development:

- Transfusion. NICE guideline. Publication expected November 2015.
- Major trauma. NICE guideline. Publication expected February 2016.
- Neonatal jaundice. NICE guideline. Publication date TBC.
- Sepsis. NICE guideline. Publication date TBC.

3 Methods

This chapter sets out in detail the methods used to review the evidence and to generate the recommendations that are presented in subsequent chapters. This guidance was developed in accordance with the methods outlined in the NICE guidelines manual 2012.[29] The revised NICE guidelines manual 2014 was not employed for the purposes of this guideline as it was published during development.

3.1 Developing the review questions and outcomes

Review questions were developed in a PICO framework (patient, intervention, comparison and outcome) for intervention reviews. This was to guide the literature searching process and to facilitate the development of recommendations by the guideline development group (GDG).

This use of a framework guided the literature searching process, critical appraisal and synthesis of evidence, and facilitated the development of recommendations by the GDG. The review questions were drafted by the NCGC technical team and refined and validated by the GDG. The questions were based on the key clinical areas identified in the scope (Appendix A). The GDG considered the relative importance of these and prioritised areas for developing review questions.[29] This decision to prioritise certain areas took into consideration factors such as whether the area is a key clinical issue for the NHS, patient safety, cost (to the NHS), equality and variations in practice.

A total of 12 review questions were identified.

Full literature searches, critical appraisals and evidence reviews were completed for all the specified review questions.

Chapter	Review questions	Outcomes
Assessment and reassessment	How effective is assessing body weight compared with body surface area for predicting IV fluid requirements in children? (Review question 1)	• Mortality • Adverse effects (including hypovolaemia, dehydration, hypervolaemia, neurological complications) • Fluid balance • Quality of life
Assessment and reassessment	What are the key components to be measured and documented on an IV fluid balance and/or prescription chart to ensure appropriate prescribing of IV fluids? (Review question 2)	• Mortality • Adverse effects (including hypovolaemia, dehydration, hypervolaemia, neurological complications, hypoglycaemia) • Quality of life • Length of hospital stay
Assessment and reassessment	What is the clinical- and cost-effectiveness of laboratory-based methods versus point-of-care testing for assessing electrolyte estimations in children? (Review question 3)	• Mortality • Test turnaround time • Adverse effects (including hypovolaemia,

Chapter	Review questions	Outcomes
		dehydration, hypervolaemia, neurological complications) • Fluid balance • Quality of life • Length of hospital stay
Assessment and reassessment	What are the most clinically- and cost-effective methods for assessing dehydration and hypovolaemia? (Review question 4)	• Mortality • Adverse effects (including hypervolaemia, dehydration, neurological complications, hypoglycaemia) • Quality of life • Length of hospital stay
Resuscitation	What is the most clinically- and cost-effective fluid type for fluid resuscitation in children? (Review question 5)	• Mortality at 28 days • Neurological compromise (return to baseline activity, ischaemic injury, cerebral oedema) • Cardiovascular compromise (blood pressure (BP)/arterial pressure, heart rate) • Length of hospital stay • Hyperchloraemic acidosis • Quality of life • Hypoglycaemia • Hypernatraemia • Hyponatraemia
Resuscitation	What is the most clinically- and cost-effective volume and rate of administration for IV fluid resuscitation? (Review question 6)	• Mortality at 28 days • Neurological compromise (return to baseline activity, ischaemic injury, cerebral oedema) • Cardiovascular compromise (blood pressure (BP)/arterial pressure, heart rate) • Length of hospital stay • Hyperchloraemic acidosis • Quality of life • Hypoglycaemia • Hypernatraemia • Hyponatraemia

Chapter	Review questions	Outcomes
Routine maintenance	What is the most clinically- and cost-effective fluid type for IV fluid maintenance in children? (Review question 7)	• Mortality at 28 days • Neurological compromise (return to baseline activity, ischaemic injury, cerebral oedema) • Cardiovascular compromise (blood pressure (BP)/arterial pressure, heart rate) • Length of hospital stay • Hyperchloraemic acidosis • Quality of life • Hypoglycaemia • Hypernatremia • Hyponatraemia
Routine maintenance	What is the most clinically- and cost-effective rate of administration of IV fluids for routine maintenance? (Review question 8)	• Mortality at 28 days • Neurological compromise (return to baseline activity, ischaemic injury, cerebral oedema) • Cardiovascular compromise (blood pressure (BP)/arterial pressure, heart rate) • Other organ dysfunction, for example, renal, respiratory compromise • Length of hospital stay • Hyperchloraemic acidosis • Quality of life • Hypoglycaemia • Hypernatremia • Hyponatraemia
Replacement and redistribution	What fluid types are the most clinically- and cost-effective to address abnormal deficits or excesses, or to replace abnormal losses? (Review question 9)	• Mortality at 28 days • Neurological compromise (return to baseline activity, ischaemic injury, cerebral oedema) • Cardiovascular compromise (blood pressure (BP)/arterial pressure, heart rate) • Length of hospital stay • Hyperchloraemic

Chapter	Review questions	Outcomes
		acidosis • Quality of life • Hypoglycaemia • Hypernatraemia • Hyponatraemia
Hypernatraemia and hyponatraemia	What are the most clinically- and cost-effective methods to address hypernatraemia developing during IV fluid administration? (Review question 10)	• Mortality at 28 days • Rate of return to normal electrolyte levels • Adverse events (for example hypovolaemia, hypervolaemia, neurological compromise, cardiac arrest) • Return to normal electrolyte levels • Length of hospital stay • Quality of life
Hypernatraemia and hyponatraemia	What are the most clinically- and cost-effective methods to address hyponatraemia developing during IV fluid administration? (Review question 11)	• Mortality at 28 days • Rate of return to normal electrolyte levels • Adverse events (for example hypovolaemia, hypervolaemia, neurological compromise, cardiac arrest) • Return to normal electrolyte levels • Length of hospital stay • Quality of life
Education and training	What skills are needed for the adequate training and education of healthcare professionals involved in prescribing and administering IV fluids? (Review question 12)	Qualitative outcomes: Specific focus includes: • Body surface area versus body weight • Recognition and treatment of hyponatraemia • Recognition and treatment of hypoglycaemia • Fluid overload in children • Calculation of fluid balance

3.1.2 Issues with evidence related to guideline development

The GDG noted that the guideline population was cross-cutting and that recommendations would provide general principles of managing IV fluids across a range of in-hospital patient populations. The GDG noted that specific in-hospital patient populations (for example, renal versus surgical patients) present with different fluid requirements and may respond differently to IV therapy.

The GDG also highlighted the lack of high quality clinical evidence (RCTs or sufficiently large cohort studies) to inform many of the research areas.

3.1.3 Hierarchy of evidence

In the absence of high quality evidence the GDG developed a pragmatic process on which to make recommendations:

Order of preference for study designs:

- Systematic reviews of RCTs which meet our criteria
- Randomised control trials

Where no RCTs are available, we will consider:

- Abstracts on RCTs

Where no RCTs or abstracts of RCTs are available:

- Non-randomised trials: prospective or retrospective cohort studies of 50 children or more
- Non-blinded, single and double-blinded trials will be included

Where no randomised or non-randomised evidence in children are available (when applicable):

- Systematic reviews of RCTs which meet our criteria in adults
- Randomised controlled trials in adults

Where no RCTs in adults are available, we will consider:

- Abstracts on RCTs in adults

Where no RCTs or abstracts of RCTs in adults are available:

- Non-randomised trials: prospective or retrospective cohort studies of 1000 adults or more

3.1.4 Indirect evidence

When RCT evidence was not available within the guideline population (that is, children and young people) the initial approach was to consider indirect evidence using RCTs in other populations. The GDG pre-specified specific conditions in which extrapolation was appropriate and explicitly how these populations informed recommendations. Further information on indirectness is contained in Section 3.3.4.

3.1.5 Evidence from non-randomised studies

RCT data in children was only available for a selected number of clinical questions, and the GDG agreed a standardised approach for inclusion of non-randomised studies for this guideline. Non-randomised studies in a direct population (that is, in children) were required to have a minimum of 50 patients and were limited to populations meeting the guideline condition. Where non-randomised studies in adults were considered a minimum of 1000 patients were required, except for the point-of-care versus

laboratory testing clinical review question (Review question 3), where the GDG felt the adult data applied equally to children and adults and set a minimum sample size of 50 patients.

3.1.6 Recommendations based on consensus

The GDG acknowledged that it was unlikely to be possible to undertake clinical evidence reviews for certain areas of the guideline due to the lack of evidence. Areas which were exceptions to the normal systematic review process included:

- Body surface area versus body weight (Review question 1)
- Key components to be measured and documented on an IV fluid balance and/or prescription chart (Review question 2)
- Assessment of dehydration and hypovolaemia (Review question 4)
- Volume and rate of resuscitation fluid (Review question 6)
- Treatment of hypernatraemia (Review question 10)
- Treatment of hyponatraemia (Review question 11)

The GDG therefore chose to take into consideration their own clinical experience, principles of physiology and pathophysiology of IV fluids and other accepted standard clinical guidance and drafted recommendations based on formal consensus in a format intended to be useful to a clinician.[9,39] The discussion is documented in the 'Linking evidence to recommendations' section in each chapter.

3.1.7 Excluded studies – fluid types

The GDG agreed that the evidence should primarily include proprietary IV solutions and restricted the protocol to solutions commonly used within the NHS.

The GDG noted that in June 2013, the MHRA[26] suspended the use of all hydroxyethyl (HES) starches. Following a review of this decision in October 2013, the European Medicines Agency[16] chose to amend the suspension to allow the use of hydroxyethyl (HES) starches in specific clinical scenarios, namely in patients with hypovolaemia caused by acute blood loss, in whom crystalloids are considered inadequate. HES starches were included in the original protocols but the GDG chose to exclude HES starches from all evidence reviews, as it was their opinion that HES starches were not commonly used in clinical practice.

The GDG noted that, because of the risk of developing hyponatraemia, 0.18% sodium chloride solution is contraindicated in children except under expert medical supervision in paediatric specialist settings, such as renal, cardiac, liver, high dependency and intensive care units, as outlined in the National Patient Safety Agency Alert issued in 2007.[31] The GDG excluded 0.18% sodium chloride solutions at the protocol stage for use as maintenance fluid in a non-specialist unit.

3.2 Searching for evidence

3.2.1 Clinical literature search

Systematic literature searches were undertaken to identify all published clinical evidence relevant to the review questions. Searches were undertaken according to the parameters stipulated within the guidelines manual 2012.[29] Databases were searched using relevant medical subject headings, free-text terms and study-type filters where appropriate. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English. All searches were conducted in MEDLINE, Embase, and The Cochrane Library. Additional subject specific databases were used for some questions: PsycINFO and CINAHL for the training and education

question. All searches were updated on 22 December 2014. No papers published after this date were considered.

Search strategies were quality assured by cross-checking reference lists of highly relevant papers, analysing search strategies in other systematic reviews, and asking GDG members to highlight any additional studies. The questions, the study types applied, the databases searched and the years covered can be found in Appendix F.

The titles and abstracts of records retrieved by the searches were sifted for relevance, with potentially significant publications obtained in full text. These were assessed against the inclusion criteria.

During the scoping stage, a search was conducted for guidelines and reports on the websites listed below from organisations relevant to the topic. Searching for unpublished literature was not undertaken. All references sent by stakeholders were considered.

- Guidelines International Network database (www.g-i-n.net)
- National Guideline Clearing House (www.guideline.gov/)
- National Institute for Health and Care Excellence (NICE) (www.nice.org.uk)
- National Institutes of Health Consensus Development Program (consensus.nih.gov/)
- NHS Evidence Search (www.evidence.nhs.uk/).

3.2.2 Health economic literature search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to IV fluid therapy for children in the NHS economic evaluation database (NHS EED), the Health Economic Evaluations Database (HEED) and health technology assessment (HTA) databases with no date restrictions. Additionally, the search was run on MEDLINE and Embase, with a specific economic filter, from 2011, to ensure recent publications that had not yet been indexed by these databases were identified. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English language.

The search strategies for health economics are included in Appendix F. All searches were updated on 22 December 2014. No papers published after this date were considered.

3.3 Evidence of effectiveness

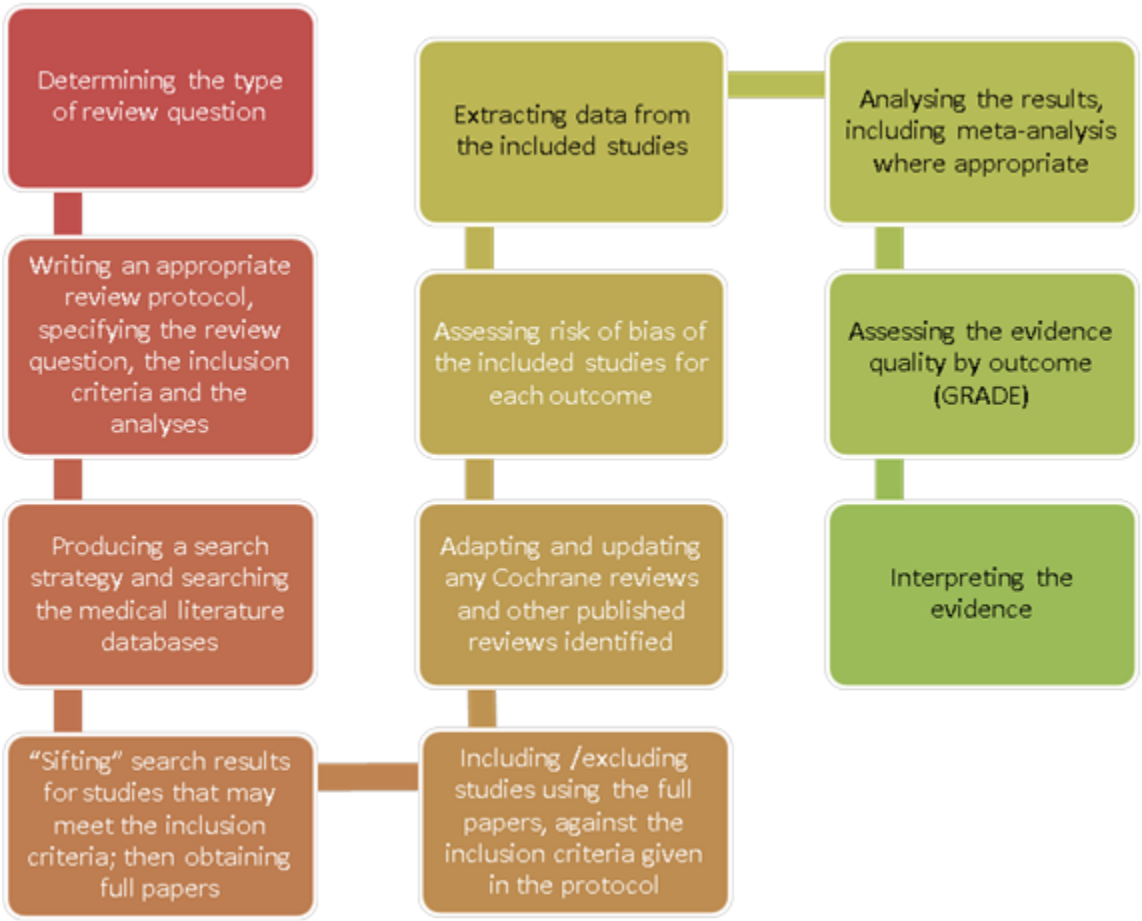
The evidence was reviewed following the steps shown schematically in Figure 1:

- Potentially relevant studies were identified for each review question from the relevant search results by reviewing titles and abstracts. Full papers were then obtained.
- Full papers were reviewed against pre-specified inclusion and exclusion criteria to identify studies that addressed the review question in the appropriate population (review protocols are included in Appendix C).
- Relevant studies were critically appraised using the appropriate checklist as specified in The guidelines manual.[29]
- Key information was extracted on the study's methods, PICO factors and results. These were presented in summary tables (in each review chapter) and evidence tables (in Appendix G).
- Summaries of evidence were generated by outcome (included in the relevant review chapters) and were presented in GDG meetings

- Randomised studies: data were meta-analysed where appropriate and reported in GRADE profiles (for intervention reviews).
- Observational studies: data were presented as a range of values in GRADE profiles.
- Qualitative studies: each study was summarised in a table where possible, otherwise presented in a narrative.

A 20% sample of each of the above stages of the reviewing process was quality assured by a second reviewer to eliminate any potential of reviewer bias or error.

Figure 1: Step-by-step process of review of evidence in the guideline



3.3.1 Inclusion and exclusion criteria

- The inclusion and exclusion of studies was based on the review protocols, which can be found in Appendix C. Excluded studies by review question (with the reasons for their exclusion) are listed in Appendix K. The GDG was consulted about any uncertainty regarding inclusion or exclusion.
- The guideline population was neonates born at term, infants, children and young people up to their 16th birthday receiving IV fluids in hospital. Babies born prematurely with a corrected age of term or more were also included.
- The GDG considered applicability of the population for each clinical question according to the clinical context of the review question. In areas where evidence was anticipated to be lacking the GDG considered evidence from indirect populations and settings which were directly applicable to the clinical question. Some examples are the inclusion of studies of dengue fever or malaria for management of sepsis.

More information about indirect populations is outlined in Section 3.3.4.

- Systematic reviews, including Cochrane reviews appropriately matching protocol and randomised trials meeting the guideline condition, were preferentially included in the clinical review. Cochrane reviews meeting the PICO were quality assessed and presented. Any papers included in the Cochrane that were not reviewed in the original guideline and deemed to be important were ordered and considered for inclusion. In the absence of RCT evidence non-randomised trials and observational studies within the guideline population were included. The GDG only considered prospective or retrospective cohort studies of at least 50 children to be of sufficient quality on which to base recommendations.
- The GDG agreed to consider RCTs in a population of adults only for questions in which the clinical evidence could be appropriately extrapolated to the guideline population. For example adult evidence, in the absence of studies in children, could be applied to fluid type questions (routine maintenance and resuscitation), but not rate of fluid administration.
- Conference abstracts were not automatically excluded from the review but were initially assessed against the inclusion criteria and then further processed only if no other full publication was available for that review question, in which case the authors of the selected abstracts would be contacted for further information. However, no clinical reviews presented with appropriate conference abstract data.
- Laboratory studies (including human, animal or in vitro) were excluded as these settings were considered to be artificial and not comparable to the guideline population. Literature reviews, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

The review protocols are presented in Appendix C.

3.3.2 Methods of combining clinical studies

3.3.2.1 Data synthesis for intervention reviews

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for the binary outcomes, such as mortality and neurological sequelae. Hazard ratios will be presented wherever possible for outcomes that are time dependent, that is, mortality.

For continuous outcomes, measures of central tendency (mean) and variation (standard deviation) were required for meta-analysis. Data for continuous outcomes, such as ICU length of stay, were analysed using an inverse variance method for pooling weighted mean differences. When the only evidence was based on studies that summarised results by presenting medians (and interquartile ranges), or only p values were given, this information was assessed in terms of the study's sample size and was included in the GRADE tables without calculating the relative or absolute effects (that is, ICU length of stay in the replacement and redistribution clinical review). Consequently, aspects of quality assessment such as imprecision of effect could not be assessed for evidence of this type.

Stratified analyses were predefined for some review questions at the protocol stage when the GDG identified that these strata are different in terms of biological and clinical characteristics and the interventions were expected to have a different effect on subpopulations. For example, for questions regarding resuscitation the protocol was stratified by patients undergoing resuscitation for trauma, surgery or sepsis. Additionally, other questions considering direct administration of fluid were stratified by population age (for example for Review question 7, the following age strata were chosen: 0–48 hours, 48 hours–28 days, 28 days–16 years).

Data were recorded and presented by the authors. In the case in which we have missing data with a difference >10% between the groups, and the study has an impact on the conclusion (that is, a large

study) we will conduct an available case analysis and compare it to what the authors reported (ITT) in a sensitivity analysis.

Statistical heterogeneity was assessed by visually examining the forest plots, and by considering the chi-squared test for significance at $p<0.1$ or an I-squared inconsistency statistic (with an I-squared value of more than 50% indicating considerable heterogeneity). Where considerable heterogeneity was present, we carried out predefined subgroup analyses. Sensitivity analysis based on the quality of studies was also carried out, eliminating studies at overall high or very high risk of bias (randomisation, allocation concealment and blinding, missing outcome data).

Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. If no sensitivity analysis was found to completely resolve statistical heterogeneity then a random-effects (DerSimonian and Laird) model was employed to provide a more conservative estimate of the effect.

The means and standard deviations of continuous outcomes were required for meta-analysis. Where p values were reported as 'less than', a conservative approach was undertaken. For example, if the p value was reported as '$p\leq0.001$', the calculations for standard deviations will be based on a p value of 0.001. If these statistical measures were not available then the methods described in Section 16.1.3 of the Cochrane Handbook (March 2011) 'Missing standard deviations' were applied as the last resort.

For interpretation of the binary outcome results, differences in the absolute event rate were calculated using the GRADEpro software for the median event rate across the control arms of the individual studies in the meta-analysis. Absolute risk differences were presented in the GRADE profiles and in clinical summary of findings tables, for discussion with the GDG.

3.3.2.2 Data synthesis for qualitative study reviews

Where possible, a meta-synthesis would be conducted to combine qualitative study results. The main aim of the synthesis of qualitative data is a description of the main topics that may influence the experience of care of the child, rather than to build new theories or reconceptualise the topic under review. Only one review question (Review question 12, on training and education of healthcare professionals) was identified as being qualitative, and no studies were found from searches that met the inclusion criteria. Therefore, a qualitative review was not conducted.

3.3.2.3 Type of studies

For intervention reviews in this guideline, parallel randomised controlled trials (RCTs) were included because they are considered the most robust type of study design that can produce an unbiased estimate of the intervention effects. If the GDG believed RCT data were not appropriate or there was limited evidence from RCTs, well-conducted non-randomised studies were included.

Please refer to Appendix C for full details on the study design of studies selected for each review question. For example, observational data was included in the clinical review for management of hyponatraemia as conducting an RCT with a time critical and potentially devastating condition could be considered unethical and is therefore unlikely.

3.3.2.4 Appraising the quality of evidence by outcomes

The evidence for outcomes from the included RCTs and observational studies were evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software developed by the GRADE working group (GRADEpro) was used to assess the quality of each outcome, taking into account individual study quality factors and the meta-analysis results. Results were presented in GRADE profiles ('GRADE tables'), which consist of 2 sections: the 'Clinical evidence profile' table includes details of the quality assessment while the 'Clinical evidence summary of findings' table includes pooled outcome data

(where appropriate), an absolute measure of intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate summary measures and measures of dispersion (such as mean and standard deviation or median and range) for continuous outcomes and frequency of events (n: the sum across studies of the number of patients with events divided by sum of the number of completers) for binary outcomes. Reporting or publication bias was only taken into consideration in the quality assessment and included in the 'Clinical evidence profile' table if it was apparent.

The evidence for each outcome was examined separately for the quality elements listed and defined in Table 1. Each element was graded using the quality levels listed in Table 2. The main criteria considered in the rating of these elements are discussed below (see Section 3.3.2.5 Grading of evidence). Standardised footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome (Table 3).

Table 1: Description of the elements in GRADE used to assess the quality of intervention studies

Quality element	Description
Risk of bias ('Study limitations')	Limitations in the study design and implementation may bias the estimates of the treatment effect. High risk of bias for the majority of the evidence decreases confidence in the estimate of the effect.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results.
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made, such that the effect estimate is changed.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect. Imprecision results if the confidence interval crosses the clinically important threshold.
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.

Table 2: Levels of quality elements in GRADE

Level	Description
None	There are no serious issues with the evidence
Serious	The issues are serious enough to downgrade the outcome evidence by 1 level
Very serious	The issues are serious enough to downgrade the outcome evidence by 2 levels

Table 3: Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

3.3.2.5 Grading the quality of clinical evidence

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

1. A quality rating was assigned, based on the study design. RCTs start as High, observational studies as Low.

2. The rating was then downgraded for the specified criteria: risk of bias (study limitations), inconsistency, indirectness, imprecision and publication bias. These criteria are detailed below. Evidence from observational studies (which had not previously been downgraded) was upgraded if there was: a large magnitude of effect, a dose–response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have 'serious' or 'very serious' risk of bias was rated down by 1 or 2 points respectively.
3. The downgraded or upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as High and the overall quality became Moderate, Low or Very low if 1, 2 or 3 points were deducted respectively.
4. The reasons or criteria used for downgrading were specified in the footnotes.

The details of the criteria used for each of the main quality element are discussed further in the following Sections 3.3.2.6–3.3.2.7.

3.3.2.6 Risk of bias

Bias can be defined as anything that causes a consistent deviation from the truth. Bias can be perceived as a systematic error, for example if a study was to be carried out several times and there was a consistently wrong answer, the results would be inaccurate. The risk of bias for a given study and outcome is associated with the risk of over- or underestimation of the true effect.

A study with a poor methodological design does not automatically imply high risk of bias; the bias is considered individually for each outcome and it is assessed whether this poor design will impact on the estimation of the intervention effect.

The GDG accepted that investigator blinding and/or participant blinding would not be possible with some interventions (that is, patient education and point-of-care versus laboratory testing). Nevertheless, open-label studies would still be downgraded to maintain a consistent approach in quality rating across the guideline (particularly if the outcome was subjective, for example health-related quality of life). The risks of bias and limitations for RCTs and observational/cohort studies are listed in Table 4 and Table 5.

Table 4: Risk of bias in randomised controlled trials

Risk of bias	Explanation
Allocation concealment	Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (this is a major problem in 'pseudo' or 'quasi' randomised trials with, for example, allocation by day of the week, birth date, chart number)
Lack of blinding	Patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated
Incomplete accounting of patients and outcome events	Missing data not accounted for and failure of the trialists to adhere to the intention-to-treat principle when indicated
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results
Other risks of bias	For example: • Stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules • Use of unvalidated patient-reported outcomes • Recruitment bias in cluster-randomised trials

Table 5: Study limitations of cohort /observational studies

Limitation	Explanation

Limitation	Explanation
Failure to develop and apply appropriate eligibility criteria (inclusion of control population)	• under- or over-matching in case-control studies • selection of exposed and unexposed in cohort studies from different populations
Flawed measurement of both exposure and outcome	• differences in measurement of exposure (for example, recall bias in case-control studies) • differential surveillance for outcome in exposed and unexposed in cohort studies
Failure to adequately control confounding	• failure of accurate measurement of all known prognostic factors • failure to match for prognostic factors and/or adjustment in statistical analysis

3.3.2.7 Qualitative studies

For qualitative studies, quality would be assessed using the checklist for qualitative studies (Appendix I in The guidelines manual[29]). The quality rating (Low, High, Unclear) is derived by assessing the risk of bias across 6 domains:

- theoretical approach
- study design
- data collection
- validity
- analysis
- ethics.

3.3.3 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results. When estimates of the treatment effect across studies differ widely (that is, there is heterogeneity or variability in results), this suggests true differences in underlying treatment effect. Heterogeneity in meta-analyses was examined and sensitivity and subgroup analyses performed as pre-specified in the protocols (Appendix C).

When heterogeneity exists (chi-squared $p<0.1$, I-squared inconsistency statistic of >50%, or evidence from examining forest plots), but no plausible explanation can be found (for example, duration of intervention or different follow-up periods), the quality of evidence was downgraded by 1 or 2 levels, depending on the extent of uncertainty to the results contributed by the inconsistency in the results. Where subgroup analysis gave a plausible explanation of heterogeneity, the quality of the evidence was not downgraded.

In addition to the I-squared and chi-squared values, the decision for downgrading was also dependent on factors such as whether the intervention is associated with benefit in all other outcomes or whether the uncertainty about the magnitude of benefit (or harm) of the outcome showing heterogeneity would influence the overall judgment about net benefit or harm (across all outcomes).

3.3.4 Indirectness

Directness refers to the extent to which the populations, intervention, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention.

In this guideline, indirect evidence was an important source of information due to the lack of clinical evidence. Evidence for the target population was often not available and indirect evidence was applied and interpreted based on the clinical expertise and experience of the GDG.

Examples include:

- Indirect population: evidence from patients with malaria or dengue fever was considered for reviews on sepsis. The GDG noted that malaria or dengue fever would not be commonly found in an NHS setting. Moreover, it was noted that in some of these studies a different resuscitation protocol was used to that commonly used in the UK (that is, intubation of patients was not standard). Adults were generally considered to be an indirect population and the evidence downgraded in GRADE, however for review questions where the GDG considered no difference between adults and children it was not downgraded.
- Indirect outcome: serum sodium levels were used as surrogate outcomes (that is, sodium less than 130 mmol – severe hyponatraemia), for incidence of hyponatraemia. The GDG specified thresholds for hyponatraemia prior to presentation of clinical evidence.

Whenever indirect evidence was identified and applied, the evidence was downgraded for indirectness in GRADE and also discussed in the sections linking evidence to recommendations in the guideline. The GDG would consider the magnitude of the indirectness and downgrade the quality of evidence by 1 or 2 levels, depending on the extent of indirectness of the population or intervention.

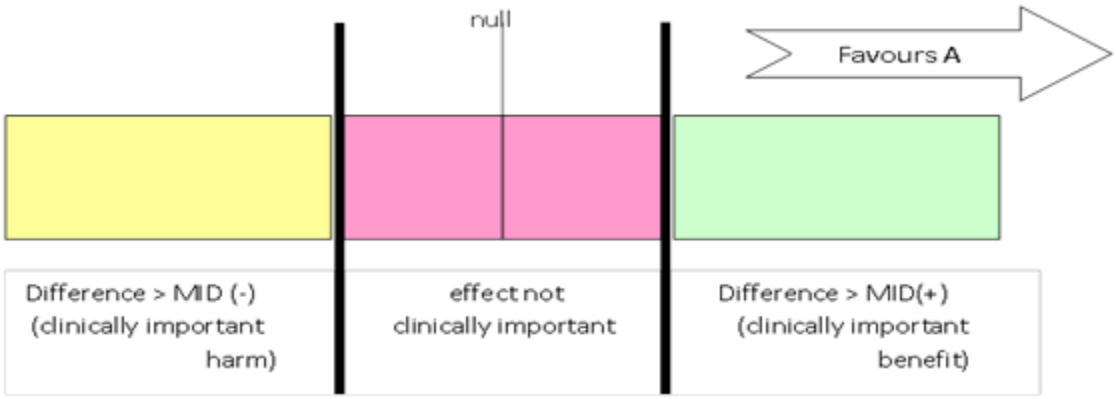
3.3.5 Imprecision

Imprecision in guidelines concerns whether the uncertainty (confidence interval) around the effect estimate means that it is not clear whether there is a clinically important difference between interventions or not. Therefore, imprecision differs from the other aspects of evidence quality in that it is not really concerned with whether the point estimate is accurate or correct (has internal or external validity); instead, it is concerned with the uncertainty about what the point estimate is. This uncertainty is reflected in the width of the confidence interval.

The 95% confidence interval (95% CI) is defined as the range of values that contain the population value with 95% probability. The larger the trial, the smaller the 95% CI and the more certain the effect estimate.

Imprecision in the evidence reviews was assessed by considering whether the width of the 95% CI of the effect estimate is relevant to decision-making, considering each outcome in isolation. Figure 2 considers a positive outcome for the comparison of treatment A versus B. Three decision-making zones can be identified, bounded by the thresholds for clinical importance (minimal important difference – MID) for benefit and for harm. The MID for harm for a positive outcome means the threshold at which drug A is less effective than drug B by an amount that is clinically important to patients (favours B).

Figure 2: Illustration of a precise outcome based on the confidence interval of outcomes in a forest plot



When the confidence interval of the effect estimate is wholly contained in 1 of the 3 zones (for example, clinically important benefit), we are not uncertain about the size and direction of effect (whether there is a clinically important benefit, or the effect is not clinically important, or there is a clinically important harm), so there is no imprecision.

When a wide confidence interval lies partly in each of 2 zones, it is uncertain in which zone the true value of effect estimate lies, and therefore there is uncertainty over which decision to make (based on this outcome alone). The confidence interval is consistent with 2 decisions and so this is considered to be imprecise in the GRADE analysis and the evidence is downgraded by 1 level ('serious imprecision').

If the confidence interval of the effect estimate crosses into 3 zones, this is considered to be very imprecise evidence because the confidence interval is consistent with 3 clinical decisions and there is a considerable lack of confidence in the results. The evidence is therefore downgraded by 2 levels in the GRADE analysis ('very serious imprecision').

Implicitly, assessing whether the confidence interval is in, or partially in, a clinically important zone, requires the GDG to estimate an MID or to say whether they would make different decisions for the 2 confidence limits.

The literature was searched for established MIDs for the selected outcomes in the evidence reviews. In addition, the GDG was asked whether they were aware of any acceptable MIDs in the clinical community. There were no published MIDs for any of the outcomes and default thresholds were used.

The GDG considered it clinically acceptable to use the GRADE default MID to assess imprecision: a 25% relative risk reduction or relative risk increase was used, which corresponds to clinically important thresholds for a risk ratio of 0.75 and 1.25 respectively. This default MID was used for all the outcomes in the interventions evidence reviews. For continuous outcomes 2 approaches were used. When only 1 trial was included as the evidence base for an outcome, the mean difference was converted to the standardized mean difference (SMD) and checked to see if the confidence interval crossed 0.5. However, the mean difference (95% confidence interval) was still presented in the Grade tables. If 2 or more included trials reported a quantitative outcome then the default approach of multiplying 0.5 by standard deviation (taken as the median of the standard deviations across the meta-analysed studies) was employed.

3.3.6 Assessing clinical importance

The GDG assessed the evidence by outcome in order to determine if there was, or potentially was, a clinically important benefit, a clinically important harm or no clinically important difference between interventions. To facilitate this, binary outcomes were converted into absolute risk differences (ARDs)

using GRADEpro software: the median control group risk across studies was used to calculate the ARD and its 95% CI from the pooled risk ratio.

The assessment of benefit, harm, or no benefit or harm was based on the point estimate of absolute effect for intervention studies which was standardised across the reviews. The GDG considered for most of the outcomes in the intervention reviews that if at least 100 participants per 1000 (10%) achieved (if positive) the outcome of interest in the intervention group compared to the comparison group then this intervention would be considered beneficial. The same point estimate but in the opposite direction would apply if the outcome was negative. The GDG assessed the clinical importance of several outcomes (that is, mortality and severe hyponatraemia in routine maintenance) with a lower threshold. The GDG agreed that these outcomes have a significant effect on the patient.

This assessment was carried out by the GDG for each critical outcome, and an evidence summary table was produced to compile the GDG's assessments of clinical importance per outcome, alongside the evidence quality and the uncertainty in the effect estimate (imprecision).

Where median and interquartile ranges were provided the GDG made a decision on whether the medians were clinically different or not based on their clinical knowledge.

3.3.7 Evidence statements

Evidence statements are summary statements that are presented after the GRADE profiles, summarising the key features of the clinical effectiveness evidence presented. The wording of the evidence statements reflects the certainty or uncertainty in the estimate of effect. The evidence statements are presented by outcome and encompass the following key features of the evidence:

- the number of studies and the number of participants for a particular outcome
- a brief description of the participants
- an indication of the direction of effect (if one treatment is beneficial or harmful compared to the other, or whether there is no difference between the 2 tested treatments)
- a description of the overall quality of evidence (GRADE overall quality).

3.3.8 Evidence of cost effectiveness

The GDG is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits (that is, their 'cost effectiveness') rather than the total implementation cost.[29] Thus, if the evidence suggests that a strategy provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population.

Evidence on cost effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economist:

- Undertook a systematic review of the published economic literature.
- Undertook new economic analysis in priority areas.

3.3.9 Literature review

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against prespecified inclusion and exclusion criteria to identify relevant studies (see below for details).

3.3.10 Inclusion and exclusion criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost–benefit and cost–consequences analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially includable as economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost effectiveness without disaggregated costs and effects, were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant section.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist (Appendix F of The guidelines manual[29] and the health economics review protocol in Appendix C).

When no relevant economic studies were found from the economic literature review, relevant UK NHS unit costs related to the compared interventions were presented to the GDG to inform the possible economic implications of the recommendations.

3.3.11 Undertaking new health economic analysis

As well as reviewing the published economic literature for each review question, as described above, new economic analysis was undertaken by the health economist in selected areas. Priority areas for new health economic analysis were agreed by the GDG after formation of the review questions and consideration of the available health economic evidence.

The GDG identified clinical assessment and reassessment as the highest priority area for original economic modelling. The monitoring of fluid balance in children could include the measurement and recording of weight as well as the recording of fluid balance (including input and output) on a fluid balance chart. Well performed and recorded monitoring is important as this may prevent the occurrence of fluid-related complications. Monitoring should be performed at regular intervals and at an optimum frequency since this information may tailor intervention. However, excessive monitoring may increase costs unnecessarily and may provide little additional health benefit. A cost and threshold analysis was thus undertaken to inform recommendations regarding the optimal monitoring strategy.

The following general principles were adhered to in developing the cost-effectiveness analysis:

- Methods were consistent with the NICE reference case.[30]
- The GDG was involved in the design of the model, selection of inputs and interpretation of the results.
- Model inputs were based on the systematic review of the clinical literature supplemented with other published data sources where possible.
- When published data were not available, GDG expert opinion was used to populate the model.
- Model inputs and assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- The model was peer-reviewed by another health economist at the NCGC.

Full methods for the cost and threshold analysis for monitoring strategies are described in Appendix M.

3.3.12 Cost-effectiveness criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money.[28] In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- the intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- the intervention cost less than £20,000 per QALY gained compared with the next best strategy.

If the GDG recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'Recommendations and link to evidence' section of the relevant chapter, with reference to issues regarding the plausibility of the estimate or to the factors set out in 'Social value judgements: principles for the development of NICE guidance'.[28]

3.3.13 In the absence of economic evidence

When no relevant published studies were found, and a new analysis was not prioritised, the GDG made a qualitative judgement about cost effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs, alongside the results of the clinical review of effectiveness evidence.

The UK NHS costs reported in the guideline are those that were presented to the GDG and were correct at the time recommendations were drafted. They may have changed subsequently before the time of publication. However, we have no reason to believe they have changed substantially.

3.4 Developing recommendations

Over the course of the guideline development process, the GDG was presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in Appendices G and H.
- Summaries of clinical and economic evidence and quality (as presented in Chapters 5–10).
- Forest plots (Appendix J).
- A description of the methods and results of the cost (and threshold) analysis undertaken for the guideline (Appendix M).

Recommendations were drafted on the basis of the GDG's interpretation of the available evidence, taking into account the balance of benefits, harms and costs between different courses of action. This was either done formally in an economic model, or informally. Firstly, the net benefit over harm (clinical effectiveness) was considered, focusing on the critical outcomes. When this was done informally, the GDG took into account the clinical benefits and harms when one intervention was compared with another. The assessment of net benefit was moderated by the importance placed on the outcomes (the GDG's values and preferences), and the confidence the GDG had in the evidence (evidence quality). Secondly, whether the net benefit justified any differences in costs was assessed.

When clinical and economic evidence was of poor quality, conflicting or absent, the GDG drafted recommendations based on their expert opinion. The considerations for making consensus-based

recommendations include the balance between potential harms and benefits, the economic costs compared to the economic benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were agreed through discussions in the GDG. The GDG also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation (see Section 3.4.1 below).

The GDG considered the 'strength' of recommendations. This takes into account the quality of the evidence but is conceptually different. Some recommendations are 'strong' in that the GDG believes that the vast majority of healthcare and other professionals and patients would choose a particular intervention if they considered the evidence in the same way that the GDG has. This is generally the case if the benefits clearly outweigh the harms for most people and the intervention is likely to be cost effective. However, there is often a closer balance between benefits and harms, and some patients would not choose an intervention whereas others would. This may happen, for example, if some patients are particularly averse to some side effect and others are not. In these circumstances the recommendation is generally weaker, although it may be possible to make stronger recommendations about specific groups of patients.

The GDG focused on the following factors in agreeing the wording of the recommendations:

- The actions health professionals need to take.
- The information readers need to know.
- The strength of the recommendation (for example the word ‘offer’ was used for strong recommendations and ‘consider’ for weak recommendations).
- The involvement of patients (and their carers if needed) in decisions on treatment and care.
- Consistency with NICE’s standard advice on recommendations about drugs, waiting times and ineffective interventions (see Section 9.3 in The guidelines manual[29]).

The main considerations specific to each recommendation are outlined in the ‘Recommendations and link to evidence’ sections within each chapter.

3.4.1 Research recommendations

When areas were identified for which good evidence was lacking, the GDG considered making recommendations for future research. Decisions about inclusion were based on factors such as:

- the importance to patients or the population
- national priorities
- potential impact on the NHS and future NICE guidance
- ethical and technical feasibility.

For details of all research recommendations, see Appendix N.

3.4.2 Validation process

This guidance is subject to a 6-week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE website.

3.4.3 Updating the guideline

Following publication, and in accordance with the NICE guidelines manual, NICE will undertake a review of whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

3.4.4 Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

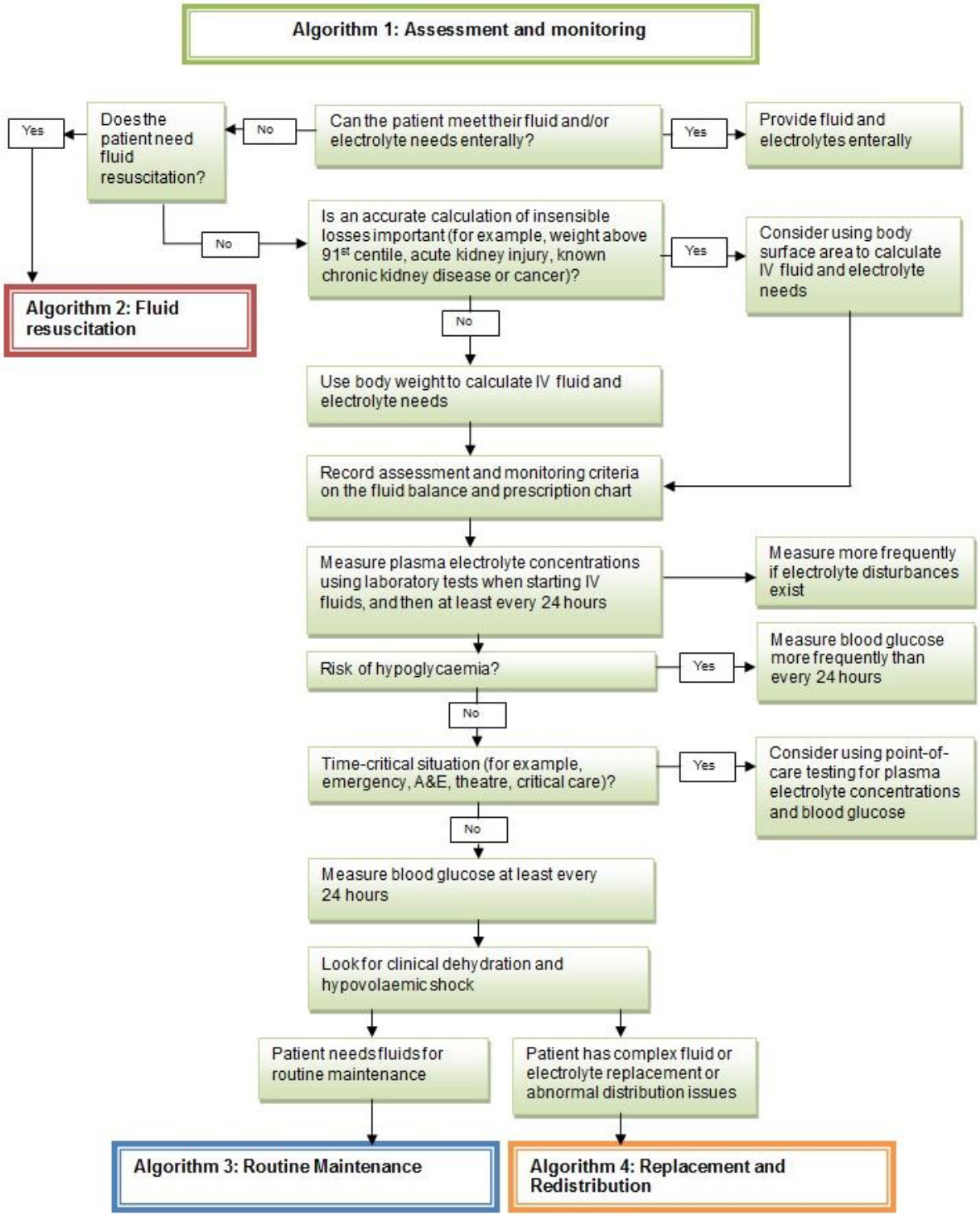
The National Clinical Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of this guideline and the literature used in support of this guideline.

3.4.5 Funding

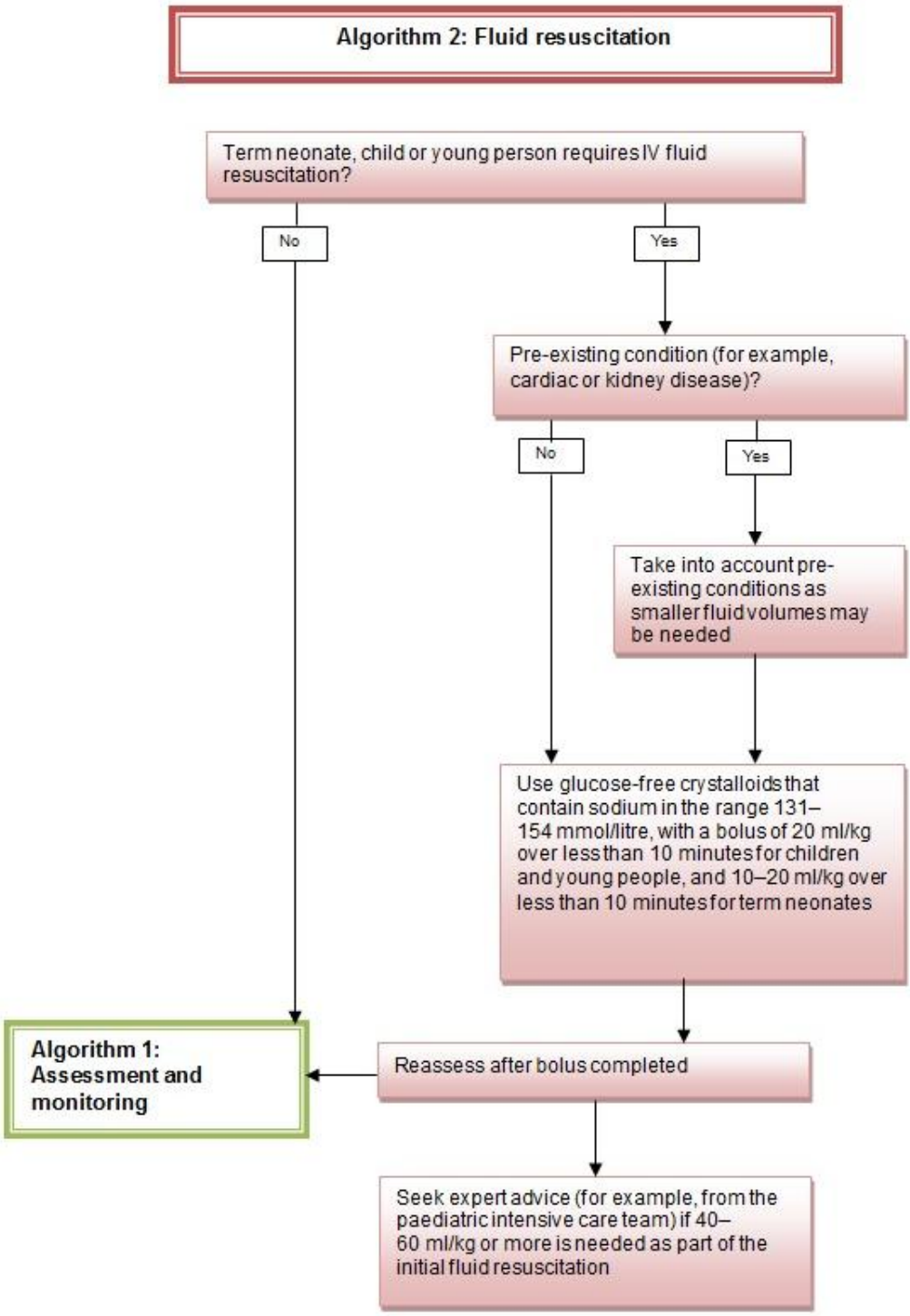
The National Clinical Guideline Centre was commissioned by the National Institute for Health and Care Excellence to undertake the work on this guideline.

4 Guideline summary

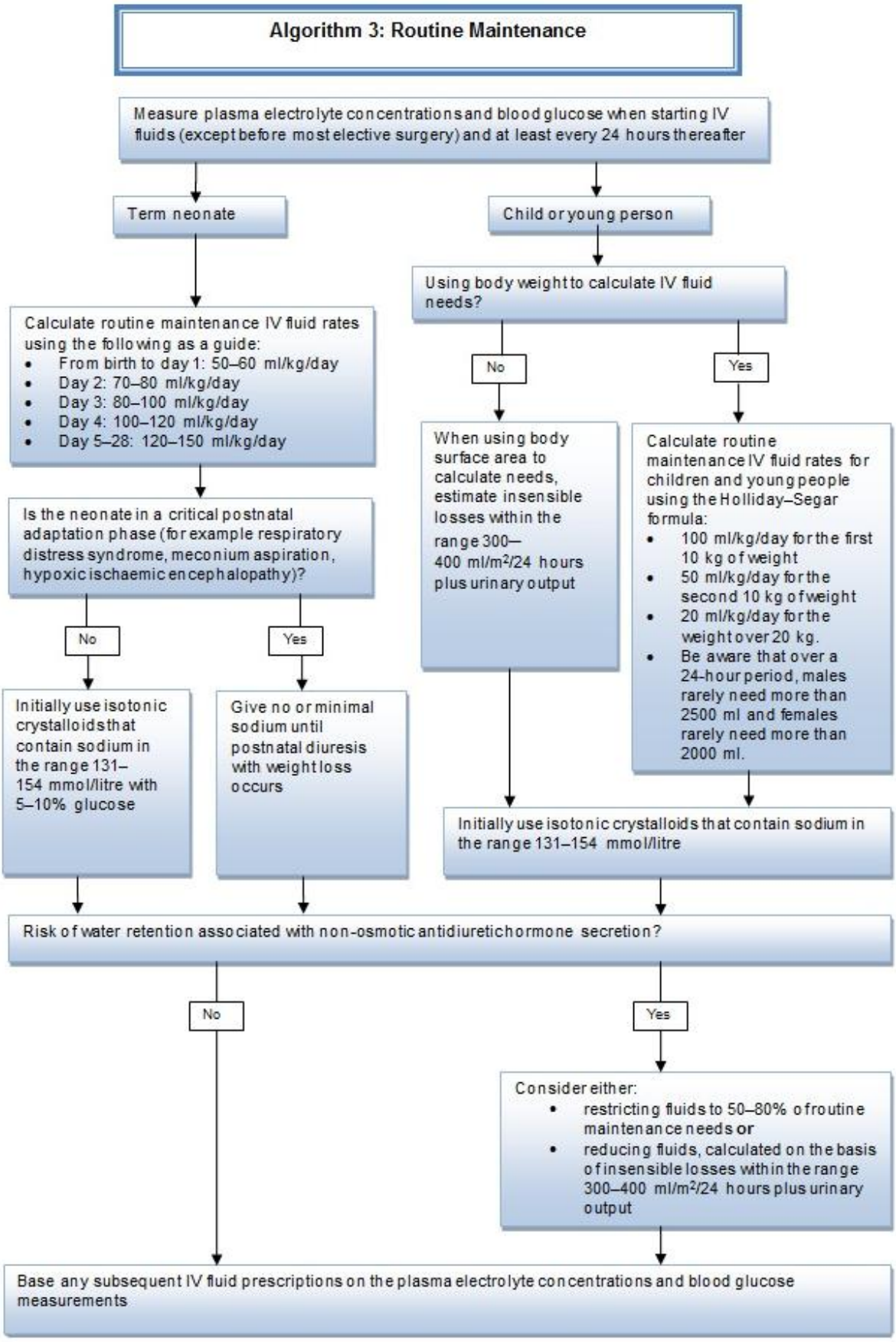
4.1 Algorithms for IV fluid therapy in children and young people in hospital



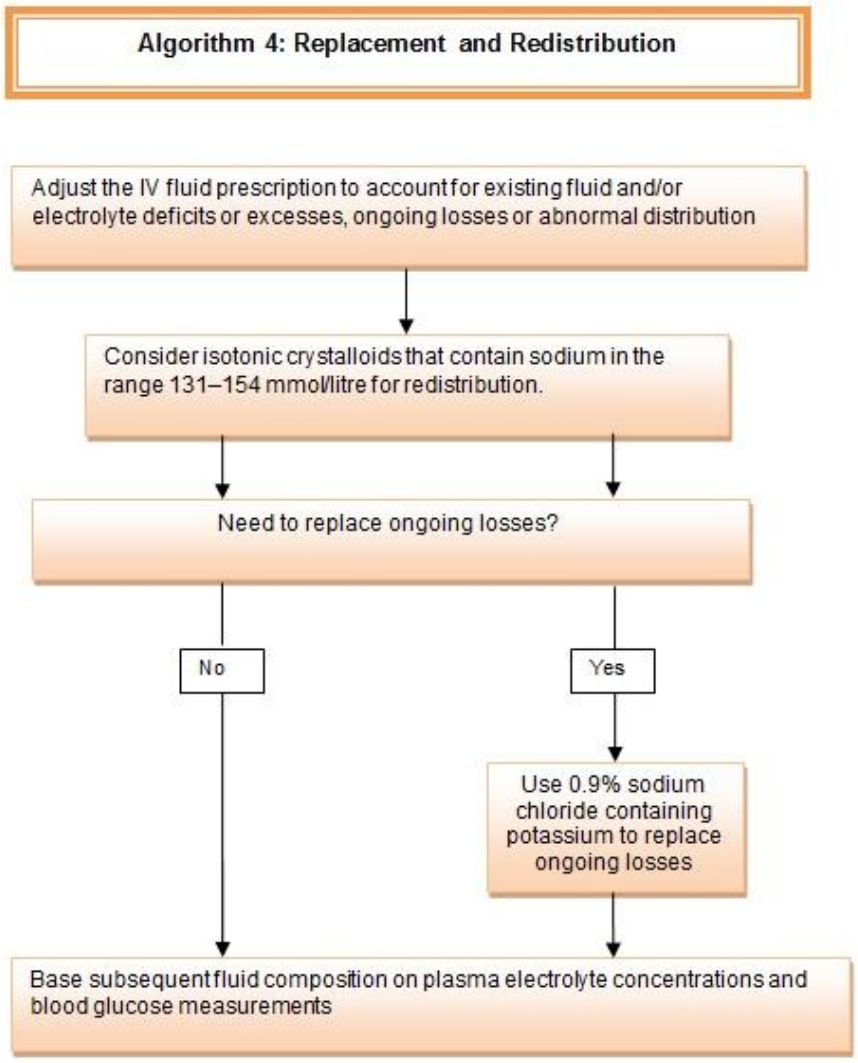
Algorithms for IV fluid therapy in children and young people in hospital



Algorithms for IV fluid therapy in children and young people in hospital



Algorithms for IV fluid therapy in children and young people in hospital



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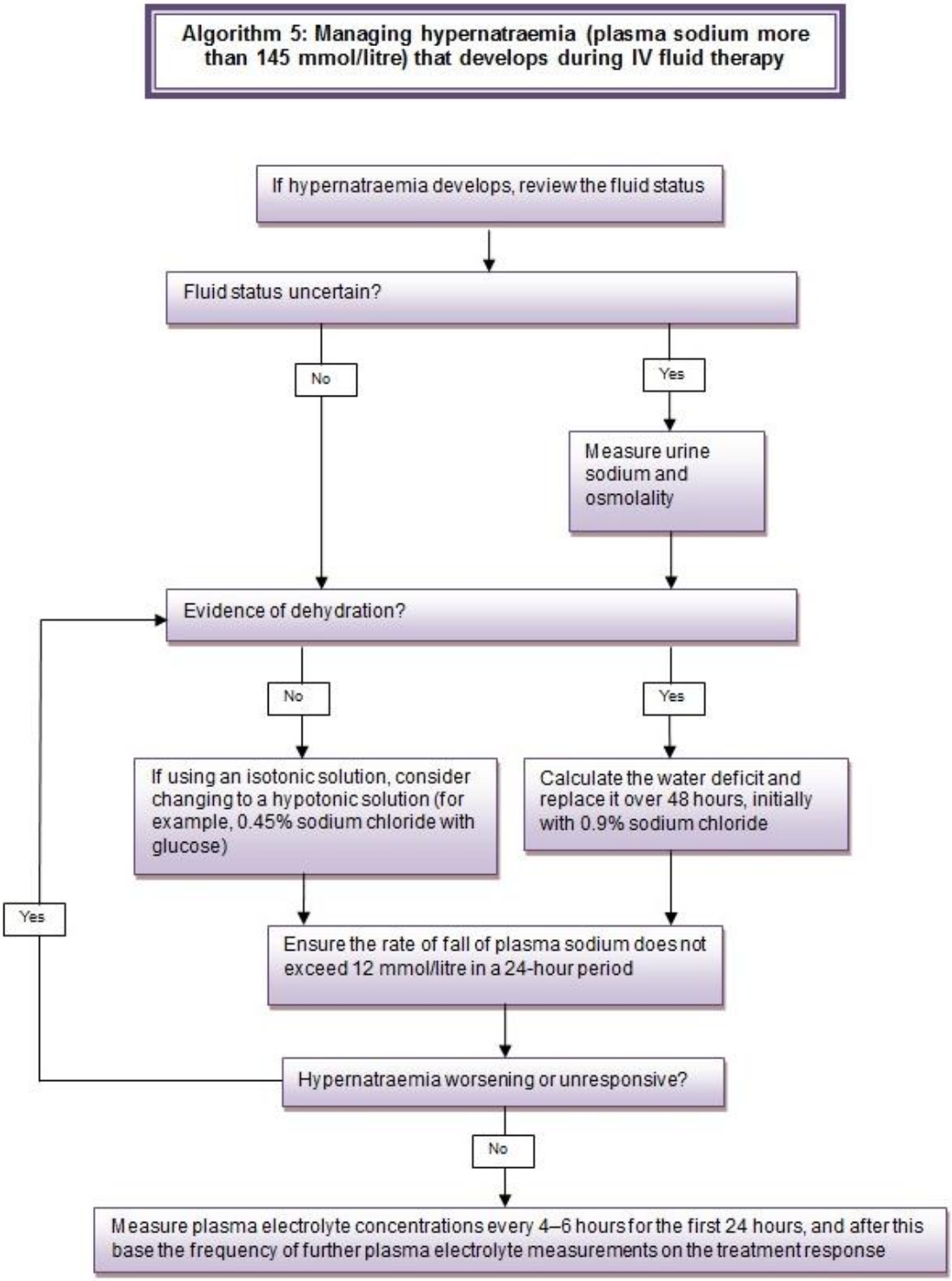
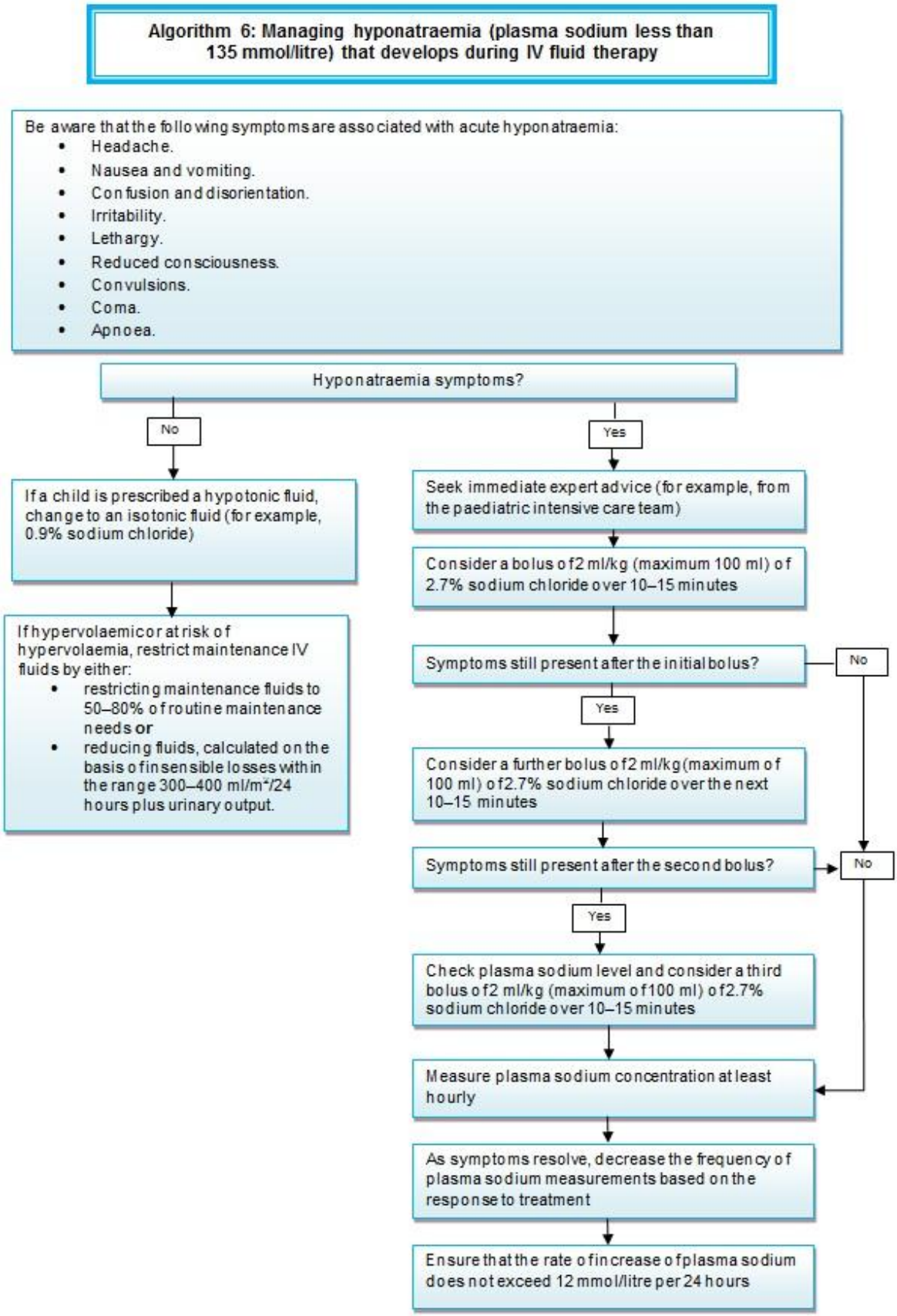
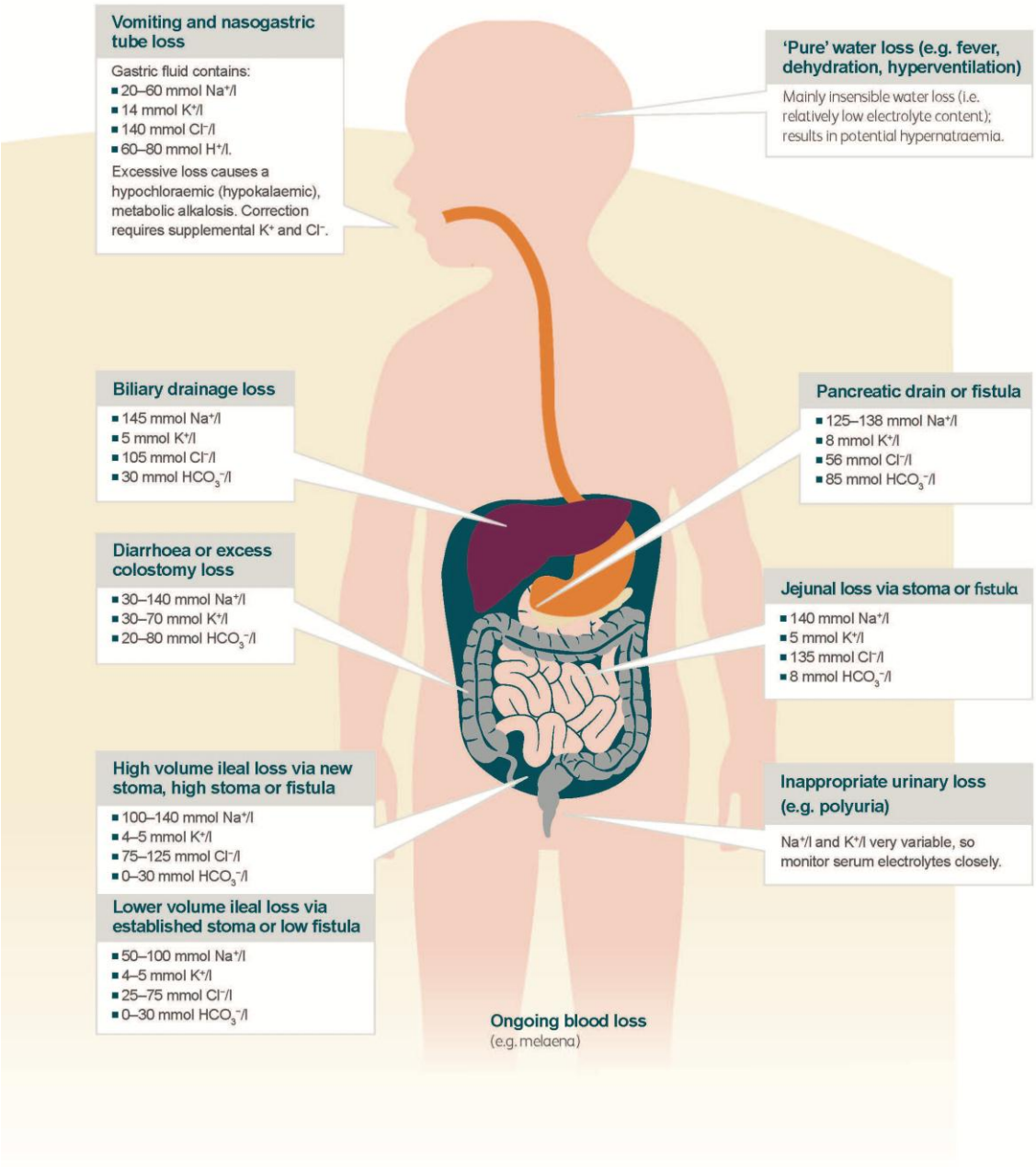


Algorithms for IV fluid therapy in children and young people in hospital



4.2 Diagram of ongoing losses

Figure 3: Diagram of ongoing losses for children and young people



4.3 Table of intravenous fluid types

Table 6: Intravenous fluid types for children and young people

Fluid with recommendation reference	Fluid type[a]	Osmolality (compared with plasma)	Tonicity (with reference to cell membrane)	Sodium content (mmol/litre)	Potassium content (mmol/litre)
Isotonic crystalloids that contain sodium in the range 131–154 mmol/litre [10, 11, 17, 26, 29, 32]	0.9% sodium chloride	Isosmolar	Isotonic	154	0
	Hartmann's solution	Isosmolar	Isotonic	131	5
Isotonic crystalloids with glucose that contain sodium in the range 131–154 mmol/litre [21]	0.9% sodium chloride with 5% glucose	Hyperosmolar	Isotonic	150	0
Hypotonic fluids [29, 32]	0.45% sodium chloride with 5% glucose	Hyperosmolar	Hypotonic	75	0
	0.45% sodium chloride with 2.5% glucose	Isosmolar	Hypotonic	75	0
	0.45% sodium chloride	Hyposmolar	Hypotonic	75	0
	5% glucose	Isosmolar	Hypotonic	0	0
	10% glucose	Hyperosmolar	Hypotonic	0	0

(a) Fluids given are examples of appropriate fluids; for further details, see the British national formulary for children.

4.4 Key priorities for implementation

From the full set of recommendations, the GDG selected 11 key priorities for implementation. The criteria used for selecting these recommendations are listed in detail in The guidelines manual.[29] The reason that each of these recommendations was chosen are shown in the table linking the evidence to the recommendation in the relevant chapter.

Assessment and monitoring

- In term neonates, children and young people who are receiving IV fluids, assess and document the following:
  - Actual or estimated daily body weight. Record the weight from the current day, the previous day, and the difference between the two. If an estimate was used, the actual weight should be measured as soon as clinically possible.
  - Fluid input, output and balance over the previous 24 hours.
  - Any special instructions for prescribing, including relevant history.
  - An assessment of the fluid status.

- The results of laboratory and point-of-care assessments, including:
  - full blood count
  - urea
  - creatinine
  - plasma electrolyte concentrations (including chloride, sodium and potassium; see recommendation 6)
  - blood glucose (see recommendation 7)
  - urinary electrolyte concentrations.
- Details of any ongoing losses (see recommendation 26 and the diagram of ongoing losses).
- Calculations of fluid needs for routine maintenance, replacement, redistribution and resuscitation.
- The fluid and electrolyte prescription (in ml per hour), with clear signatures, dates and times.
- Types and volumes of fluid input and output (urine, gastric and other), recorded hourly and with running totals.
- 12-hourly fluid balance subtotals.
- 24-hourly fluid balance totals.
- 12-hourly reassessments of:
  - the fluid prescription
  - current hydration status
  - whether oral fluids can be started
  - urine and other outputs.

Fluid resuscitation

- If children and young people need IV fluid resuscitation, use glucose-free crystalloids[a] that contain sodium in the range 131–154 mmol/litre, with a bolus of 20 ml/kg over less than 10 minutes. Take into account pre-existing conditions (for example, cardiac disease or kidney disease), as smaller fluid volumes may be needed.
- If term neonates need IV fluid resuscitation, use glucose-free crystalloids[b] that contain sodium in the range 131–154 mmol/litre, with a bolus of 10–20 ml/kg over less than 10 minutes.

Routine maintenance

- If children and young people need IV fluids for routine maintenance, initially use isotonic crystalloids[c] that contain sodium in the range 131–154 mmol/litre.
- Measure plasma electrolyte concentrations and blood glucose when starting IV fluids for routine maintenance (except before most elective surgery), and at least every 24 hours thereafter.
- If there is a risk of water retention associated with non-osmotic antidiuretic hormone (ADH) secretion, consider either:

[a] At the time of publication (December 2015), some glucose free-crystalloids did not have a UK marketing authorisation for use in children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[b] At the time of publication (December 2015), some glucose free-crystalloids did not have a UK marketing authorisation for use in children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[c] At the time of publication (December 2015), some isotonic crystalloids with 5–10% glucose did not have a UK marketing authorisation for use in children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

- restricting fluids to 50–80% of routine maintenance needs **or**
- reducing fluids, calculated on the basis of insensible losses within the range 300–400 ml/m^2/24 hours plus urinary output.

Replacement and redistribution

- Consider isotonic crystalloids[d] that contain sodium in the range 131–154 mmol/litre for redistribution.

Managing hyponatraemia that develops during intravenous fluid therapy

- If asymptomatic hyponatraemia develops in term neonates, children and young people, review the fluid status and take action as follows:
  - If a child is prescribed a hypotonic fluid, change to an isotonic fluid (for example, 0.9% sodium chloride).
  - Restrict maintenance IV fluids in children and young people who are hypervolaemic or at risk of hypervolaemia (for example, if there is a risk of increased ADH secretion) by either:
    - restricting maintenance fluids to 50–80% of routine maintenance needs **or**
    - reducing fluids, calculated on the basis of insensible losses within the range 300–400 ml/m^2/24 hours plus urinary output.
- Be aware that the following symptoms are associated with acute hyponatraemia during IV fluid therapy:
  - Headache.
  - Nausea and vomiting.
  - Confusion and disorientation.
  - Irritability.
  - Lethargy.
  - Reduced consciousness.
  - Convulsions.
  - Coma.
  - Apnoea.

[d] At the time of publication (December 2015), some isotonic crystalloids with 5–10% glucose did not have a UK marketing authorisation for use in children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

4.5 Full list of recommendations

Principles and protocols for intravenous fluid therapy

1. For guidance on the principles and protocols for intravenous (IV) fluid therapy, see the principles and protocols for intravenous fluid therapy section in 'Intravenous fluid therapy in adults' (NICE guideline CG174; recommendations 1.1.1, 1.1.2, 1.1.3, 1.1.5, 1.1.6, 1.1.7 and 1.1.8 apply to all ages).

2. Offer IV fluid therapy as part of a protocol (see algorithms for IV fluid therapy in children and young people in hospital):

    - Assess fluid and electrolyte needs following algorithm 1: Assessment and monitoring.
    - If term neonates, children and young people need IV fluids for fluid resuscitation, follow algorithm 2: Fluid resuscitation.
    - If term neonates, children and young people need IV fluids for routine maintenance, follow algorithm 3: Routine maintenance.
    - If term neonates, children and young people need IV fluids to address existing deficits or excesses, ongoing abnormal losses or abnormal fluid distribution, follow algorithm 4: Replacement and redistribution.
    - If hypernatraemia develops, follow algorithm 5: Managing hypernatraemia that develops during IV fluid therapy.
    - If hyponatraemia develops, follow algorithm 6: Managing hyponatraemia that develops during IV fluid therapy.

Assessment and monitoring

3. Use body weight to calculate IV fluid and electrolyte needs for term neonates, children and young people.

4. Consider using body surface area to calculate IV fluid and electrolyte needs if accurate calculation of insensible losses is important (for example, if the weight is above the 91st centile, or with acute kidney injury, known chronic kidney disease or cancer).

5. In term neonates, children and young people who are receiving IV fluids, assess and document the following:

    - Actual or estimated daily body weight. Record the weight from the current day, the previous day, and the difference between the two. If an estimate was used, the actual weight should be measured as soon as clinically possible.
    - Fluid input, output and balance over the previous 24 hours.
    - Any special instructions for prescribing, including relevant history.
    - An assessment of the fluid status.
    - The results of laboratory and point-of-care assessments, including:
        - full blood count
        - urea
        - creatinine
        - plasma electrolyte concentrations (including chloride, sodium and potassium; see recommendation 6)

    - blood glucose (see recommendation 7)
    - urinary electrolyte concentrations.
- Details of any ongoing losses (see recommendation 26 and the diagram of ongoing losses).
- Calculations of fluid needs for routine maintenance, replacement, redistribution and resuscitation.
- The fluid and electrolyte prescription (in ml per hour), with clear signatures, dates and times.
- Types and volumes of fluid input and output (urine, gastric and other), recorded hourly and with running totals.
- 12-hourly fluid balance subtotals.
- 24-hourly fluid balance totals.
- 12-hourly reassessments of:
    - the fluid prescription
    - current hydration status
    - whether oral fluids can be started
    - urine and other outputs.

6. Measure plasma electrolyte concentrations using laboratory tests when starting IV fluids, and then at least every 24 hours or more frequently if there are electrolyte disturbances.

7. Measure blood glucose when starting IV fluids, and then at least every 24 hours or more frequently if there is a risk of hypoglycaemia.

8. Consider point-of-care testing for measuring plasma electrolyte concentrations and blood glucose in time-critical situations when IV fluids are needed (for example, during emergency situations and in A&E, theatre and critical care).

9. Diagnose clinical dehydration and hypovolaemic shock using the clinical features listed in Table 16, but be aware that it can be difficult to identify the clinical features in term neonates.

Fluid resuscitation

10. If children and young people need IV fluid resuscitation, use glucose-free crystalloids[e] that contain sodium in the range 131–154 mmol/litre, with a bolus of 20 ml/kg over less than 10 minutes. Take into account pre-existing conditions (for example, cardiac disease or kidney disease), as smaller fluid volumes may be needed.

11. If term neonates need IV fluid resuscitation, use glucose-free crystalloids[f] that contain sodium in the range 131–154 mmol/litre, with a bolus of 10–20 ml/kg over less than 10 minutes.

12. Do not use tetrastarch for fluid resuscitation.

[e] At the time of publication (December 2015), some glucose free-crystalloids did not have a UK marketing authorisation for use in children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[f] At the time of publication (December 2015), some glucose free-crystalloids did not have a UK marketing authorisation for use in children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

13. For guidance on using IV fluids for fluid resuscitation in children and young people with diabetic ketoacidosis, see the diabetic ketoacidosis section in 'Diabetes (type 1 and type 2) in children and young people' (NICE guideline NG18).

14. Reassess term neonates, children and young people after completion of the IV fluid bolus, and decide whether they need more fluids.

15. Seek expert advice (for example, from the paediatric intensive care team) if 40–60 ml/kg of IV fluid or more is needed as part of the initial fluid resuscitation.

Routine maintenance

16. Calculate routine maintenance IV fluid rates for children and young people using the Holliday–Segar formula (100 ml/kg/day for the first 10 kg of weight, 50 ml/kg/day for the next 10 kg and 20 ml/kg/day for the weight over 20 kg). Be aware that over a 24-hour period, males rarely need more than 2500 ml and females rarely need more than 2000 ml of fluids.

17. Calculate routine maintenance IV fluid rates for term neonates according to their age, using the following as a guide:

    - From birth to day 1: 50–60 ml/kg/day.
    - Day 2: 70–80 ml/kg/day.
    - Day 3: 80–100 ml/kg/day.
    - Day 4: 100–120 ml/kg/day.
    - Days 5–28: 120–150 ml/kg/day.

18. If children and young people need IV fluids for routine maintenance, initially use isotonic crystalloids[g] that contain sodium in the range 131–154 mmol/litre.

19. Measure plasma electrolyte concentrations and blood glucose when starting IV fluids for routine maintenance (except before most elective surgery), and at least every 24 hours thereafter.

20. Be aware that plasma electrolyte concentrations and blood glucose are not routinely measured before elective surgery unless there is a need to do so, based on the child's medical condition or the type of surgery.

21. Base any subsequent IV fluid prescriptions on the plasma electrolyte concentrations and blood glucose measurements.

22. If term neonates need IV fluids for routine maintenance, initially use isotonic crystalloids[h] that contain sodium in the range 131–154 mmol/litre with 5–10% glucose.

23. For term neonates in critical postnatal adaptation phase (for example, term neonates with respiratory distress syndrome, meconium aspiration, hypoxic ischaemic encephalopathy), give no or minimal sodium until postnatal diuresis with weight loss occurs.

24. If there is a risk of water retention associated with non-osmotic antidiuretic hormone (ADH) secretion, consider either:

    - restricting fluids to 50–80% of routine maintenance needs **or**

[g] At the time of publication (December 2015), some isotonic crystalloids with 5–10% glucose did not have a UK marketing authorisation for use in children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[h] At the time of publication (December 2015), some isotonic crystalloids with 5–10% glucose did not have a UK marketing authorisation for use in children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

- reducing fluids, calculated on the basis of insensible losses within the range 300–400 ml/m^2 /24 hours plus urinary output.

25. When using body surface area to calculate IV fluid needs for routine maintenance (see recommendation 4), estimate insensible losses within the range 300–400 ml/m^2/24 hours plus urinary output.

Replacement and redistribution

26. If term neonates, children and young people need IV fluids for replacement or redistribution, adjust the IV fluid prescription (in addition to maintenance needs) to account for existing fluid and/or electrolyte deficits or excesses, ongoing losses (see the diagram of ongoing losses) or abnormal distribution, for example, tissue oedema seen in sepsis.

27. Consider isotonic crystalloids[i] that contain sodium in the range 131–154 mmol/litre for redistribution.

28. Use 0.9% sodium chloride containing potassium to replace ongoing losses (see the diagram of ongoing losses).

29. Base any subsequent fluid prescriptions on the plasma electrolyte concentrations and blood glucose measurements.

Managing hypernatraemia that develops during intravenous fluid therapy

30. If hypernatraemia develops in term neonates, children and young people, review the fluid status and take action as follows:

    - If there is no evidence of dehydration and an isotonic fluid is being used, consider changing to a hypotonic fluid (for example, 0.45% sodium chloride with glucose)[j].
    - If dehydration is diagnosed, calculate the water deficit and replace it over 48 hours, initially with 0.9% sodium chloride.
    - If the fluid status is uncertain, measure urine sodium and osmolality.
    - If hypernatraemia worsens or is unchanged after replacing the deficit, review the fluid type and consider changing to a hypotonic solution (for example, 0.45% sodium chloride with glucose).

31. When correcting hypernatraemia, ensure that the rate of fall of plasma sodium does not exceed 12 mmol/litre in a 24-hour period.

32. Measure plasma electrolyte concentrations every 4–6 hours for the first 24 hours, and after this base the frequency of further plasma electrolyte measurements on the treatment response.

Managing hyponatraemia that develops during intravenous fluid therapy

33. If asymptomatic hyponatraemia develops in term neonates, children and young people, review the fluid status and take action as follows:

[i] At the time of publication (December 2015), some isotonic crystalloids with 5–10% glucose did not have a UK marketing authorisation for use in children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[j] At the time of publication (December 2015), some hypotonic solutions did not have a UK marketing authorisation for use in children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

- If a child is prescribed a hypotonic fluid, change to an isotonic fluid (for example, 0.9% sodium chloride).
- Restrict maintenance IV fluids in children and young people who are hypervolaemic or at risk of hypervolaemia (for example, if there is a risk of increased ADH secretion) by either:
    - restricting maintenance fluids to 50–80% of routine maintenance needs **or**
    - reducing fluids, calculated on the basis of insensible losses within the range 300–400 ml/m^2/24 hours plus urinary output.

34. Be aware that the following symptoms are associated with acute hyponatraemia during IV fluid therapy:
    - Headache.
    - Nausea and vomiting.
    - Confusion and disorientation.
    - Irritability.
    - Lethargy.
    - Reduced consciousness.
    - Convulsions.
    - Coma.
    - Apnoea.
35. If acute symptomatic hyponatraemia develops in term neonates, children and young people, review the fluid status, seek immediate expert advice (for example, from the paediatric intensive care team) and consider taking action as follows:
    - Use a bolus of 2 ml/kg (maximum 100 ml) of 2.7% sodium chloride over 10–15 minutes.
    - Use a further bolus of 2 ml/kg (maximum 100 ml) of 2.7% sodium chloride over the next 10–15 minutes if symptoms are still present after the initial bolus.
    - If symptoms are still present after the second bolus, check the plasma sodium level and consider a third bolus of 2 ml/kg (maximum 100 ml) of 2.7% sodium chloride over 10–15 minutes.
    - Measure the plasma sodium concentration at least hourly.
    - As symptoms resolve, decrease the frequency of plasma sodium measurements based on the response to treatment.
36. Do not manage acute hyponatraemic encephalopathy using fluid restriction alone.
37. After hyponatraemia symptoms have resolved, ensure that the rate of increase of plasma sodium does not exceed 12 mmol/litre in a 24-hour period.

Training and education

38. For guidance on training and education for healthcare professionals involved in prescribing and delivering IV fluid therapy, see the training and education section in ‘Intravenous fluid therapy in adults’ (NICE guideline CG174).

4.6 Key research recommendations

1. **What is the incidence of complications during, and as a consequence of, IV fluid therapy in children and young people?**

2. **What is the most appropriate glucose concentration in IV fluids for children and young people of different ages?**

3. **For children and young people receiving IV fluids, does the use of a standardised national fluid balance chart reduce the rate of complications arising as a result of prescription and/or administration errors?**

4. **Does ensuring that all hospital healthcare professionals involved in prescribing and delivering IV fluids for children and young people are appropriately trained in the principles of fluid prescribing and IV fluid therapy-related complications lead to a reduction in IV fluid-related complications and associated healthcare costs?**

5 Assessment and monitoring

5.1 Methods of assessing IV fluid requirements

5.1.1.1 Body weight versus body surface area

5.1.1.2 Introduction

When administering IV fluids, the correct amount needs to be prescribed to meet the physiological needs of the child. Too little fluid risks hypovolaemia leading to decreased organ perfusion, and too much may lead to fluid overload, oedema and cardiac failure. As the size and weight of children varies, this needs to be taken into account in any system used in the calculation of the amount of fluids to be prescribed. In addition, some children may have an illness or condition which leads to excessive fluid loss or the inappropriate retention of fluids.

Basal metabolism leads to insensible water loss, including that lost through sweating, from the respiratory tract, and faeces (although in optimum health, water loss in faeces is minimal). The amount of water lost in urine is a function of the amount of solutes that need excreting, and although normal kidneys have great powers to concentrate the urine there will be a basic minimum amount of water needed for excretion. Therefore, the minimum water intake needs to replace water lost in insensible losses and in the urine.

Studies in the first part of the 20th century found that insensible water losses are proportional to the calories spent in the body's metabolism, which in turn have a close relationship to body surface area. It was found that insensible water losses had no direct relationship with body weight, which in clinical practice is more easily measured than surface area. For its accurate calculation, surface area needs a weight and height measurement as well as healthcare professional's access to surface area nomograms. In the 1950s, Holliday and Segar[19]derived formulae to enable fluid prescriptions in hospitalised children to be calculated on the basis of weight.

However, the calculations used may need to be modified in certain clinical circumstances such as extreme obesity, severe infections, or in diseases which interfere with the kidneys' capacity to handle water excretion or affect the mechanism of central control of diuresis through the secretion of antidiuretic hormone (ADH).

5.1.1.3 Review question 1: How effective is assessing body weight compared with body surface area for predicting IV fluid requirements in children?

For full details see the review protocols in Appendix C.

Table 7: PICO characteristics of review question

Population	Neonates born at term, infants, children and young people up to their 16th birthday receiving IV fluids in hospital
Intervention(s)	Measuring body weight
Comparison(s)	Measuring body surface area
Outcomes	**Critical** • Mortality • Adverse effects (including hypovolaemia, dehydration, hypervolaemia, neurological complications) • Fluid balance

	Important • Quality of life
Study design	Order of preference for study designs: • Systematic reviews of RCTs which meet our PICOs • Randomised control trials Where no RCTs are available, we will consider: • Abstracts on RCTs Where no RCTs or abstracts of RCTs are available, we will consider: • Non-randomised trials: prospective or retrospective cohort studies of 50 children or more. • Non-blinded, single and double-blinded trials will be included

5.1.1.4 Clinical evidence

We searched for systematic reviews, RCTs and cohort studies in children.

The GDG did not consider that evidence in an adult population was relevant as fluid requirements in children are higher than those for adults, and algorithms for body surface area and weight could not be extrapolated.

No relevant clinical evidence comparing measurement of body weight with body surface area was identified.

5.1.1.5 Economic evidence

5.1.1.5.1 Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

5.1.1.6 Evidence statements

5.1.1.6.1 Clinical

- No relevant clinical evidence was identified.

5.1.1.6.2 Economic

- No relevant economic evaluations were identified.

5.1.1.7 Recommendations and link to evidence

Recommendations	**1. For guidance on the principles and protocols for intravenous (IV) fluid therapy, see the principles and protocols for intravenous fluid therapy section in 'Intravenous fluid therapy in adults' (NICE guideline CG174; recommendations 1.1.1, 1.1.2, 1.1.3, 1.1.5, 1.1.6, 1.1.7 and 1.1.8 apply to all ages).** **2. Offer IV fluid therapy as part of a protocol (see algorithms for IV fluid therapy in children and young people in hospital):** • **Assess fluid and electrolyte needs following algorithm 1: Assessment and monitoring.** • **If term neonates, children and young people need IV fluids for fluid resuscitation, follow algorithm 2: Fluid resuscitation.** • **If term neonates, children and young people need IV fluids for routine maintenance, follow algorithm 3: Routine maintenance.** • **If term neonates, children and young people need IV fluids to address existing deficits or excesses, ongoing abnormal losses or abnormal fluid distribution, follow algorithm 4: Replacement and redistribution.** • **If hypernatraemia develops, follow algorithm 5: Managing hypernatraemia that develops during IV fluid therapy.** • **If hyponatraemia develops, follow algorithm 6: Managing hyponatraemia that develops during IV fluid therapy.** **3. Use body weight to calculate IV fluid and electrolyte needs for term neonates, children and young people.** **4. Consider using body surface area to calculate IV fluid and electrolyte needs if accurate calculation of insensible losses is important (for example, if the weight is above the 91st centile, or with acute kidney injury, known chronic kidney disease or cancer).**
Relative values of different outcomes	Mortality at 28 days was considered a critical outcome that would demonstrate a potential consequence of poor fluid management. Incidence of serious adverse events (for example neurological compromise, dehydration, hypervolaemia and hypovolaemia) and maintenance or restoration of normal fluid balance were also considered to be critical outcomes. These outcomes were selected as they best reflected successful administration of IV fluids in children. Quality of life was considered an important outcome.

Trade-off between clinical benefits and harms	As no clinical evidence was identified, a recommendation was made using informal consensus. The GDG chose to recommend the use of weight to calculate fluid requirements in the majority of term neonates, children and young people, reflecting different sizes of children, but identified that the use of body surface area may be more appropriate for certain groups of individuals, most notably in disease states where there is loss of normal central or renal physiological mechanisms that control urine output. The GDG acknowledged that for a child in either a polyuric or oliguric state, fluid requirements should take into consideration insensible losses, urine output and other losses (for example, gastrointestinal losses), and that in these children the use of body surface area to calculate fluid requirements may be more accurate. The GDG also felt that the use of body weight in children with a BMI above the 91st centile may overestimate fluid requirements. A more accurate prescription in this group of children may be made using body surface area to calculate fluid requirements.
Economic considerations	No evidence on health outcomes was available, and any difference in the utilisation of resources between the 2 calculation methods was considered to be negligible. Therefore, the recommendation was based on GDG consensus over the accuracy of the 2 methods. In children with more complex needs, the approach using body surface area was considered cost effective in comparison to the approach using body weight because the GDG consensus was that the body surface area method would lead to improved outcomes.
Quality of evidence	No evidence was identified on the use of body surface area rather than weight for the routine calculation of fluid requirements in children. The GDG did not consider it appropriate to extrapolate from adult studies and therefore used consensus to develop the recommendation.
Other considerations	The use of body weight to estimate IV fluid requirements is established clinical practice, and no evidence exists to suggest that body surface area is preferable for routine use. For children that cannot be weighed or cannot have their height measured, formulae exist for the estimation of body weight and body surface area. The GDG noted that there were resources available to allow clinicians to calculate body surface area in children (for example, British National Formulary for Children, MedCalc, QxMD).

5.2 Methods of calculating IV fluid requirements

5.2.1 Measurement and documentation

5.2.1.1 Introduction

A good fluid balance chart is an essential tool when measuring input and output for children receiving IV fluid therapy. It is very important to be able to keep a timely and accurate record of what type of fluid has been given and the type of fluid that has been lost, as well as any electrolytes lost in bodily fluids.

Currently there is no standard chart used nationally, which means that different hospitals, as well as units within hospitals, use different charts. Some charts record more detail than others, which can make it difficult for staff moving between hospitals and within hospital departments to determine an accurate fluid balance for the child. This prompted the National Patient Safety Agency (NPSA)[32] to release example fluid prescription charts taking into consideration various factors felt to be important when monitoring and prescribing IV fluid therapy, including how to calculate fluid administration rate, fluid deficit in dehydration and replacement of fluid losses. There have been no standard fluid balance

and prescription charts produced which encompass all of the aspects considered important in monitoring, prescribing and safely administering IV fluid therapy in children.

5.2.1.2 Review question 2: What are the key components to be measured and documented on an IV fluid balance and/or prescription chart to ensure appropriate prescribing of IV fluids?

For full details see the review protocols in Appendix C.

Table 8: PICO characteristics of review question

Population	Neonates born at term, infants, children and young people up to their 16th birthday receiving IV fluids in hospital
Intervention(s)	Measures to assess needs for fluid administration: • Weight or body surface area (previous day's/current/difference) • Clinical history including fluid intake in previous 24 hours, abnormal losses, any relevant comorbidities (for example renal, cardiovascular disease, neurological) • Clinical examination including pulse, blood pressure (BP), capillary refill, jugular venous pressure (JVP) in older children, level of dehydration, presence of pulmonary or peripheral oedema • Review switch to oral fluid or nasogastric administration • Results of laboratory assessments including full blood count (FBC), urea, creatinine, serum electrolyte levels (chloride, sodium, potassium), urinary electrolytes, acid base status (if in hypovolaemic shock) • Previous 24 hours input/output • Ongoing losses
Comparison(s)	Combination of any chart including any of the components above
Outcomes	**Critical** • Mortality • Adverse effects (including hypovolaemia, dehydration, hypervolaemia, neurological complications, hypoglycaemia) **Important** • Quality of life • Length of hospital stay
Study design	Order of preference for study designs: • Systematic reviews of RCTs which meet our PICOs • Randomised control trials Where no RCTs are available, we will consider: • Abstracts on RCTs Where no RCTs or abstracts of RCTs are available, we will consider: • Non-randomised trials: prospective or retrospective cohort studies of 50 children or more. • Non-blinded, single and double-blinded trials will be included

5.2.1.3 Clinical evidence

We searched for systematic reviews, RCTs and cohort studies in children.

The GDG did not consider that evidence in an adult population was relevant as adult fluid balance charts would include different components to that of children.

No relevant clinical evidence comparing different IV fluid balance or prescription charts was identified.

5.2.1.4 Economic evidence

5.2.1.4.1 Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

5.2.1.4.2 New analysis

No published studies relating to the cost effectiveness of monitoring strategies were found. The GDG considered monitoring to be a high priority for de novo economic modelling. However, given the lack of evidence of clinical effectiveness, a cost analysis was conducted instead. A threshold sensitivity analysis around the number of major complications that would need to be averted was also undertaken; see Appendix M for more details. We considered different strategies that were differentiated by the frequency of measuring patient weight and the frequency and completeness of fluid balance recording.

Nine strategies were considered in the analysis (see Figure 4), ranging from no weight measurement and no fluid balance recording to twice-daily weight measurement and complete fluid balance recording. The cost of weighing a patient was estimated to be £13.53 each time. The cost of partial fluid balance recording (where only IV fluid inputs are recorded) was estimated to be £53.38 per patient per 24 hour day (82 minutes per patient), while the cost of complete fluid balance recording (where all IV fluid inputs and outputs are recorded) was estimated to be £84.44 per patient per 24 hour day (130 minutes per patient).

Figure 4: Monitoring strategies compared in the analysis

		Fluid balance recording		
		None	**Partial**	**Complete**
Weight measurement	None	*Strategy 1*	*Strategy 2*	*Strategy 6*
	Twice weekly		*Strategy 3*	*Strategy 7*
	Daily		*Strategy 4*	*Strategy 8*
	Twice daily		*Strategy 5*	*Strategy 9*

A major fluid-related complication was considered to be a complication that is likely to require prolonged length of stay (for example oedema). Therefore, the cost of a major complication was estimated using the non-elective inpatient long stay categories of the NHS reference costs [14] and calculated as a weighted average of all NHS reference costs 2012-2013 for fluid and electrolyte disorders relating to paediatric non-elective inpatient long stay categories. This was found to be £3799 (or £4563 including a critical care episode).

The cost of each monitoring strategy is shown in Table 9 along with the number of major complications that would need to be averted to make each strategy cost neutral.

Table 9: Costs of monitoring strategies and the number of major complications that need to be averted for cost neutrality

Strategy			Total costs for each monitoring strategy over the duration of IV fluid administration[a] (£)	Number of extra major complications that would have to be avoided per 1000 patients to make strategy cost neutral compared to no monitoring (strategy 1)	Number of extra major complications that would have to be avoided per 1000 patients to make strategy cost neutral compared to no monitoring (strategy 1) including cost of critical care
#	Weight measurement	Fluid balance recording (FBR)			
1	None	No FBR	£0	0	0
2	None	Partial FBR	£107	28	23
3	Twice a week	Partial FBR	£120	32	26
4	Daily	Partial FBR	£134	35	29
5	Twice a day	Partial FBR	£161	42	35
6	None	Complete FBR	£169	44	37
7	Twice a week	Complete FBR	£182	48	40
8	Daily	Complete FBR	£196	52	43
9	Twice a day	Complete FBR	£223	59	49

(a) IV fluids administered for 2 days

Based on this analysis and other sensitivity analyses that were conducted (see Appendix M for more details) together with clinical experience, the GDG concluded that strategy 8 represented a good use of NHS resources as the number of major complications that need to be averted for cost neutrality compared to current practice (strategy 3) is plausible. This analysis does not include the quality of life loss associated with complications, and the GDG also highlighted that the complication costs reported here may be underestimated as they do not include any staff time costs that maybe incurred during the investigation of any serious adverse events. Hence, the numbers of complications that need to be averted are likely to be overestimates.

5.2.1.5 Evidence statements

5.2.1.5.1 Clinical

- No relevant clinical evidence was identified.

5.2.1.5.2 Economic

- An original comparative cost analysis showed that the cost of the various monitoring strategies considered ranged from £0 to £223. It also showed that a strategy of daily weight measurement and complete fluid balance recording would be cost neutral compared to no weight measurement and no fluid balance recording if it avoids 52 extra major complications per 1000 children (43 if critical care cost is included).
- The same original comparative cost analysis showed that a strategy of daily weight measurement and complete fluid balance recording would be cost neutral compared to current practice (twice-weekly weight measurement and partial fluid balance recording) if it avoids 20 major complications per 1000 children (17 if critical care cost is included).
- This analysis was assessed as partially applicable with potentially serious limitations.

5.2.1.6 Recommendations and link to evidence

Recommendations	**5. In term neonates, children and young people who are receiving IV fluids, assess and document the following:** • **Actual or estimated daily body weight. Record the weight from the current day, the previous day, and the difference between the two. If an estimate was used, the actual weight should be measured as soon as clinically possible.** • **Fluid input, output and balance over the previous 24 hours.** • **Any special instructions for prescribing, including relevant history.** • **An assessment of the fluid status.** • **The results of laboratory and point-of-care assessments, including:** **-full blood count** **-urea** **-creatinine** **-plasma electrolyte concentrations (including chloride, sodium and potassium; see recommendation 6)** **-blood glucose (see recommendation 7)** **-urinary electrolyte concentrations.** • **Details of any ongoing losses (see recommendation 26 and the diagram of ongoing losses).** • **Calculations of fluid needs for routine maintenance, replacement, redistribution and resuscitation.** • **The fluid and electrolyte prescription (in ml per hour), with clear signatures, dates and times.** • **Types and volumes of fluid input and output (urine, gastric and other), recorded hourly and with running totals.** • **12-hourly fluid balance subtotals.** • **24-hourly fluid balance totals.** • **12-hourly reassessments of:** **-the fluid prescription** **-current hydration status** **-whether oral fluids can be started** **-urine and other outputs.**
Relative values of different outcomes	Mortality at 28 days, adverse effects (including hypovolaemia, dehydration, hypervolaemia, neurological complications and hypoglycaemia) and logistic regression to fluid factors associated most closely with fluid requirements were considered to be critical outcomes. Length of hospital stay and quality of life were considered important outcomes.

Trade-off between clinical benefits and harms	No evidence was identified which compared different fluid balance charts against each other to establish which components should be documented in a fluid balance chart. Therefore, the GDG chose to develop a recommendation using informal consensus. The GDG agreed that in current practice there is variation in what is recorded and documented in a patient's chart and that providing guidance on what core information is required may lead to improvements in care. The GDG therefore chose to develop a recommendation which detailed the minimum data to be recorded in a fluid balance chart, and highlighted that it may be necessary to document additional components in particular settings (for example, patients on dialysis). The GDG agreed that having a combined fluid balance and prescription chart was helpful. The GDG discussed the frequency of measuring weight and agreed that, in most children, this does not occur daily, except in renal patients where more frequent weighing is likely. With illness, fluid overload and fluid depletion can occur in a short period of time and this can be reflected in acute changes in children's weight. However, the group felt that children's weight is often not monitored regularly enough, and daily weighing and recording should be the recommended option. The GDG felt that the chart should also record the total fluid going into and out of the patient to assist in monitoring fluid balance over a 24-hour period. The GDG also felt that recording serial blood results was useful; if these were documented only in notes, they may not be so readily noted when prescribing IV fluids. The GDG agreed that the frequency of assessment and monitoring would be the same in babies and children. The GDG wished to highlight that electrolyte concentrations should be measured at least 24 hourly in children receiving IV fluids, and more frequently if electrolyte disturbances exist. The prescribed fluids affect the level of hydration of the child, which changes electrolyte concentrations. An accurate knowledge of serum electrolytes will guide subsequent prescription of IV fluids, thus preventing severe electrolyte derangement secondary to IV therapy. The GDG also wished to highlight that blood glucose should be measured at least every 24 hours and more frequently for children at risk of hypoglycaemia. Glucose metabolism in children is adversely affected by disease and stress. Hyperglycaemia caused by a stress response can quickly change to hypoglycaemia when glucose intake is restricted.

Economic considerations	No economic evaluations were identified for this question. It was not possible to conduct a cost-effectiveness analysis given the lack of evidence of clinical effectiveness, however we conducted a threshold analysis to estimate the number of major complications that a more frequent or thorough assessment would need to avert for it to be cost neutral compared to a less frequent or thorough assessment. Specifically, we compared strategies with a frequency of weight measurement and recording from none to twice-daily and complete or partial fluid balance recording. Twice-weekly weight measurement and partial fluid balance recording (only fluid inputs) is believed to be the most common practice in the NHS. The original analysis conducted showed that, under base case assumptions, the cost of current practice is £120 per patient over the duration of IV fluid administration, while the strategy with daily weight measurement and complete fluid balance recording costs £196. This analysis indicated that, to be cost neutral compared to the cheapest strategy (no weight measurement and no fluid balance recording), daily weight measurement and complete fluid balance recording (to include both fluid inputs and outputs) would need to prevent 52 major complications per 1000 children. This figure seemed plausible to the GDG as it was acknowledged that the analysis did not capture the possible health gain from the reduced number of minor complications. Sensitivity analyses were also conducted where the cost of complications included critical care costs. This analysis showed that the number of extra complications to be averted, for cost neutrality with the cheapest strategy, reduced to 43. When the time required for fluid balance recording was doubled, the number of extra complications to be averted, for cost neutrality, increased to 92. Longer and shorter durations of IV fluid administration also resulted in changing the number of extra complications that need to be averted to 77 and 26. For this reason the GDG concluded that daily weight measurement and complete fluid balance recording (including fluid inputs and outputs) could be justified in light of the costs and quality of life loss that are likely to result from any major complication as well as the possibility of preventing deaths. The GDG believed that twice-daily weight recording has increased costs with no further benefits compared to a daily weight measurement. This is because the variation in weight may be due to other reasons and the healthcare professional may not change the patient's management based on a change within the same day.
Quality of evidence	No evidence was identified therefore the recommendation was based on the cost analysis conducted and GDG consensus. The GDG considered the prescription chart template for IV infusions produced by the NPSA,[32] and also drew on fluid balance and prescription charts in use in their own areas of practice.
Other considerations	The GDG noted that this recommendation was applicable to all children who are receiving IV fluid therapy in hospital. However, guidance on the assessment of dehydration and hypovolaemia in children receiving IV fluid resuscitation can be found in Section 5.2.3. The GDG highlighted that they were aware of the introduction of standardised fluid balance and prescription charts, for example in Northern Ireland. http://www.dhsspsni.gov.uk/hss-md-30-2013-attachment-2.pdf

5.2.2 Laboratory-based methods versus point-of-care testing

5.2.2.1 Introduction

Children requiring IV fluids may have disease processes that affect fluid loss or retention and sodium and potassium excretion; for example an infant with bronchiolitis is at high risk of secreting excessive antidiuretic hormone and retaining water, leading to hyponatraemia. Fluid overload or dehydration and electrolyte abnormalities such as hyponatraemia, hypernatraemia, hypokalaemia and hyperkalaemia often lead to increased morbidity and mortality. Accurate and timely estimation of the child's plasma electrolyte levels is a vital component of the healthcare practitioner's assessment and reassessment of the child's IV fluid requirements. Delay in obtaining plasma electrolyte levels will prevent the healthcare practitioner from changing the IV prescription at an appropriate time when these levels are abnormal.

Laboratory analysis of plasma sodium and potassium levels may incur a time delay of 1 to 4 hours before the healthcare practitioner has access to the results. Point-of-care analysers give an estimation of plasma electrolytes within 5 minutes of obtaining a blood sample and often require a smaller blood volume than laboratory analysis. These analysers are now available within and outside the hospital environment; they can be in a fixed site or portable and are accurate and reliable when used correctly. Point-of-care analysers are expensive to purchase and maintain, incurring extra costs in consumables, routine maintenance and quality assurance tests and the training of staff to use the machines.

5.2.2.2 Review question 3: What is the clinical- and cost-effectiveness of laboratory-based methods versus point-of-care testing for assessing electrolyte estimations in children?

For full details see the review protocols in Appendix C.

Table 10: PICO characteristics of review question

Population	Neonates born at term, infants, children and young people up to their 16th birthday receiving IV fluids in hospital
Intervention(s)	Laboratory-based testing for assessing fluid requirement including: • Plasma (albumin, sodium, potassium, chloride, urea, creatinine, pH, lactate bicarbonate and glucose) • Urine (sodium and potassium, osmolality)
Comparison(s)	Point-of-care testing for assessing fluid requirement including: • Plasma (sodium, potassium, chloride, urea, creatinine, pH, lactate bicarbonate and glucose) • Urine (sodium and potassium)
Outcomes	**Critical** • Mortality • Test turnaround time • Adverse effects (including hypovolaemia, dehydration, hypervolaemia, neurological complications) **Important** • Fluid balance • Quality of life • Length of hospital stay
Study design	Order of preference for study designs: • Systematic reviews of RCTs which meet our PICOs • Randomised controlled trials

	Where no RCTs are available, we will consider: • Abstracts on RCTs Where no RCTs or abstracts of RCTs are available, we will consider: • Non-randomised trials: prospective or retrospective cohort studies of 50 children or more. • Non-blinded, single and double-blinded trials will be included Where no randomised or non-randomised evidence in children are available, we will consider: • Systematic reviews of RCTs which meet our PICOs in adults • Randomised controlled trials in adults • Non-randomised trials: prospective or retrospective cohort studies of 50 adults or more.

5.2.2.3 Clinical evidence

We searched for systematic reviews, RCTs and cohort studies in children, or adults if no evidence in children was available.

The GDG considered findings from adult studies as protocols and performance of biochemical testing devices would not vary between adults and children.

A single before-and-after cohort study[42] comparing point-of-care testing with laboratory-based methods was found. The study was conducted in adults with sepsis and is summarised in Table 11 below.

Table 11: Summary of studies included in the review

Study	Intervention/comparison	Population	Outcomes
Singer 2014	Point-of-care measure for lactate (Abbott Point of Care) versus standard laboratory testing	Adult patients presenting to an emergency department (ED) with suspected sepsis	Mortality

Table 12: Clinical evidence summary: Point-of-care versus laboratory testing

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with laboratory	Risk difference with point of care versus laboratory testing (95% CI)
Mortality	160 (1 study)	VERY LOW[a,b] due to risk of bias, indirectness and imprecision	RR 0.31 (0.12 to 0.81)	200 per 1000	138 fewer per 1000 (from 38 fewer to 176 fewer)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

5.2.2.4 Economic evidence

5.2.2.4.1 Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

5.2.2.4.2 Unit costs

Relevant unit costs are presented in the table below.

Table 13: Unit costs of laboratory and point-of-care electrolyte tests

Test	Description	Unit cost [a]	Source
Laboratory	Phlebotomy test	£3.64	NHS reference costs database, 2012-13. Currency code DAPS08[14]
Laboratory	Clinical biochemistry	£1.25	NHS reference costs database, 2012-13. Currency code DAPS04[14]
Point-of-care	I-Stat handheld blood analyser	£6,884[b]	NHS supply chain catalogue April 2014[35]
Point-of-care	CHEM8+ single use cartridges for I-Stat[c]	£10.83 [c]	NHS supply chain catalogue April 2014[35]

(a) VAT is not included in these unit costs
(b) The GDG advised that the I-Stat handheld blood analyser could be provided for free by the manufacturer. Another test is also available, blood gas analyser, however the GDG advised that every intensive care unit (ICU) unit will already have the equipment available for this test
(c) Analyses chemistries/electrolytes (sodium, potassium, chloride, TCO_2, anion gap, ionised calcium, glucose, urea nitrogen/urea, creatinine, haematocrit, haemoglobin). Other types of I-Stat cartridges are available which measure different sets of serum markers; these range in price from £2.94 to £7.73

5.2.2.5 Evidence statements

5.2.2.5.1 Clinical

Point-of-care versus laboratory testing

- Very-low-quality evidence from a single observational study comprising 160 participants demonstrated a clinical benefit for point-of-care testing compared to laboratory testing for mortality. The evidence was at a very serious risk of bias and showed serious imprecision.

5.2.2.5.2 Economic

- No relevant economic evaluations were identified.

5.2.2.6 Recommendations and link to evidence

Recommendations	**6. Measure plasma electrolyte concentrations using laboratory tests when starting IV fluids, and then at least every 24 hours or more frequently if there are electrolyte disturbances.** **7. Measure blood glucose when starting IV fluids, and then at least every 24 hours or more frequently if there is a risk of hypoglycaemia.** **8. Consider point-of-care testing for measuring plasma electrolyte concentrations and blood glucose in time-critical situations when IV fluids are needed (for example, during emergency situations and in A&E, theatre and critical care).**
Relative values of different outcomes	Mortality at 28 days, adverse effects (including hypovolaemia, dehydration, hypervolaemia, neurological complications and hypoglycaemia) and test turnaround time were considered to be critical outcomes. Length of hospital stay, quality of life and fluid balance were considered important outcomes.
Trade-off between clinical benefits and harms	No evidence directly compared the method of measuring electrolytes in term neonates, children or young people who require IV fluids in normal clinical care. The GDG therefore used consensus to develop a recommendation for these patients and felt that the use of laboratory tests to estimate electrolytes was likely to be adequate for the majority of situations, given the additional cost impact of using point-of-care testing for these results and the increased accuracy from laboratory results. A single comparative cohort study in adults was identified and compared lactate measurements in an emergency situation. A clinically significant reduction in mortality was reported with point-of-care testing. The GDG felt the results underlined that the benefit of point-of-care testing is timely availability of results. The GDG noted that children in particular can deteriorate very quickly, and therefore the use of point-of-care testing may be appropriate in this population in emergency or time-critical situations (for example, symptomatic hyponatraemia) where results are required instantly. The GDG identified that time-critical situations in which there may be a benefit include within A&E, theatre or critical care settings such as paediatric intensive care unit (PICU) or neonatal intensive care unit (NICU). The GDG therefore chose to use informal consensus to develop recommendations for blood glucose and plasma electrolyte concentrations to be measured at least every 24 hours using laboratory tests. The GDG felt that this should be more frequent in certain situations, for example where there are electrolyte disturbances or the potential for electrolyte disturbances and children at risk of hypoglycaemia. Also, the GDG chose to develop a recommendation highlighting that, in time-critical situations, this may be conducted using point-of-care testing.
Economic considerations	There are additional costs associated with the provision of point-of-care devices, as well as their ongoing use, compared to laboratory-based tests. Furthermore, there are economic implications in providing training to healthcare professionals in operating devices and the staff time incurred in operating the point-of-care device. It was the GDG's opinion that point-of-care testing could potentially provide less accurate results. For these reasons, the GDG felt that this should not be used as a routine form of providing electrolyte estimations. However the GDG acknowledged that in some circumstances, when the timing of results is crucial, point-of-care testing could save lives and increase health benefits. In these situations the health gains are likely to offset the increase in cost.

Quality of evidence	Limited evidence was identified for the comparison between point-of-care and laboratory testing. A single retrospective cohort study in adults compared laboratory testing to point-of-care testing for lactate measurements in an emergency setting. The GDG felt that adult data could be appropriately used for this comparison but noted the potential risk of bias as the pharmacological company sponsoring the study were involved in the study design. Overall the evidence was of very low quality due to risk of bias and imprecision.
Other considerations	The GDG noted that quality assurance tests under the control of biochemists should be regularly undertaken for all point-of-care devices to ensure accuracy of results. Recommendations on the assessment of dehydration and hypovolaemia in children receiving IV fluids can be found in Section 5.2.3. Guidance on the patient groups who may be at risk of developing hypoglycaemia can be found in the NICE Information for the Public.

5.2.3 Assessing dehydration and hypovolaemia

5.2.3.1 Introduction

Dehydration is one of the leading causes of morbidity and mortality in children throughout the world. It is a condition that can occur from excess loss of water and other body fluids or from decreased intake of fluid. Children are particularly susceptible to dehydration. Many childhood illnesses including gastroenteritis, bronchiolitis, pyloric stenosis; and focal bacterial infections such as pneumonia, meningitis, and urinary tract infections can all lead to dehydration.

Considerable care is required in the assessment and management of dehydration in children as inaccurate assessment of dehydration can have important consequences. Clinical assessment of dehydration can be difficult, especially in younger children. Unrecognised and untreated fluid deficits can create electrolyte disturbances, acidosis and ultimately hypovolaemic shock resulting in organ failure.

Conversely, unnecessary interventions can occur if the fluid deficit is overestimated, resulting in inappropriate rehydration therapy. It is therefore essential to make an accurate assessment of the degree of dehydration in children in order to make appropriate treatment decisions. Dehydration is most often isonatraemic (with a normal serum sodium concentration) but may also be either hyponatraemic or hypernatraemic.

It is important to recognise that the following groups are particularly at risk of dehydration:

- children less than 1 year, particularly those younger than 6 months
- younger children who were of low birth weight
- children who have had large stool or stoma losses in the previous 24 hours
- children who have vomited more than twice in the previous 24 hours
- children who have not been offered or have not been able to tolerate supplementary oral fluids before presentation
- younger children who have stopped feeding during illness
- children with renal insufficiency and complex cardiac disease
- children with endocrine disease such as diabetes or congenital adrenal hyperplasia.

Clinical assessment therefore comprises multiple indicators of dehydration, including those associated with weight loss, clinical signs, capillary refill and assessment of circulation status.

5.2.3.2 Review question 4: What are the most clinically- and cost-effective methods for assessing dehydration and hypovolaemia?

For full details see the review protocols in Appendix C.

Table 14: PICO characteristics of review question

Population	Neonates born at term, infants, children and young people up to their 16th birthday. Patients who need IV fluids to address existing deficits, ongoing losses, or abnormal fluid distribution including: chest tubes in place, uncontrolled vomiting, continuing diarrhoea, and drain losses or constant gastric losses.
Intervention(s)	Measures to assess needs for fluid administration: • Weight loss • Clinical history: water intake in previous 24 hours, losses (fluid balance), any relevant comorbidities (for example renal, cardiovascular disease, neurological) • Clinical examination including pulse, BP, capillary refill, JVP in older children, altered consciousness • Pinch test (skin turgor) • Other clinical examination: sunken eyes, dry mucus membrane • Urine output • Urine testing for specific gravity, sodium, creatinine and osmolality • Blood tests (sodium, renal function, glucose)
Comparison(s)	Combination of any chart including any of the components above
Outcomes	**Critical** • Mortality • Adverse effects (including hypervolaemia, dehydration, neurological complications, hypoglycaemia) • Logistic regression to fluid factors associated most closely with fluid requirements. **Important** • Quality of life • Hospital stay
Study design	Order of preference for study designs: • Systematic reviews of RCTs which meet our PICOs • Randomised control trials Where no RCTs are available, we will consider: • Abstracts on RCTs Where no RCTs or abstracts of RCTs are available, we will consider: • Non-randomised trials: prospective or retrospective cohort studies of 50 children or more Non-blinded, single and double-blinded trials will be included.

5.2.3.3 Clinical evidence

We searched for systematic reviews, RCTs and cohort studies in children.

The GDG did not consider that evidence in an adult population was relevant as methods for identifying dehydration and hypovolaemia in adults were likely to differ from those used to assess dehydration and hypovolaemia in children.

No relevant clinical studies comparing methods of assessing dehydration and hypovolaemia were identified.

5.2.3.4 Economic evidence

5.2.3.4.1 Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

5.2.3.4.2 Unit costs

The GDG considered that the only resource use element that may differ between the different approaches considered is staff time. Hence, the unit costs of staff time are presented in Table 15.

Table 15: Unit costs of staff time

Healthcare professional	Cost (£)/hour	Cost (£)/minute	Source
Clinical support worker (CSW) [a]	£21	£0.35	PSSRU 2013[13]
Ward nurse [b]	£41	£0.68	PSSRU 2013[13]

(a) PSSRU description: Clinical support worker (hospital) Agenda for Change Band 2, 2012/13
(b) PSSRU description: Nurse, day ward (includes staff nurse, registered nurse, registered practitioner) Agenda for Change band 5, 2012/13

5.2.3.5 Evidence statements

5.2.3.5.1 Clinical

- No relevant clinical evidence was identified.

5.2.3.5.2 Economic

- No relevant economic evaluations were identified.

5.2.3.6 Recommendations and link to evidence

Recommendations	**9. Diagnose clinical dehydration and hypovolaemic shock using the clinical features listed in Table 16, but be aware that it can be difficult to identify the clinical features in term neonates.** **Notes:** **Within the category of 'clinical dehydration' there is a spectrum of severity indicated by increasingly numerous and more pronounced clinical features. For hypovolaemic shock, one or more of the clinical features listed would be expected to be present. Dashes (–) indicate that these features do not specifically indicate hypovolaemic shock.** **This table has been adapted from section 1.2 in 'Diarrhoea and vomiting in children' (NICE guideline CG84).**
Relative values of different outcomes	Mortality at 28 days, adverse effects (including hypovolaemia, dehydration, hypervolaemia, neurological complications and hypoglycaemia) and logistic regression to fluid factors associated most closely with fluid requirements were considered to be critical outcomes. Length of hospital stay and quality of life were considered important outcomes.

Trade-off between clinical benefits and harms	The GDG felt that it was important for healthcare professionals to be aware of which clinical features to look for in assessing dehydration and hypovolaemic shock in term neonates, children and young people. The results of assessment should inform subsequent management. The GDG noted that 'Diarrhoea and vomiting in children' (NICE guideline CG84) included a recommendation outlining the signs and symptoms of clinical dehydration and hypovolaemic shock in children under 5 years. The GDG noted that although the guidance refers specifically to children less than 5 years, it was appropriate to extrapolate to all children in the assessment of dehydration and hypovolaemic shock, and therefore chose to reference this recommendation within the current guideline, amending the table for clarity. The GDG wished to highlight however that the signs of hypovolaemic shock may be difficult to elicit in term neonates. The GDG felt that it was important to differentiate between the clinical features of dehydration and hypovolaemia and that one does not necessarily lead to the other but the two may co-exist. The GDG wished to specifically differentiate as managing dehydration too aggressively could lead to fluid overload and associated clinical complications (for example circulatory overload, pulmonary oedema and peripheral oedema and cardiac dysfunction).
Economic considerations	No economic evaluations were identified. Unit costs of staff time were presented to the GDG. The GDG felt that timely identification of the clinical features of dehydration and hypovolaemia is critical in preventing further deterioration and more serious complications that could result in substantial downstream costs. Hence, the cost of staff time will be off-set by the cost saving that would be achieved through prevention of major complications from hypovolaemia and dehydration. The GDG also acknowledged that all the clinical and laboratory assessments for detecting hypovolaemia and dehydration that were considered in the review already represent current practice and no major changes are expected to how these investigations are undertaken as a result of the recommendation.
Quality of evidence	No evidence was identified for this comparison, therefore the recommendation was based on GDG consensus.
Other considerations	Table 16 gives generic clinical features which would be looked for in any child. The GDG noted that dehydration and hypovolaemic shock present with a number of similar features and it is important to distinguish between them. Furthermore, it was noted that dehydration would make up one of the clinical features of hypovolaemic shock.

Table 16: Clinical features of dehydration and hypovolaemic shock

No clinically detectable dehydration	Clinical dehydration	Hypovolaemic shock
Alert and responsive	Red flag Altered responsiveness (for example, irritable, lethargic)	Decreased level of consciousness
Appears well	Red flag Appears to be unwell or deteriorating	–
Eyes not sunken	Red flag Sunken eyes	–
Moist mucous membranes (except after a drink)	Dry mucous membranes (except for 'mouth breather')	–
Normal blood pressure	Normal blood pressure	Hypotension (decompensated shock)
Normal breathing pattern	Red flag Tachypnoea	Tachypnoea
Normal capillary refill time	Normal capillary refill time	Prolonged capillary refill time
Normal heart rate	Red flag Tachycardia	Tachycardia
Normal peripheral pulses	Normal peripheral pulses	Weak peripheral pulses
Normal skin turgor	Red flag Reduced skin turgor	–
Normal urine output	Decreased urine output	–
Skin colour unchanged	Skin colour unchanged	Pale or mottled skin
Warm extremities	Warm extremities	Cold extremities

Notes:
Within the category of 'clinical dehydration' there is a spectrum of severity indicated by increasingly numerous and more pronounced clinical features. For hypovolaemic shock, one or more of the clinical features listed would be expected to be present. Dashes (–) indicate that these features do not specifically indicate hypovolaemic shock. This table has been adapted from the assessing dehydration and shock section in 'Diarrhoea and vomiting in children' (NICE guideline CG84).

6 IV fluid therapy for fluid resuscitation

6.1 Introduction

IV fluid resuscitation is a therapy commonly used in the treatment of sepsis, in patients undergoing major surgery, and following severe trauma. In critically ill children, fluid resuscitation rapidly expands blood volume, restores or maintains organ perfusion and can be a lifesaving intervention.

IV fluid resuscitation protocols are largely based on consensus guidelines due to an absence of sufficient clinical evidence. These guidelines[38] are currently considered to be the gold standard and recommend rapid fluid resuscitation in ill children with shock. The administration of 20 ml/kg aliquots of 0.9% sodium chloride is advised, with an escalation to more complex management options if the fluid administered is not reversing shock.

No ideal resuscitation fluid exists and recent trials have demonstrated iatrogenic effects following fluid administration. For example, the adult literature has demonstrated an increasing incidence of acidosis, associated with worsening outcome, in shocked patients following the administration of 0.9% sodium chloride.

Although the use of resuscitation fluids is one of the most common interventions in medicine, a large degree of uncertainty remains about the best fluid to use and the rate at which to administer it. The intention of this chapter is to examine the clinical evidence surrounding fluid resuscitation and develop recommendations for its safe administration to children.

6.1.1 Fluid type for fluid resuscitation

6.1.1.1 Review question 5: What is the most clinically- and cost-effective fluid type for fluid resuscitation in children?

For full details see the review protocols in Appendix C.

Table 17: PICO characteristics of review question

Population	• Neonates born at term, infants, children and young people (up to their 16th birthday), in hospital. • Critically ill patients, for instance those: undergoing surgery with expected blood loss >10% blood volume; with severe sepsis or septic shock, severe burns, acute gastroenteritis, gastrointestinal haemorrhage, dengue shock syndrome; admitted to an intensive care and a trauma unit with suspected hypovolaemia and/or hypotension and other electrolyte disturbances (for example, hypernatraemia, hypokalaemia, metabolic acidosis or alkalosis). **Strata** • Age (neonate <28 days versus >28 days) • Sepsis (data from dengue fever and malaria will be considered in this stratum as indirect evidence) • Trauma • Perioperative patients
Intervention(s)	**Crystalloids** • Balanced crystalloid solutions (Hartmann's solution; Ringer's lactate solution; Plasma-Lyte) • Isotonic sodium chloride • Hypertonic sodium chloride **Albumin**

	4-5% albumin **Synthetic Colloids** • Gelatin • Haemaccel; Gelofusine • Dextran (Dextran 60, Dextran 70)
Comparison(s)	• To each other
Outcomes	**Critical** • Mortality at 28 days • Neurological compromise (return to baseline activity, ischaemic injury, cerebral oedema) • Cardiovascular compromise (BP/arterial pressure, heart rate) **Important** • Length of hospital stay • Hyperchloraemic acidosis • Quality of life • Hypoglycaemia • Hypernatraemia • Hyponatraemia
Study design	Order of preference for study designs: • Systematic reviews of RCTs which meet our PICOs • Randomised control trials Where no RCTs are available, we will consider: • Abstracts on RCTs Where no RCTs or abstracts of RCTs are available, we will consider: • Non-randomised trials: prospective or retrospective cohort studies of 50 children or more Where no randomised or non-randomised evidence in children is available, we will consider: • Systematic reviews of RCTs which meet our PICOs in adults • Randomised control trials in adults Where no RCTs in adults are available, we will consider: • Abstracts on RCTs in adults Where no RCTs or abstracts of RCTs in adults are available: • Non-randomised trials: prospective or retrospective cohort studies of 1000 adults or more

6.1.1.2 Clinical evidence

We searched for systematic reviews, RCTs and cohort studies in children, or adults if no evidence in children was available. The GDG considered that findings from studies conducted in adults could be transferred to an infant and child population, and therefore the literature search included an adult population. Two systematic reviews were found which met the protocol (Akech 2010 and Perel

2013)[2,37] however they did not include all outcomes specified in the protocol. In addition, Perel[37] included adults as well as children and Akech 2010[2] did not report all domains of risk of bias which were required for assessment of the individual studies, therefore we reviewed all primary studies individually. The studies were grouped according to the type of fluid included: colloids versus crystalloids, colloids versus colloids, albumin versus colloids, albumin versus crystalloids and balanced crystalloids versus hypertonic sodium chloride. We have arranged the review by the stratum investigated, which included: sepsis, trauma and perioperative patients.

6.1.1.2.1 Colloids versus crystalloids

There were 4 studies included in the review.[15,34,43,44]

6.1.1.2.2 Colloids versus colloids

There were 2 studies included in the review.[15,34]

6.1.1.2.3 Albumin versus colloids

One study was included in the review.[1] This study[1] included children with severe malaria comparing gelatin and 4.5% albumin.

6.1.1.2.4 Albumin versus crystalloids

Four studies were included in the review.[18,23-25] The studies all included resuscitation with albumin or 0.9% sodium chloride. One of the studies (Maitland 2005)[25] included children with severe malaria, and Maitland (2005A)[24] included children with severe malarial anaemia. Maitland (2011)[23] included children with severe infection (57% had malaria). These 3 studies were all part of the FEAST study. Han (2009)[18] included children under 1 month with moderate-to-severe dehydration with metabolic acidosis.

6.1.1.2.5 Balanced crystalloids versus hypertonic sodium chloride

Four studies were included in the review: Belba 2009[5]; Bowser-Wallace 1986[7]; Caldwell 1979[8]; Simma 1998.[41]

The studies included in the review are summarised in Table 18 below. Evidence from these studies is summarised in the clinical evidence summary tables below (Table 19, Table 20, Table 21, Table 22, Table 23, Table 24, Table 25, Table 26, Table 27 and Table 28). See also the study selection flow chart in Appendix D, study evidence tables in Appendix G, forest plots in Appendix J, GRADE tables in Appendix I and excluded studies list in Appendix K.

The fluids included in the review (see table below) are classified as follows: colloids (dextran, gelatin and haemaccel); crystalloids (0.9% sodium chloride); balanced crystalloids (Ringer's lactate solution) and hypertonic sodium chloride.

Table 18: Summary of studies included in the review

Study	Intervention/ Comparison	Population	Outcomes	Comments
Akech 2006[1]	Gelatin (Gelofusine) versus 4.5% albumin	Children with severe malaria	Mortality; neurological compromise	Serious population indirectness – malaria
Belba 2009[5]	Ringer's lactate solution versus hypertonic sodium chloride	Children with severe burns	Mortality	
Bowser-Wallace 1986[7]	Ringer's lactate solution versus hypertonic sodium chloride	Children with severe burns	Mortality	
Caldwell 1979[8]	Ringer's lactate solution versus hypertonic sodium chloride	Children with severe burns	Mortality	
Dung 1999[15]	Dextran, gelatin, Ringer's lactate solution and 0.9% sodium chloride	Children with dengue shock syndrome	Mortality; cardiovascular compromise (decrease in heart rate (beats per minute))	Serious population indirectness – dengue shock syndrome
Han 2009[18]	5% albumin versus 0.9% sodium chloride	Children up to 1 month with moderate-to-severe dehydration with metabolic acidosis	Length of hospital stay	
Maitland 2005[25] (FEAST study)	4.5% albumin versus 0.9% sodium chloride	Children with severe malaria	Mortality at 8 hours; pulmonary oedema; neurological deterioration; neurological sequelae	Serious population indirectness – malaria
Maitland 2005A[24] (FEAST study)	4.5% albumin versus 0.9% sodium chloride	Children with severe malarial anaemia	Mortality at 8 hours; pulmonary oedema	Serious population indirectness – malaria
Maitland 2011[23] (FEAST study)	5% albumin versus 0.9% sodium chloride	Children with severe infection (57% with malaria)	Mortality at 28 days; pulmonary oedema; neurological sequelae	Serious population indirectness – malaria
Ngo 2001[34]	Dextran, gelatin, Ringer's lactate solution and 0.9% sodium chloride	Children with dengue shock syndrome	Mortality; cardiovascular compromise (decrease in heart rate (beats per minute))	Serious population indirectness – dengue shock syndrome
Simma 1998[41]	Ringer's lactate solution versus hypertonic sodium chloride	Children with traumatic head injury	Mortality; cardiovascular compromise; length of hospital	

Study	Intervention/ Comparison	Population	Outcomes	Comments
			stay	
Upadhyay 2005[43]	Haemaccel versus 0.9% sodium chloride	Children with septic shock	Mortality; cardiovascular compromise (haemodynamically stable at 6 hours; haemodynamically stable at 12 hours)	
Wills 2005[44]	Dextran, Ringer's lactate solution	Children with dengue shock syndrome	Mortality	Serious population indirectness – dengue shock syndrome

6.1.1.2.6 Sepsis

Colloids versus crystalloids

Table 19: Clinical evidence summary: Dextran 6% compared to Ringer's lactate solution: Dengue shock syndrome

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Ringer's lactate solution – dengue shock syndrome	Risk difference with dextran 6% versus Ringer's lactate solution (95% CI)
Mortality	389 (3 studies)	LOW[a,b] due to risk of bias, indirectness	Not estimable	0 per 1000	0 per 1000
Length of hospital stay (days)	247 (1 study)	VERY LOW[a,b,c] due to risk of bias, indirectness	Not estimable	Median 4 days (90% range 4–7)	Median 4 days (90% range 4–7)
Decrease in pulse at 1 or 2 hours (beats per minute)	93 (2 studies)	LOW[a,b] due to risk of bias, indirectness		10.75	The mean decrease in pulse at 1 or 2 hours (beats per minute) in the intervention groups was 3.06 higher (2.01 lower to 8.13 higher)

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Ringer's lactate solution – dengue shock syndrome	Risk difference with dextran 6% versus Ringer's lactate solution (95% CI)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Downgraded by 1 increment because patients had dengue shock syndrome rather than sepsis
(c) Imprecision could not be assessed as only median and range reported

Table 20: Clinical evidence summary: Gelatin compared to 0.9% sodium chloride: Sepsis

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 0.9% sodium chloride – sepsis	Risk difference with gelatin versus 0.9% sodium chloride (95% CI)
Mortality	60 (1 study)	LOW[a] due to imprecision	RR 0.94 (0.43 to 2.03)	290 per 1000	20 more per 1000 (from 148 fewer to 383 more)
Haemodynamically stable at 12 hours	55 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 1.1 (0.29 to 4.13)	793 per 1000	15 more per 1000 (from 267 fewer to 147 more)

(a) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
(b) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 21: Clinical evidence summary: Gelatin compared to 0.9% sodium chloride: Dengue shock syndrome

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 0.9% sodium chloride – dengue shock syndrome	Risk difference with gelatin versus 0.9% sodium chloride (95% CI)
Mortality	137 (2 studies)	MODERATE[a] due to indirectness	Not estimable	0 per 1000	0 per 1000
Decrease in pulse at 1 or 2 hours (beats per minute)	137 (2 studies)	LOW[a,b] due to risk of bias, indirectness		12.9	The mean decrease in pulse at 1 or 2 hours (beats per minute) in the intervention groups was 4.65 higher (1 to 8.31 higher)

(a) Downgraded by 1 increment because patients had dengue shock syndrome rather than sepsis
(b) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 22: Clinical evidence summary: Dextran 6% compared to 0.9% sodium chloride: Dengue shock syndrome

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 0.9% sodium chloride – dengue shock syndrome	Risk difference with dextran 6% versus 0.9% sodium chloride (95% CI)
Mortality	135 (2 studies)	LOW[a,b] due to risk of bias, indirectness	Not estimable	0 per 1000	0 per 1000
Decrease in pulse at 1 or 2 hours (beats per minute)	135 (2 studies)	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision		12.9	The mean decrease in pulse at 1 or 2 hours (beats per minute) in the intervention groups was 1.78 higher (1.63 lower to 5.18 higher)

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 0.9% sodium chloride – dengue shock syndrome	Risk difference with dextran 6% versus 0.9% sodium chloride (95% CI)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Downgraded by 1 increment because patients had dengue shock syndrome rather than sepsis
(c) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 23: Clinical evidence summary: Gelatin compared to Ringer's lactate solution: Dengue shock syndrome

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Ringer's lactate solution – dengue shock syndrome	Risk difference with gelatin versus Ringer's lactate solution (95% CI)
Mortality	137 (2 studies)	MODERATE[a] due to indirectness	Not estimable	0 per 1000	0 per 1000
Decrease in pulse at 1 hour (beats per minute)	137 (2 studies)	MODERATE[a] due to indirectness		12.45	The mean decrease in pulse at 1 hour (beats per minute) in the intervention groups was 4.8 higher (1.15 to 8.45 higher)

(a) Downgraded by 1 increment because patients had dengue shock syndrome rather than sepsis

Table 24: Clinical evidence summary: Dextran versus gelatin: Sepsis

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with gelatin	Risk difference with dextran versus gelatin (95% CI)
Mortality	134 (2 studies)	LOW[a,b] due to risk of bias, indirectness	Not estimable	0 per 1000	0 per 1000
Cardiovascular compromise (change in heart rate)	134 (2 studies)	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision		The mean change in heart rate in the control groups was 18.3	The mean cardiovascular compromise (change in heart rate) in the intervention groups was 6.05 lower (9.06 to 3.03 lower)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias
(b) Downgraded by 1 increment because the majority of the evidence came from a population with dengue fever
(c) Downgraded by 1 increment if the confidence interval crossed 1 MID

Colloids versus albumin

Table 25: Clinical evidence summary: Colloids versus albumin: Sepsis

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with albumin – sepsis	Risk difference with colloid versus albumin (95% CI)
Mortality	88 (1 study)	LOW[a,b] due to indirectness, imprecision	RR 7 (0.9 to 54.55)	23 per 1000	138 more per 1000 (from 2 fewer to 1000 more)
Neurological sequelae	81 (1 study)	VERY LOW[a,b] due to indirectness, imprecision	Peto OR 0.29 (0.04 to 2.18)	81 per 1000	56 fewer per 1000 (from 77 fewer to 80 more)

(a) Downgraded by 1 increment as the evidence was based on a population with malaria

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with albumin – sepsis	Risk difference with colloid versus albumin (95% CI)

(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 26: Clinical evidence summary: Albumin versus crystalloids (0.9% sodium chloride): Malaria

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with crystalloid (0.9% sodium chloride) – malaria	Risk difference with albumin versus crystalloid (95% CI)
Mortality at 28 days	2126 (1 study)	LOW[a,b,c] due to indirectness, imprecision	RR 1.01 (0.81 to 1.27)	127 per 1000	1 more per 1000 (from 24 fewer to 34 more)
Mortality at 8 hours (combined)	160 (2 studies)	VERY LOW[b,c,d,e,f] due to risk of bias, inconsistency, indirectness, imprecision	RR 0.49 (0.08 to 2.86)	165 per 1000	84 fewer per 1000 (from 152 fewer to 307 more)
Pulmonary oedema	2257 (3 studies)	VERY LOW[b,c,d,e] due to risk of bias, inconsistency, indirectness, imprecision	RR 1.11 (0.13 to 9.71)	6 per 1000	1 more per 1000 (from 5 fewer to 52 more)
Neurological deterioration	117 (1 study)	VERY LOW[b,c,d] due to risk of bias, indirectness, imprecision	RR 0.12 (0.02 to 0.93)	148 per 1000	130 fewer per 1000 (from 10 fewer to 145 fewer)

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with crystalloid (0.9% sodium chloride) – malaria	Risk difference with albumin versus crystalloid (95% CI)
Neurological sequelae	2090 (2 studies)	VERY LOW[b,c,d] due to risk of bias, indirectness, imprecision	RR 1.26 (0.73 to 2.19)	40 per 1000	10 more per 1000 (from 11 fewer to 48 more)

(a) Unclear if patients with hypotension analysed in a separate subgroup are analysed at 48 hours or 28 days
(b) Downgraded by 1 increment as the evidence was based on a population with malaria
(c) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
(d) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(e) Downgraded by 1 increment because of heterogeneity
(f) Downgraded by 1 increment because mortality was at 8 hours rather than at 28 days

Table 27: Clinical evidence summary: Albumin versus crystalloids (0.9% sodium chloride): Dehydration and moderate to severe metabolic acidosis

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with crystalloids (0.9% sodium chloride)	Risk difference with albumin versus crystalloids (95% CI)
Length of hospital stay (days)	33 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	–	9.36 (SD 4.16)	The mean length of hospital stay in the intervention groups was 1.23 days fewer (from 3.75 lower to 1.29 higher)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

6.1.1.2.7 *Trauma*

Balanced crystalloids (Ringer's lactate solution) versus 0.9% sodium chloride

Table 28: Clinical evidence summary: Ringer's lactate solution versus hypertonic sodium chloride: Trauma

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with hypertonic sodium chloride (0.9% sodium chloride)	Risk difference with balanced crystalloid (Ringer's lactate solution) versus 0.9% sodium chloride (95% CI)
Mortality	217 (4 studies) 3-15 days	VERY LOW[a,b,c] due to inconsistency, indirectness, imprecision	RR 1.31 (0.51 to 3.44)	46 per 1000	14 more per 1000 (from 23 fewer to 108 more)
Incidence of acute respiratory distress syndrome	32 (1 study) 3 days	VERY LOW[c,d] due to risk of bias, imprecision	Peto OR 8.04 (1.02 to 63.46)	0 per 1000	240 more per 1000 (from 20 more to 450 more)
Arrhythmia	32 (1 study) 3 days	VERY LOW[c,d] due to risk of bias, imprecision	Peto OR 6.22 (0.35 to 111.47)	0 per 1000	180 more per 1000 (from 30 fewer to 380 more)
Length of hospital stay (days)	32 (1 study)	LOW[c,d] due to risk of bias, imprecision		The mean length of hospital stay in the control groups was 50 days	The mean length of hospital stay in the intervention groups was 8 days fewer (33.45 fewer to 17.45 more)

(a) Downgraded by 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis
(b) Downgraded by 1 increment as the evidence was based on comparisons of different time points
(c) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
(d) Downgraded by 1 increment if the majority of the evidence was at high risk of bias

6.1.1.3 Economic evidence

6.1.1.3.1 Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

6.1.1.3.2 Unit costs

The table below presents the unit costs of IV fluids used for resuscitation.

Table 29: Unit costs of IV fluid therapy for resuscitation

IV fluid	Unit cost (500ml pre-mixed bag)[a]	Source
Isotonic crystalloids		
0.9% sodium chloride	£0.63	Department of Health Commercial Medicines Unit (CMU)[11]
Hartmann's solution (compound sodium lactate)	£0.70	Department of Health Commercial Medicines Unit (CMU)[11]
Ringer's lactate solution	£0.70	Department of Health Commercial Medicines Unit (CMU)[11]
Plasma-Lyte 148	1000 ml = £1.04	Nottingham University Hospitals NHS Trust, Pharmacy Department
Hypertonic crystalloids		
2.7% sodium chloride	£2.75	Nottingham University Hospitals NHS Trust, Pharmacy Department
Non-synthetic colloids		
4.5% albumin	500 ml bottle = £33.75	Nottingham University Hospitals NHS Trust, Pharmacy Department
Synthetic colloids		
Succinylated gelatin (Gelofusine)	£2.20	Nottingham University Hospitals NHS Trust, Pharmacy Department
Dextran 70	250 ml = £28.50	BNF66[20]

(a) VAT is not included in these unit costs

6.1.1.4 Evidence statements

6.1.1.4.1 Clinical

6.1.1.4.1.1 Colloids versus crystalloids

Dextran 6% versus Ringer's lactate solution in children with dengue shock syndrome

- Low-quality evidence from 3 RCTs comprising 389 participants demonstrated no clinical difference between dextran 6% and Ringer's lactate solution for mortality. The evidence was at serious risk of bias and indirectness but showed no serious imprecision.
- Very-low-quality evidence from a single RCT comprising 247 participants demonstrated no clinical difference between dextran 6% and Ringer's lactate solution for days in hospital. The evidence was at serious risk of bias and indirectness but as median values were reported, imprecision or estimate of effect could not be derived.

- Low-quality evidence from 2 RCTs comprising 93 participants demonstrated no clinical difference between dextran 6% and Ringer's lactate solution for decrease in pulse rate at 1 or 2 hours. The evidence was at serious risk of bias and indirectness but showed no serious imprecision.

Gelatin versus 0.9% sodium chloride in children with sepsis

- Low-quality evidence from a single RCT comprising 60 participants demonstrated no clinical difference between gelatin and 0.9% sodium chloride for mortality. The evidence showed very serious imprecision.
- Very-low-quality evidence from a single RCT comprising 55 participants demonstrated no clinical difference between gelatin and 0.9% sodium chloride for haemodynamic stability at 12 hours. The evidence was at serious risk of bias and showed serious imprecision.

Gelatin versus 0.9% sodium chloride in children with dengue shock syndrome

- Moderate-quality evidence from 2 RCTs comprising 137 participants demonstrated no clinical difference between gelatin and 0.9% sodium chloride for mortality. The evidence showed serious indirectness.
- Low-quality evidence from 2 RCTs comprising 137 participants demonstrated no clinical difference between gelatin and 0.9% sodium chloride for decrease in pulse rate at 1 or 2 hours. The evidence was at serious risk of bias and showed serious indirectness.

Dextran 6% versus 0.9% sodium chloride in children with dengue shock syndrome

- Low-quality evidence from 2 RCTs comprising 135 participants demonstrated no clinical difference between dextran 6% and 0.9% sodium chloride for mortality. The evidence was at serious risk of bias and showed serious indirectness.
- Very-low-quality evidence from 2 RCTs comprising 135 participants demonstrated no clinical difference between dextran 6% and 0.9% sodium chloride for decrease in pulse rate at 1 or 2 hours. The evidence was at serious risk of bias and showed serious indirectness and imprecision.

Gelatin versus Ringer's lactate solution in children with dengue shock syndrome

- Moderate-quality evidence from 2 RCTs comprising 137 participants demonstrated no clinical difference between gelatin and Ringer's lactate solution for mortality and decrease in pulse at 1 hour. The evidence showed serious indirectness.

Dextran versus gelatin in children with sepsis

- Low-quality evidence from 2 RCTs comprising 134 participants demonstrated no clinical difference between dextran and gelatin for mortality. The evidence was at serious risk of bias and showed serious indirectness.
- Very-low-quality evidence from 2 RCTs comprising 134 participants demonstrated a clinical benefit of gelatin compared to dextran for mean cardiovascular compromise (change in heart rate). The evidence was at serious risk of bias and showed serious indirectness and imprecision.

Albumin versus colloids in children with sepsis

- Low-quality evidence from a single RCT comprising 88 participants demonstrated a clinical benefit of albumin over colloids for mortality. The evidence showed serious indirectness and imprecision.
- Very-low-quality evidence from a single RCT comprising 81 participants demonstrated a clinical benefit of colloids over albumin for neurological sequelae. The evidence showed serious indirectness and very serious imprecision.

6.1.1.4.1.2 Albumin versus crystalloids in children with malaria

Albumin versus 0.9% sodium chloride

- Low-quality evidence from a single RCT comprising 2126 participants demonstrated no clinical difference between albumin and 0.9% sodium chloride for mortality at 28 days. The evidence showed serious indirectness and imprecision.
- Very-low-quality evidence from 2 RCTs comprising 160 participants demonstrated a clinical benefit of albumin over 0.9% sodium chloride for mortality at 8 hours. The evidence was at high risk of bias and showed serious inconsistency, and very serious indirectness and imprecision.
- Very-low-quality evidence from 3 RCTs comprising 2257 participants demonstrated no clinical difference between albumin and 0.9% sodium chloride for pulmonary oedema. The evidence was at serious risk of bias and showed serious inconsistency, indirectness and very serious imprecision.
- Very-low-quality evidence from a single RCT comprising 117 participants demonstrated a clinical benefit of albumin over 0.9% sodium chloride for neurological deterioration. The evidence was at high risk of bias and showed serious indirectness and imprecision.
- Very-low-quality evidence from 2 RCTs comprising 2090 participants demonstrated a clinical benefit of albumin for neurological sequelae. The evidence was at serious risk of bias and showed serious indirectness and very serious imprecision.

6.1.1.4.1.3 Albumin versus crystalloids

Albumin versus 0.9% sodium chloride

- Very-low-quality evidence from a single RCT comprising 33 participants demonstrated no clinical difference between albumin and crystalloids for length of hospital stay. The evidence was at very serious risk of bias and showed serious imprecision.

6.1.1.4.1.4 Balanced crystalloids versus hypertonic sodium chloride in children with trauma

Ringer's lactate solution versus hypertonic sodium chloride

- Very-low-quality evidence from 4 RCTs comprising 217 participants demonstrated no clinical difference between Ringer's lactate solution and hypertonic sodium chloride for mortality. The evidence showed very serious inconsistency, serious indirectness and very serious imprecision.
- Very-low-quality evidence from a single RCT comprising 32 participants demonstrated a clinical benefit of hypertonic sodium chloride over Ringer's lactate solution for incidence of acute respiratory distress syndrome. The evidence was at serious risk of bias and showed serious imprecision.
- Very-low-quality evidence from a single RCT comprising 32 participants demonstrated a clinical benefit of hypertonic sodium chloride over Ringer's lactate solution for arrhythmia. The evidence was at serious risk of bias and showed very serious imprecision.
- Low-quality evidence from a single RCT comprising 32 participants demonstrated a clinical benefit of Ringer's lactate solution over hypertonic sodium chloride for length of hospital stay. The evidence was at serious risk of bias and showed serious imprecision.

6.1.1.4.2 Economic

- No relevant economic evaluations were identified.

6.1.2 Volume and rate of administration for fluid resuscitation

6.1.2.1 Review question 6: What is the most clinically- and cost-effective volume and rate of administration for IV fluid resuscitation?

For full details see the review protocols in Appendix C.

Table 30: PICO characteristics of review question

Population	• Neonates born at term, infants, children and young people (up to their 16th birthday) in hospital; • Critically ill patients, for instance those undergoing surgery with expected blood loss over 10% blood volume, with severe sepsis or septic shock, severe burns, acute gastroenteritis, gastrointestinal haemorrhage, dengue shock syndrome, admitted to an intensive care and a trauma unit with suspected hypovolaemia and/or hypotension and other electrolyte disturbances (for example hypernatraemia, hypokalaemia, metabolic acidosis or alkalosis).
Intervention(s)	Isotonic crystalloid solution; 0.9% sodium chloride at "x" ml/kg/15 minutes
Comparison(s)	Isotonic crystalloid solution; 0.9% sodium chloride at "y" ml/kg/15 minutes
Outcomes	**Critical** • Mortality at 28 days (dichotomous) • Neurological compromise (return to baseline activity, ischaemic injury, cerebral oedema) (dichotomous) • Cardiovascular compromise (blood pressure (BP)/arterial pressure, heart rate) (dichotomous) **Important** • Length of hospital stay (continuous) • Hyperchloraemic acidosis (dichotomous) • Quality of life (continuous) • Hypoglycaemia (dichotomous) • Hypernatraemia (dichotomous) • Hyponatraemia (dichotomous)
Study design	Order of preference for study designs: • Systematic reviews of RCTs which meet our PICOs • Randomised control trials Where no RCTs are available, we will consider: • Abstracts on RCTs Where no RCTs or abstracts of RCTs are available, we will consider: • Non-randomised trials: prospective or retrospective cohort studies of 50 children or more • Non-blinded, single and double-blinded trial will be included

6.1.2.2 Clinical evidence

We searched for systematic reviews, RCTs and cohort studies in children.

The GDG did not consider that evidence in an adult population was relevant as the optimum rate of fluid administration is likely to differ for children and adults as the fluid requirements for children are higher.

No relevant clinical studies comparing sodium chloride at different rates were identified.

6.1.2.3 Economic evidence

6.1.2.3.1 Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

6.1.2.4 Evidence statements

6.1.2.4.1 Clinical

- No relevant clinical evidence was identified.

6.1.2.4.2 Economic

- No relevant economic evaluations were identified.

6.1.2.5 Recommendations and link to evidence

Recommendations	**10. If children and young people need IV fluid resuscitation, use glucose-free crystalloids[k] that contain sodium in the range 131–154 mmol/litre, with a bolus of 20 ml/kg over less than 10 minutes. Take into account pre-existing conditions (for example, cardiac disease or kidney disease), as smaller fluid volumes may be needed.** **11. If term neonates need IV fluid resuscitation, use glucose-free crystalloids[l] that contain sodium in the range 131–154 mmol/litre, with a bolus of 10–20 ml/kg over less than 10 minutes.** **12. Do not use tetrastarch for fluid resuscitation.** **13. For guidance on using IV fluids for fluid resuscitation in children and young people with diabetic ketoacidosis, see the diabetic ketoacidosis section in 'Diabetes (type 1 and type 2) in children and young people' (NICE guideline NG18).** **14. Reassess term neonates, children and young people after completion of the IV fluid bolus, and decide whether they need more fluids.** **15. Seek expert advice (for example, from the paediatric intensive care team) if 40–60 ml/kg of IV fluid or more is needed as part of the initial fluid resuscitation.**
Relative values of different outcomes	Mortality at 28 days, neurological compromise and cardiovascular compromise were considered to be critical outcomes. The GDG felt that it was crucial that neurological and cardiovascular compromise were specified as actual clinical outcomes (that is, cerebral oedema, vascular event) and that surrogate measures should not be

[k] At the time of publication (December 2015), some glucose free-crystalloids did not have a UK marketing authorisation for use in children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[l] At the time of publication (December 2015), some glucose free-crystalloids did not have a UK marketing authorisation for use in children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

	considered as these are less likely to have an effect on clinical outcomes. Length of hospital stay, hyperchloraemic acidosis, quality of life, hypoglycaemia, hypernatraemia and hyponatraemia were considered important outcomes.
Trade-off between clinical benefits and harms	**Fluid type** **In children and young people with sepsis** No clinical difference was found for dextran compared to Ringer's lactate solution, gelatin compared to 0.9% sodium chloride, dextran compared to 0.9% sodium chloride, gelatin compared to Ringer's lactate solution and albumin compared to 0.9% sodium chloride. All of these studies were in a population of children with dengue shock syndrome except gelatin compared to 0.9% sodium chloride for which there was evidence in a direct and indirect population. A clinical benefit was found for gelatin compared to dextran in a direct population for change in heart rate at 8 hours, but no difference for mortality was found for the same comparison. There was a clinical benefit of albumin compared to synthetic colloids for mortality. There was a clinical benefit of synthetic colloids compared to albumin for change in neurological compromise. In an indirect population with malaria there was no clinical difference for mortality at 28 days or pulmonary oedema, but a clinical benefit of albumin at 8 hours (indirect time) and for neurological deterioration and neurological sequelae. **In children and young people with trauma** There was no clinical difference between hypertonic sodium chloride and Ringer's lactate solution for mortality. There was a clinical benefit of hypertonic sodium chloride compared to Ringer's lactate solution for cardiovascular compromise and a clinical benefit of Ringer's lactate solution compared to hypertonic sodium chloride for length of stay in hospital. It was noted that the majority of the evidence was in children with burns. **Overall** The majority of the evidence included was considered to be indirect as the studies were conducted in populations of children with dengue shock syndrome or malaria. The GDG noted that the countries where the studies were conducted used procedures that largely differed from the UK. The direct evidence was sparse and did not show convincing benefits to overturn common practice and therefore this recommendation was based on GDG consensus. Overall, the GDG agreed that isotonic crystalloids are used in current practice and would be considered for term neonates, children and young people who require fluids. Given the lack of evidence to suggest a benefit of using an alternate fluid, the GDG chose to recommend the use of isotonic crystalloids. There was a lack of evidence to recommend one isotonic crystalloid over another, and therefore the GDG chose not to specify which isotonic fluid to use but noted that there was likely to be a range of fluids available to most healthcare professionals. However, the GDG noted that 0.9% sodium chloride would be appropriate for the majority of clinical scenarios. Resuscitation fluids containing potassium should be used cautiously in children at risk of hyperkalaemia as a rapid increase in potassium is cardiotoxic and has been associated with mortality. **Rate of fluid administration** **Children and young people** Children with shock need immediate restoration of intravascular blood volume. It is current practice to administer 20 ml/kg over less than 10 minutes. No evidence was

	identified to change current practice. The GDG felt it important to reassess the circulation following completion of the fluid bolus and administer further fluids if indicated. Children often require multiple fluid boluses. Specialist advice should be sought for further management when 60 ml/kg has been administered as intensive care support or input may be necessary. **Term neonates** For term neonates, the GDG considered that it was appropriate to treat shock with an initial bolus of 10 ml/kg–20 ml/kg, given over less than 10 minutes. When babies are born their percentage composition of water is higher, hence an initial bolus of 10 ml/kg may be more appropriate for resuscitation of the newborn. They also have low glomerular filtration rates. The GDG recommended higher volumes, up to 20 ml/kg over less than 10 minutes, for resuscitation in term neonates outside of the newborn period. There is no evidence that would indicate a change of practice is required. HES starches were not included in the review. Further details on the exclusion of HES starches from this review can be found in Chapter 3.
Economic considerations	No economic evidence was found in relation to the optimum fluid type or rate of fluid administration for term neonates, children or young people. **Fluid type** The unit costs of isotonic crystalloids (0.9% sodium chloride, Hartmann's solution, Ringer's lactate solution and Plasma-Lyte) are not significantly different from each other and no differences in administration or monitoring costs are expected to be associated with different fluid strategies. The consensus view of the GDG was that isotonic crystalloids were effective in treating resuscitation in children, but no convincing evidence existed to show a difference in clinical benefit between specific types of isotonic crystalloids. It was therefore considered likely that they are equally cost effective given their low and similar unit cost. As no convincing evidence on effectiveness was found to support the use of synthetic or non-synthetic colloids over isotonic crystalloids for routine use, and as these fluids have a higher unit cost, the GDG considered it unlikely that they would be cost effective. **Rate of fluid administration** The GDG believed that no differences in administration or monitoring costs are expected to be associated with the different rates of IV fluid administration for resuscitation, given that the different volumes per bolus are to be administered over the same time period (10 minutes for initial resuscitation). The administered volume is determined on an individual basis and has to be tailored according to the child's condition and clinical need. The GDG believed that this would lead to optimised outcomes and, hence, is likely to be cost effective. As no evidence on effectiveness was found, the recommendations were based on the GDG's expert opinion and current practice.
Quality of evidence	**Fluid type** The GDG considered that the evidence identified was graded as low to very low quality. The majority of studies were in an indirect population for sepsis (that is, those with dengue shock syndrome and malaria). For evidence that did show a clinical benefit there was serious to very serious imprecision in the results and the evidence was graded as low to very low quality.

	The GDG identified that in a number of studies, the care provided is not representative of care in the UK and therefore it was not suitable to base recommendations on these studies. The GDG did not feel that there was any consistent evidence identified to support the use of albumin for routine use, and noted the studies' indirect populations. No studies were identified for children during the perioperative period. No studies including term neonates were found for any fluid type for resuscitation. **Rate of fluid administration** No evidence was identified on the optimum rate of fluid administration in term neonates, children or young people.
Other considerations	The GDG noted the FEAST study[23-25] findings which included fluid boluses of albumin versus 0.9% sodium chloride compared to no fluid bolus in children in Africa with severe infection. Administration of fluid without a bolus was not included as a comparison in our protocol as the GDG did not consider this to be clinical practice within the UK. However, the study did demonstrate more deaths for both albumin and 0.9% sodium chloride fluid boluses when compared to no fluid bolus. The deaths were caused by underlying conditions, but there remains a question as to why the fluid boluses increased the likelihood of death. The FEAST study acknowledges that this challenges whether boluses should be used for resuscitation in resource-limited settings for children with shock who do not have hypotension, and questions their use in other settings. The GDG felt that although this is an important finding, the situation is not directly applicable to the UK clinical setting. The GDG also noted that another large study (the SAFE study[17]) looked at 0.9% sodium chloride compared to 4% albumin in adults. There was little difference in outcomes within this study between the 2 fluids, however albumin is of much greater cost than 0.9% sodium chloride. Recommendations on the prescription and administration of resuscitation fluid in children and young people who have diabetic ketoacidosis can be found in NICE clinical guideline 'Diabetes (type 1 and type 2) in children and young people' (NICE guideline NG18). Recommendations on the prescription and administration of IV fluids in children with major trauma can be found in 'Major trauma' (NICE guideline, publication expected February 2016). The GDG identified that there may be some religious groups who choose to abstain from certain fluids (for example, Jehovah's witnesses and the use of albumin) and people who choose to abstain from the use of IV fluids because of fasting. It was identified that where there was a clinical need for the fluid and the parent/carer refused treatment, the child should become a ward of court and legally, the appropriate clinical treatment may then be given.

7 IV fluid therapy for routine maintenance

7.1 Introduction

IV maintenance fluid is widely administered in general paediatric practice, but there is considerable debate about the best IV fluids to use, particularly for seriously ill children. Isotonic solutions (0.9% sodium chloride) are most commonly used, as they are physiologically similar to plasma, but 0.9% sodium chloride has been associated with an increase of acidosis in adults. Hypotonic solutions can provide the daily sodium requirements in healthy patients, but may be associated with increased risk of adverse effects (including hyponatraemia) in ill patients. The paucity of high-quality studies to inform clinical decision making has resulted in wide variation in clinical practice.
Deciding on the optimal composition and rate of IV fluid administration can be a difficult and complex task, and decisions must be based on careful assessment of the patient's individual needs.

Errors in prescribing IV fluids and electrolytes are well described. It has been estimated that as many as 1 in 5 patients receiving IV fluids and electrolytes suffer complications due to inappropriate administration and this may be associated with cardiovascular, respiratory, neurological, renal and multi-organ compromise. Surveys have shown that many staff who prescribe IV fluids know neither the likely fluid and electrolyte needs of individual patients, nor the specific composition of the many choices of IV fluids available to them. IV fluid management in hospital requires experienced staff who have received specific training.

7.1.1 Fluid type for routine maintenance

7.1.1.1 Review question 7: What is the most clinically- and cost-effective fluid type for IV fluid maintenance in children?

For full details see the review protocols in Appendix C.

Table 31: PICO characteristics of review question

Population	Neonates born at term, infants, children and young people up to their 16th birthday receiving routine IV fluid maintenance therapy including following elective surgery, gastroenteritis, pneumonia, meningitis, bronchiolitis.
Intervention(s)	• Isotonic crystalloid (0.9% sodium chloride) • Isotonic crystalloid solution (0.9% sodium chloride/Hartmann's solution/Plasma-Lyte/Ringer's lactate solution) + glucose (up to 2.5%, 2.6%–5%, 5.1%–10%) + potassium chloride (20 mmol/litre or 40 mmol/litre) • Isotonic crystalloid solution (0.9% sodium chloride/Hartmann's solution/Plasma-Lyte/Ringer's lactate solution) + glucose (up to 2.5%, 2.6%–5%, 5.1%–10%) • Isotonic crystalloid solution (0.9% sodium chloride/Hartmann's solution/Plasma-Lyte/Ringer's lactate solution) + potassium chloride (20 mmol/litre or 40 mmol/litre) • Hypotonic sodium chloride • Hypotonic sodium chloride + glucose (up to 2.5%, 2.6%–5%, 5.1%–10%) + potassium chloride (20 mmol/litre or 40 mmol/litre) • Hypotonic sodium chloride + glucose (up to 2.5%, 2.6%–5%, 5.1%–10%) • Hypotonic sodium chloride + potassium chloride (20 mmol/litre or 40 mmol/litre) • 10% glucose (without electrolytes) (neonates)
Comparison(s)	• To each other
Outcomes	**Critical** • Mortality at 28 days

	• Neurological compromise (return to baseline activity, ischaemic injury, cerebral oedema) • Cardiovascular compromise (blood pressure (BP)/arterial pressure, heart rate) **Important** • Hospital stay • Hyperchloraemic acidosis • Quality of life • Hypoglycaemia • Hypernatraemia • Hyponatraemia
Study design	Order of preference for study designs: • Systematic reviews of randomised control trials (RCTs) which meet our PICOs • RCTs Where no RCTs are available, we will consider: • Abstracts on RCTs Where no RCTs or abstracts of RCTs are available, we will consider: • Non-randomised trials: prospective or retrospective cohort studies of 50 children or more • Non-blinded, single and double-blinded trials will be included Where no randomised or non-randomised evidence in children are available, we will consider: • Systematic reviews of RCTs which meet our PICOs in adults • Randomised control trials in adults Where no RCTs in adults are available, we will consider: • Abstracts on RCTs in adults • Non-randomised trials: prospective or retrospective cohort studies of 1000 adults or more

7.1.1.2 Clinical evidence

We searched for systematic reviews, RCTs and cohort studies in children, or adults if no evidence in children was available. The GDG considered that findings from studies conducted in adults could be transferred to an infant and child population and therefore the literature search included studies conducted in an adult population. Ten RCTs were included in the review;[3,4,6,10,12,21,27,33,36,40] these are summarised in Table 32 below.

The studies were grouped according to the type of fluid included; isotonic solution versus isotonic and glucose solution and isotonic solution versus hypotonic solution (with and without glucose). We have arranged the review by the stratum investigated, which included: term neonates up to 48 hours, term neonates from 48 hours to 28 days, infants and children from 28 days to 16 years and children being treated on a specialist ward.

Evidence from these studies is summarised in the clinical evidence summary tables below (Table 33, Table 34, Table 35, Table 36 and Table 37). See also the study selection flow chart in Appendix D, study evidence tables in Appendix G, forest plots in Appendix J, GRADE tables in Appendix I and excluded studies list in Appendix K.

Table 32: Summary of studies included in the review

Study	Intervention/comparison	Population	Outcomes
Balasubramanian 2012[3]	0.9% sodium chloride in 5% dextrose versus 0.2% sodium chloride in 5% dextrose	Full-term neonates presenting with severe non-haemolytic hyperbilirubinemia	Hyponatraemia; hypernatraemia
Baron 2013[4]	Isotonic crystalloid (sodium 154 mmol/litre) versus hypotonic crystalloid (77 sodium mmol/litre)	Children aged 1 month to 18 years old with an expected PICU stay of more than 24 hours	Mortality; length of stay in ICU; hyponatraemia; hypernatraemia
Bell 1993[6]	0.9% sodium chloride versus Ringer's lactate solution plus 5% dextrose	Non-diabetic children undergoing cardiac surgery with deep hypothermia	Mortality; cardiorespiratory arrest; mean days in ICU; mean days to discharge from hospital; hypoglycaemia
Choong 2011[10]	0.9% sodium chloride with 5% dextrose versus 0.45% sodium chloride with 5% dextrose	Euvolaemic patients, 6 months to 16 years of age, within 6 hours after elective surgery were eligible if their anticipated in-patient period was >24 hours	Hyponatraemia; hypernatraemia
Coulthard 2012[12]	Hartmann's solution and 5% dextrose solution versus 0.45% sodium chloride and 5% dextrose solution	Children were eligible for enrolment if they were admitted to the PICU following spinal instrumentation for correction of scoliosis, craniotomy for excision of brain tumours and cranial vault remodelling	Hyponatraemia; hypernatraemia
Kannan 2010[21]	0.9% sodium chloride in 5% dextrose versus 0.18% sodium chloride in 5% dextrose	Children who were judged by the treating physician to require IV fluid maintenance fluid administration for at least the following 24 hours of their hospital stay	Mortality; hyponatraemia; hypernatremia
Montanana 2008[27]	0.9% sodium chloride in 5% dextrose versus 0.45% sodium chloride in 5% dextrose	Children requiring hospitalisation when their physician prescribed IV maintenance fluid therapy	Hyponatraemia; hypernatraemia; hypoglycaemia
Neville 2010[33]	0.9% sodium chloride in 2.5% dextrose versus	Children undergoing elective or	Hyponatraemia; hypernatraemia;

Study	Intervention/comparison	Population	Outcomes
	0.45% sodium chloride in 2.5% dextrose	emergency surgery aged between 6 months and 15 years, were expected to be taking nothing by mouth for at least 8 hours after surgery and weighed more than 8 kg	hypoglycaemia
Nicolson 1992[36]	Ringer's lactate solution versus Ringer's lactate solution plus 5% dextrose	Fasted infants under 1 year of age scheduled for elective cardiac surgery using hypothermic bypass with circulatory arrest	Neurological sequelae (gross motor seizures – tonic-clonic motor activity)
Saba 2011[40]	0.9% sodium chloride in 5% dextrose versus 0.45% sodium chloride in 5% dextrose	Children with medical illnesses admitted via the emergency department (medical), and children admitted following elective surgery (surgical). Only those requiring at least 8 hours of IV fluids were eligible.	Hyponatraemia; hypernatraemia;

Table 33: Clinical evidence summary: Ringer's lactate solution versus Ringer's lactate solution plus 5% dextrose

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Ringer's lactate solution plus 5% dextrose	Risk difference with Ringer's lactate solution versus Ringer's lactate solution plus 5% dextrose (95% CI)
Neurological sequelae (gross motor seizures)	36 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.3 (0.03 to 2.6)	177 per 1000	124 fewer per 1000 (from 172 fewer to 283 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 34: Clinical evidence summary: 0.9% sodium chloride compared to Ringer's lactate solution plus 5% dextrose

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Ringer's lactate solution plus 5% dextrose	Risk difference with 0.9% sodium chloride versus Ringer's lactate solution plus 5% dextrose (95% CI)
Mortality	33 (1 study)	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	Peto OR 0.14 (0 to 7.25)	59 per 1000	50 fewer per 1000 (from 59 fewer to 254 more)
Cardiorespiratory arrest	33 (1 study)	VERY LOW[a,c] due to risk of bias, imprecision	Peto OR 0.13 (0.01 to 2.26)	118 per 1000	101 fewer per 1000 (from 117 fewer to 114 more)

Mean days in ICU	33 (1 study)	VERY LOW[a,c] due to risk of bias, imprecision		6.31 (SD 2.26)	The mean days in ICU in the intervention groups was 3.25 lower (6.51 lower to 0.01 higher)
Mean days to discharge from hospital	33 (1 study)	LOW[a] due to risk of bias		7.6 (SD 2.1)	The mean days to discharge from hospital in the intervention groups was 4.1 lower (5.83 to 2.37 lower)
Hypoglycaemia	33 (1 study)	LOW[a] due to risk of bias	Not estimable	–	

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Mortality not at 28 days; 1 of the patients with cardiorespiratory arrest subsequently died
(c) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 35: Clinical evidence summary: Isotonic versus hypotonic solutions for routine maintenance in children aged 48 hours to 28 days

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with hypotonic solutions – 48 hours to 28 days	Risk difference with isotonic solutions versus hypotonic solutions (95% CI)
Hyponatraemia <135mmol sodium	84 (1 study) 24 hours	HIGH	RR 0.17 (0.05 to 0.52)	429 per 1000	356 fewer per 1000 (from 206 fewer to 408 fewer)
Severe hyponatraemia <130 mmol sodium	84 (1 study) 8 hours	LOW[a] due to imprecision	Peto OR 0.13 (0.01 to 2.15)	48 per 1000	50 fewer per 1000 (from 120 fewer to 30 more)

Hypernatraemia >145 mmol sodium	84 (1 study) 24 hours	HIGH	RR 3.5 (1.26 to 9.76)	95 per 1000	237 more per 1000 (from 25 more to 832 more)

(a) Downgraded by 2 increments if the confidence interval crossed both MIDs

Table 36: Clinical evidence summary: Isotonic versus hypotonic solutions for routine maintenance in children aged 28 days to 16 years

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with hypotonic solutions – 28 days to 16 years	Risk difference with isotonic solutions versus hypotonic solutions (95% CI)
Mortality	114 (1 study) 28 days	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 7.14 (0.14 to 359.98)	0 per 1000	20 more per 1000 (from 30 fewer to 60 more)
Hyponatraemia <135 mmol sodium	357 (3 studies)	MODERATE[c] due to inconsistency	RR 0.5 (0.35 to 0.73)	290 per 1000	145 fewer per 1000 (from 78 fewer to 189 fewer)
Severe hyponatraemia <130 mmol sodium	471 (4 studies)	HIGH	Peto OR 0.19 (0.07 to 0.5)	31 per 1000	60 fewer per 1000 (from 100 fewer to 20 fewer)
Hypernatraemia >145 mmol sodium	471 (4 studies)	LOW[b] due to imprecision	RR 1.16 (0.46 to 2.93)	18 per 1000	3 more per 1000 (from 10 fewer to 35 more)

Hypoglycaemia <60 mg/dL glucose	62 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.67 (0.12 to 3.72)	97 per 1000	32 fewer per 1000 (from 85 fewer to 264 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
(c) The point estimate varies widely across studies, unexplained by subgroup analysis

Table 37: Clinical evidence summary: Isotonic versus hypotonic solutions for routine maintenance in children treated in a specialist unit

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with hypotonic solutions – specialist unit	Risk difference with isotonic solutions versus hypotonic solutions (95% CI)
Mortality	63 (1 study) 28 days	LOW[a] due to imprecision	Peto OR 0.13 (0.01 to 1.31)	94 per 1000	90 fewer per 1000 (from 210 fewer to 20 more)
Length of PICU stay	63 (1 study)	LOW[a,b] due to risk of bias, imprecision			The mean length of PICU stay in the intervention groups was 3.5 higher (0.97 lower to 7.97 higher)
Hyponatraemia <135 mmol sodium	264 (3 studies)	HIGH	RR 0.31 (0.14 to 0.67)	175 per 1000	121 fewer per 1000 (from 58 fewer to 150 fewer)

Severe Hyponatraemia <130 mmol sodium	264 (3 studies)	MODERATE[a] due to imprecision	Peto OR 0.14 (0.02 to 0.81)	31 per 1000	40 fewer per 1000 (from 80 fewer to 0 fewer)
Hypernatraemia >145 mmol sodium	264 (3 studies)	VERY LOW[a,c] due to inconsistency, imprecision	Peto OR 0.7 (0.12 to 4.1)	16 per 1000	10 fewer per 1000 (from 40 fewer to 30 more)
Hypoglycaemia <60 mg/dL glucose	122 (1 study)	LOW[a] due to imprecision	Peto OR 7.91 (0.16 to 399.35)	0 per 1000	20 more per 1000 (from 30 fewer to 60 more)

(a) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
(b) Downgraded by 1 increment if the majority of the evidence was at high risk of bias
(c) The point estimate varies widely across studies, unexplained by subgroup analysis

7.1.1.3 Economic evidence

7.1.1.3.1 Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

7.1.1.3.2 Unit costs

The unit costs of the IV fluids that are used for maintenance are presented in Table 38.

Table 38: Unit costs of IV fluids for maintenance of fluid balance

IV fluid	Unit cost (500 ml pre-mixed bag)[a]	Source
Isotonic crystalloids		
0.9% sodium chloride	£0.63	Nottingham University Hospitals NHS Trust, Pharmacy Department
0.9% sodium chloride, 5% glucose	£1.20	Nottingham University Hospitals NHS Trust, Pharmacy Department
0.9% sodium chloride, 5% glucose with 10 mmol/litre potassium	£2.98	Nottingham University Hospitals NHS Trust, Pharmacy Department
0.9% sodium chloride, 5% glucose with 20 mmol/litre potassium	£3.62	Nottingham University Hospitals NHS Trust, Pharmacy Department
0.9% sodium chloride, 20 mmol/litre potassium	£0.76	Nottingham University Hospitals NHS Trust, Pharmacy Department
Hartmann's solution (compound sodium lactate)	£0.70	Nottingham University Hospitals NHS Trust, Pharmacy Department
Ringer's lactate solution	£0.70	Department of Health Commercial Medicines Unit (CMU)[11]
Plasma-Lyte 148	1000 ml = £1.04	Nottingham University Hospitals NHS Trust, Pharmacy Department
Plasma-Lyte 148, 5% glucose	1000 ml = £1.04	Nottingham University Hospitals NHS Trust, Pharmacy Department
Hypertonic crystalloids		
2.7% sodium chloride	£2.75	Nottingham University Hospitals NHS Trust, Pharmacy Department
Glucose		
10% glucose (100 mg/mL)	£0.58	Nottingham University Hospitals NHS Trust, Pharmacy Department

(a) VAT is not included in these unit costs

7.1.1.4 Evidence statements

7.1.1.4.1 Clinical

7.1.1.4.1.1 Addition of glucose

Ringer's lactate solution versus Ringer's lactate solution plus 5% dextrose

- Very-low-quality evidence from a single RCT comprising 36 participants demonstrated a clinical benefit of Ringer's lactate solution compared to Ringer's lactate solution plus 5% dextrose for neurological sequelae (gross motor seizures). The evidence was at serious risk of bias and very serious risk of imprecision.

0.9% sodium chloride versus Ringer's lactate solution plus 5% dextrose

- Very-low-quality evidence from a single RCT comprising 33 participants demonstrated a clinical benefit of 0.9% sodium chloride compared to Ringer's lactate solution plus 5% dextrose for mortality. The evidence was downgraded due to very serious risk of bias and imprecision.
- Very-low-quality evidence from a single RCT comprising 33 participants demonstrated a clinical benefit of 0.9% sodium chloride compared to Ringer's lactate solution plus 5% dextrose for cardiorespiratory arrest. The evidence was downgraded due to very serious risk of bias and imprecision.
- Very-low-quality evidence from a single RCT comprising 33 participants demonstrated a clinical benefit of 0.9% sodium chloride compared to Ringer's lactate solution plus 5% dextrose for mean days in ICU. The evidence was at serious risk of bias and very serious risk of imprecision.
- Low-quality evidence from a single RCT comprising 33 participants demonstrated a clinical benefit of 0.9% sodium chloride compared to Ringer's lactate solution plus 5% dextrose for mean days to discharge from hospital. The evidence was at very serious risk of bias but demonstrated no imprecision.
- Low-quality evidence from a single RCT comprising 33 participants demonstrated no clinical difference between 0.9% sodium chloride and Ringer's lactate solution plus 5% dextrose for hypoglycaemia. The evidence was at very serious risk of bias but demonstrated no imprecision.

7.1.1.4.1.2 Children aged 48 hours to 28 days

Hypotonic solution versus isotonic solution

- High-quality evidence from a single RCT comprising 84 participants demonstrated a clinical benefit of an isotonic solution compared to a hypotonic solution for hyponatraemia.
- Low-quality evidence from a single RCT comprising 84 participants demonstrated a clinical benefit of an isotonic solution compared to a hypotonic solution for severe hyponatraemia. The evidence was at very high risk of imprecision.
- High-quality evidence from a single RCT comprising 84 participants demonstrated a clinical benefit of a hypotonic compared to an isotonic solution for hypernatraemia.

7.1.1.4.1.3 Children aged 28 days to 16 years

Hypotonic solution versus isotonic solution

- Very-low-quality evidence from a single RCT comprising 114 participants demonstrated a clinical benefit of a hypotonic solution compared to an isotonic solution for mortality. The evidence was at serious risk of bias and very serious risk of imprecision.
- Moderate-quality evidence from 3 RCTs comprising 357 participants demonstrated a clinical benefit of an isotonic solution compared to a hypotonic solution for hyponatraemia. The evidence demonstrated no imprecision or bias but was at serious risk of inconsistency.
- High-quality evidence from 4 RCTs comprising 471 participants demonstrated a clinical benefit of an isotonic solution compared to a hypotonic solution for severe hyponatraemia.
- Low-quality evidence from 4 RCTs comprising 471 participants demonstrated no clinical difference between an isotonic solution and a hypotonic solution for hypernatremia. The evidence was at very high risk of imprecision.

- Very-low-quality evidence from a single RCT comprising 62 participants demonstrated no clinical difference between an isotonic solution and a hypotonic solution for hypoglycaemia. The evidence was at serious risk of bias and very serious risk of imprecision.

7.1.1.4.1.4 Children in a specialist unit

Hypotonic solution versus isotonic solution

- Low-quality evidence from a single RCT comprising 63 participants demonstrated a clinical benefit of an isotonic solution compared to a hypotonic solution for mortality. The evidence was at very serious risk of imprecision.
- Low-quality evidence from a single RCT comprising 63 participants demonstrated a clinical benefit of a hypotonic solution compared to an isotonic solution for length of PICU stay. The evidence was at serious risk of bias and imprecision.
- High-quality evidence from 3 RCTs comprising 264 participants demonstrated a clinical benefit of an isotonic solution compared to a hypotonic solution for hyponatraemia.
- Moderate-quality evidence from 3 RCTs comprising 264 participants demonstrated a clinical benefit of an isotonic solution compared to a hypotonic solution for severe hyponatraemia. The evidence was at serious risk of imprecision.
- Very-low-quality evidence from 3 RCTs comprising 264 participants demonstrated no clinical difference between isotonic solution and hypotonic solutions for hypernatremia. The evidence demonstrated a very serious risk of imprecision and serious risk of inconsistency.
- Very-low-quality evidence from a single RCT comprising 122 participants demonstrated no clinical difference between isotonic solution and hypotonic solutions for hypoglycaemia. The evidence demonstrated a very serious risk of imprecision.

7.1.1.4.2 Economic

- No relevant economic evaluations were identified.

7.1.2 Rate of administration for routine maintenance

7.1.2.1 Review question 8: What is the most clinically- and cost-effective rate of administration of IV fluids for routine maintenance?

For full details see the review protocols in Appendix C.

Table 39: PICO characteristics of review question

Population	Neonates born at term, infants, children and young people up to their 16th birthday receiving routine IV fluid maintenance therapy including following elective surgery, gastroenteritis, pneumonia, meningitis, bronchiolitis
Intervention(s)	Any rate calculation at maintenance or reduced maintenance rate
Comparison(s)	Any other rate calculation at maintenance or reduced maintenance rate
Outcomes	**Critical** • Mortality at 28 days • Neurological compromise (return to baseline activity, ischaemic injury, cerebral oedema) • Cardiovascular compromise (blood pressure (BP)/arterial pressure, heart rate) • Other organ dysfunction, for example, renal, respiratory compromise (for rate question only) **Important** • Hospital stay

	• Hyperchloraemic acidosis • Quality of life • Hypoglycaemia • Hyponatraemia • Hypernatraemia
Study design	Order of preference for study designs: • Systematic reviews of RCTs which meet our PICOs • Randomised control trials Where no RCTs are available, we will consider: • Abstracts on RCTs Where no RCTs or abstracts of RCTs are available, we will consider: • Non-randomised trials: prospective or retrospective cohort studies of 50 children or more. • Non-blinded, single and double-blinded trials will be included

7.1.2.2 Clinical evidence

We searched for systematic reviews, RCTs and cohort studies in children. The GDG did not consider that evidence in an adult population was relevant as the fluid requirements for children are higher than adults and adult data cannot be extrapolated.

Two studies were included in the review [33,45] and are summarised in Table 40.

The studies were grouped according to the rate of fluid administered; isotonic solution at normal maintenance rate versus isotonic at restricted maintenance rate. We have arranged the review by the stratum investigated, which included: term neonates up to 48 hours, term neonates from 48 hours to 28 days, infants and children from 28 days to 16 years and children being treated on a specialist ward.

Evidence from these studies is summarised in the GRADE clinical evidence profile (Appendix I) and the clinical evidence summary tables below (Table 41 and Table 42). See also the study selection flow chart in Appendix D, study evidence tables in Appendix G, forest plots in Appendix J, GRADE tables in Appendix I and excluded studies list in Appendix K.

Table 40: Summary of studies included in the review

Study	Intervention/comparison	Population	Outcomes
Neville 2010	0.9% isotonic sodium chloride at normal maintenance rate versus 0.9% isotonic sodium chloride at half maintenance rate	Children between 6 months and 15 years undergoing elective and non-elective surgery for over 8 hours	Hyponatraemia; hypernatraemia; hypoglycaemia
Yung 2009	Isotonic crystalloid at normal maintenance rate versus isotonic crystalloid at half normal rate	Children admitted to a PICU receiving IV fluids	Hypoglycaemia

Table 41: Clinical evidence summary: Normal maintenance versus restricted maintenance rate

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with restricted maintenance rate	Risk difference with isotonic crystalloid at normal maintenance rate versus restricted maintenance rate (95% CI)
Hyponatraemia (sodium level <135 mmol/litre)	62 (1 study) 8 hours	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.2 (0.02 to 1.61)	161 per 1000	129 fewer per 1000 (from 158 fewer to 98 more)
Hyponatraemia (sodium level <135 mmol/litre)	31 (1 study) 24 hours	VERY LOW[a,b] due to risk of bias, imprecision	RR 2.53 (0.32 to 19.99)	83 per 1000	127 more per 1000 (from 56 fewer to 1000 more)
Hypernatraemia (sodium level >145 mmol/litre)	62 (1 study) 8 hours	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 0.13 (0.01 to 1.26)	97 per 1000	83 fewer per 1000 (from 96 fewer to 22 more)
Hypoglycaemia	62 (1 study) 24 hours	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 7.64 (0.47 to 124.98)	0 per 1000	60 more per 1000 (from 0 more to 170 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 42: Clinical evidence summary: Normal maintenance versus restricted maintenance rate in a specialist unit

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with restricted maintenance rate – specialist unit	Risk difference with isotonic crystalloid at normal maintenance rate versus restricted maintenance rate (95% CI)
Hypoglycaemia	24 (1 study) 24 hours	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 8.86 (0.17 to 452.79)	0 per 1000	90 more per 1000 (from 0 more to 300 more)

(a) Downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) Downgraded by 2 increments if the confidence interval crossed both MIDs

7.1.2.3 Economic evidence

7.1.2.3.1 Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

7.1.2.4 Evidence statements

7.1.2.4.1 Clinical

Normal versus restricted maintenance rate

- Very-low-quality evidence from a single RCT comprising 62 participants demonstrated a clinical benefit of normal maintenance rate compared to a restricted rate for hyponatraemia at 8 hours. The evidence was at serious risk of bias and very serious risk of imprecision.
- Very-low-quality evidence from a single RCT comprising 31 participants demonstrated a clinical benefit of restricted maintenance rate compared to a normal rate for hyponatraemia at 24 hours. The evidence was at serious risk of bias and very serious risk of imprecision.
- Very-low-quality evidence from a single RCT comprising 62 participants demonstrated a clinical benefit of normal maintenance rate compared to a restricted rate for severe hypernatraemia at 8 hours. The evidence was at serious risk of bias and very serious risk of imprecision.
- Very-low-quality evidence from 2 RCTs comprising 86 participants demonstrated clinical benefit of restricted maintenance rate compared to a normal rate for hypoglycaemia. The evidence was at very high risk of bias and imprecision.

7.1.2.4.2 Economic

- No relevant economic evaluations were identified.

7.1.2.5 Recommendations and link to evidence

Recommendations	**16. Calculate routine maintenance IV fluid rates for children and young people using the Holliday–Segar formula (100 ml/kg/day for the first 10 kg of weight, 50 ml/kg/day for the next 10 kg and 20 ml/kg/day for the weight over 20 kg). Be aware that over a 24-hour period, males rarely need more than 2500 ml and females rarely need more than 2000 ml of fluids.** **17. Calculate routine maintenance IV fluid rates for term neonates according to their age, using the following as a guide:** • **From birth to day 1: 50–60 ml/kg/day.** • **Day 2: 70–80 ml/kg/day.** • **Day 3: 80–100 ml/kg/day.** • **Day 4: 100–120 ml/kg/day.**

	• **Days 5–28: 120–150 ml/kg/day.** **18. If children and young people need IV fluids for routine maintenance, initially use isotonic crystalloids[m] that contain sodium in the range 131–154 mmol/litre.** **19. Measure plasma electrolyte concentrations and blood glucose when starting IV fluids for routine maintenance (except before most elective surgery), and at least every 24 hours thereafter.** **20. Be aware that plasma electrolyte concentrations and blood glucose are not routinely measured before elective surgery unless there is a need to do so, based on the child's medical condition or the type of surgery.** **21. Base any subsequent IV fluid prescriptions on the plasma electrolyte concentrations and blood glucose measurements.** **22. If term neonates need IV fluids for routine maintenance, initially use isotonic crystalloids[n] that contain sodium in the range 131–154 mmol/litre with 5–10% glucose.** **23. For term neonates in critical postnatal adaptation phase (for example, term neonates with respiratory distress syndrome, meconium aspiration, hypoxic ischaemic encephalopathy), give no or minimal sodium until postnatal diuresis with weight loss occurs.** **24. If there is a risk of water retention associated with non-osmotic antidiuretic hormone (ADH) secretion, consider either:** o **restricting fluids to 50–80% of routine maintenance needs or** o **reducing fluids, calculated on the basis of insensible losses within the range 300–400 ml/m^2 /24 hours plus urinary output.** **25. When using body surface area to calculate IV fluid needs for routine maintenance (see recommendation 4), estimate insensible losses within the range 300–400 ml/m^2/24 hours plus urinary output.**
Relative values of different outcomes	Mortality at 28 days, neurological compromise and cardiovascular compromise were considered to be critical outcomes. The GDG felt that it was crucial that neurological and cardiovascular compromise were specified as actual clinical outcomes (that is, cerebral oedema, vascular event) and that surrogate measures should not be considered as these are less likely to have an effect on clinical outcomes. Length of hospital stay, hyperchloraemic acidosis, quality of life, hypoglycaemia,

[m] At the time of publication (December 2015), some isotonic crystalloids with 5–10% glucose did not have a UK marketing authorisation for use in children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[n] At the time of publication (December 2015), some isotonic crystalloids with 5–10% glucose did not have a UK marketing authorisation for use in children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

	hypernatraemia and hyponatraemia were considered important outcomes.
Trade-off between clinical benefits and harms	**Fluid type** Mortality was only reported in term neonates (aged 48 hours to 28 days) and in children within a specialist unit. Data from term neonates suggested a modest benefit with administration of hypotonic solution, but the GDG felt that the study was underpowered and too imprecise to be considered for recommendation. The GDG also considered the evidence in children within a specialist unit, which demonstrated a clinical benefit with an isotonic solution for mortality. The GDG considered the larger absolute risk difference but agreed that the low event rate made the data unreliable. The GDG felt that the incidence of hyponatraemia would provide a better outcome on which to base a recommendation and could act as a surrogate measure for more serious clinical events such as cardiovascular compromise not reported in the studies. Evidence was identified to suggest a clinical benefit of the use of isotonic fluids for the incidence of hyponatraemia and severe hyponatraemia in term neonates from 48 hours to 28 days, children aged 28 days to 16 years and those being treated within a specialist unit. The GDG discussed the data and felt that the results were likely to reflect clinical conditions as isotonic fluids have a physiologically similar sodium level to plasma, and patients are less likely to develop hyponatraemia with isotonic fluids. It was also noted that isotonic solutions may increase the risk of hypernatremia, but the GDG felt that, overall, hyponatraemia was considered to be a greater concern in the paediatric population. The GDG also considered the increased length of PICU stay within the isotonic arm when considering fluid type for children within a specialist unit, but felt that these data were unreliable as they were unadjusted for the higher mortality level in the isotonic arm of the trial. No studies were found comparing isotonic solutions including sodium chloride, Hartmann's solution and Ringer's lactate solution directly against each other for any strata, so the GDG did not consider it appropriate to specify a particular isotonic fluid. The GDG therefore chose to develop a recommendation supporting the use of isotonic solutions as the primary maintenance fluid in children and young people requiring IV fluids. The GDG also noted that there was no evidence specifically in term neonates from 0–48 hours and made an informal consensus recommendation for this stratum. **Addition of glucose** The GDG considered the evidence presented on the addition of glucose to the maintenance fluid. Evidence was identified to suggest that there was a benefit of Ringer's lactate solution on neurological sequelae when compared to Ringer's lactate solution with 5% dextrose. The evidence also suggested a clinical benefit of 0.9% sodium chloride compared to Ringer's lactate solution with 5% dextrose for mortality, cardiorespiratory arrest, mean days in ICU and mean days to hospital discharge. There was no benefit of either solution on the incidence of hypoglycaemia. No evidence was identified in term neonates (0–48 hours and 48 hours–28 days) for the addition of glucose. The GDG therefore chose to use informal consensus to develop a recommendation supporting the use of 0.9% sodium chloride for term neonates who require IV fluids for routine maintenance. The GDG chose to highlight that for term neonates in critical postnatal adaptation phase, sodium should be avoided or restricted until

	postnatal diuresis with weight loss occurs. The GDG noted that it would be considered standard practice for children and often young people to receive IV fluids with glucose and that this would likely continue. However, given the lack of benefit of additional glucose, the GDG chose to develop a research recommendation to encourage further research on the addition of glucose to maintenance fluid. **Fluid rate** Two studies were identified for inclusion within the review, however the GDG considered that these studies were of insufficient quality to assist with the recommendation and chose to use informal consensus to develop the recommendation (see quality of evidence). The GDG noted that the Holliday-Segar formula is widely used for calculating the rate of IV fluids in children and young people and is considered to be embedded in current practice. However, it should be noted that this calculation is based on maintenance fluid requirements of healthy children[19] and the majority of children receiving IV fluids within a current hospital setting are at risk of developing non-osmotic ADH secretion leading to water retention and subsequent hyponatraemia. It was the view of the group that fluid restriction alone would reduce the incidence of hyponatraemia and the GDG chose to develop a recommendation to reflect current practice, which was considered by the GDG to vary between 50–80% of routine maintenance needs. No evidence was found in either term neonate population. The GDG noted that the Holliday-Segar formula was not applicable to term neonates. As no evidence was identified on the most effective means of calculating maintenance fluid requirements in this population, the GDG chose to use informal consensus based on their clinical experience to develop a recommendation. **Fluid limits** No evidence was identified on the maximum fluid volume to be administered over a 24-hour period. As such, the GDG chose to use consensus to develop a statement outlining the maximum fluid limits for males and females that should be administered in the majority of children and young people.
Economic considerations	No economic evidence was found for this question. Unit costs of fluid therapies for maintenance were presented to the GDG. The GDG noted that there was no significant difference in unit costs between fluids, and no other differences such as administration or monitoring costs were expected to be associated with the fluid strategy. The unit cost of acquisition of the fluids used for maintenance is relatively low; however hypertonic crystalloids are more expensive than isotonic fluids. There are costs associated with both hyponatraemia and hypernatraemia events, therefore a fluid type which minimises these events would increase its cost effectiveness. The clinical evidence showed an increase in hypernatraemia events with isotonic solutions, however it also showed a clinical benefit associated with the use of isotonic fluids for the incidence of mortality, hyponatraemia and severe hyponatraemia in neonates and those being treated within a specialist unit. Given

	the overall benefits seen with isotonic fluids and their low acquisition costs, the GDG considered them to be the most cost effective intervention for children who require IV fluids for maintenance. Regular monitoring of plasma electrolytes and blood glucose is associated with some costs, however its benefits were considered sufficient to justify the cost.
Quality of evidence	The evidence identified was graded as low to very low quality for most outcomes reported due to a high risk of bias and imprecision. The studies administered commonly used fluids using similar techniques to current practice with the following exceptions: **Fluid type** A single study was considered in neonates (48 hours to 28 days) in a population with severe non-haemolytic hyperbilirubinemia, but this was considered to reflect a standard population of neonates receiving IV fluids. No studies were found in neonates within the first 48 hours of life. **Addition of glucose** It was noted that studies comparing the additional effect of glucose were carried out in patients undergoing cardiovascular interventions, and these patients may not reflect a standard population of children receiving IV fluids. **Fluid rate** The GDG indicated that these studies did not directly compare tools for calculating maintenance level and were of insufficient quality to assist with the recommendation. The studies included compared methods to calculate maintenance fluid rate, but compared the same calculations at full and 50% administration rates. Additionally, the data conflicted with expected clinical findings and current practice, as fluid restriction was found to increase hyponatraemia at 8 hours.
Other considerations	**Fluid type** The GDG noted that standard practice is to give an isotonic solution when children come into hospital as their sodium level would not be known and, as isotonic solutions are physiologically comparable to normal plasma, this would be considered the safest option. The GDG identified that there may be some religious groups who choose to abstain from certain fluids (for example, Jehovah's witnesses and the use of albumin) and people who choose to abstain from the use of IV fluids because of fasting. It was identified that where there was a clinical need for the fluid and the parent/carer refused treatment, the child should become a ward of court and legally, the appropriate clinical treatment may then be given. **Fluid rate** The GDG wished to highlight that the Holliday-Segar formula is based on body weight only and does not take body surface area into consideration. Recommendation 4 outlined situations in which the use of body surface area may be considered appropriate and noted that an alternative approach to calculating maintenance IV fluid rates may be needed in these individuals. **Addition of potassium** No studies were found on the addition of potassium to routine maintenance fluid. The GDG were therefore unable to make a recommendation regarding this.

8 IV fluid therapy for replacement and redistribution

8.1 Introduction

Total body water (TBW) is subdivided into 2 major fluid compartments: intracellular fluid (ICF) and extracellular fluid (ECF). ICF is approximately two-thirds of TBW and ECF the remaining one-third. The ECF comprises interstitial fluid (two-thirds) and plasma, that is, intravascular volume (one-third). Infants and children have a higher total body water, higher metabolic rate and greater body surface area to mass, and thus require proportionally more water than adults to maintain equilibrium. They are also more prone to volume depletion, and if large fluid losses occur rapidly this may result in a reduction in intravascular volume.

Normal insensible water loss occurs as a result of trans-epidermal diffusion and through evaporative loss from the respiratory tract. This is pure water loss and is solute free. Increased insensible loss of pure water may occur during illness, though this may be accompanied by increased water and solute loss via sweating. An abnormal loss of fluid and electrolytes may also occur from the gastrointestinal tract (vomiting, diarrhoea, biliary, pancreatic or stomal losses), from the urinary tract (such as with polyuria), and as a result of burns, trauma, infective processes and in the perioperative child. The electrolyte content of each fluid loss is different, and thus the nature and extent of these losses will determine the impact on the child's physiology and biochemistry.

The purpose of replacement fluid therapy is to restore fluid lost through normal and/or abnormal physiological processes. If these losses are mild or moderate and the gut is functioning then they should be replaced using oral replacement therapy (ORT). If losses are more severe, then IV fluid therapy will be required. Extreme cases will result in a reduction in intravascular volume necessitating IV fluid resuscitation. During sepsis, critical illness, or following major surgery, there may be an internal redistribution of water and electrolytes across the intracellular and extracellular compartments with the development of tissue oedema and the sequestering of fluid within body cavities.

Prescription of IV fluids for replacement will take into account existing deficits and ongoing losses, the effects of internal redistribution and the maintenance needs of the child. Typically, provided that volume resuscitation is not required, existing losses should be replaced gradually, together with the maintenance needs of the child and any ongoing losses. This volume is usually an estimate using information from clinical history, examination and clinical signs. The rate of replacement of this deficit may be determined by the nature of the insult; for example in severe hypernatraemia the rate of correction toward normal should be controlled to prevent central nervous system complications.

The choice of fluid for replacement will reflect the nature of the deficit and ongoing losses. In addition, the laboratory results of serum and urinary electrolytes will help guide the choice of fluid used for replacement therapy. Existing guidance suggests that the deficit should be replaced with an isotonic fluid, for example 0.9% sodium chloride, Hartmann's solution, Ringer's lactate solution or a balanced crystalloid solution. Pre-prepared solutions of 0.9% sodium chloride (with or without glucose) containing potassium in a concentration of 10 or 20 mmol/litre are available; these are used when tailoring IV fluid replacement once the results of blood biochemistry are known.

The type of fluid used will determine its subsequent distribution through the TBW. 5% dextrose contains 100% free water and following infusion will be distributed throughout the TBW; that is, two-thirds will pass into the intracellular compartment and one-third will be confined to the extracellular compartment; of the extracellular fluid one-third will remain intravascular, and the remaining two-thirds will be interstitial. 0.9% sodium chloride on the other hand contains no 'free water' and will

only be distributed through the extracellular compartment; one-third will remain intravascular and two-thirds will enter the interstitial space. Colloid solutions or albumin are not usually used for replacement of losses unless there is intravascular volume depletion and resuscitation is required. A greater proportion of these solutions will remain in the intravascular compartment following infusion than crystalloid solutions. However, during illness the degree of trans-capillary leak may have an impact on this retention.

8.1.1 Review question 9: What fluid types are the most clinically- and cost-effective to address abnormal deficits or excesses, or to replace abnormal losses?

For full details see the review protocols in Appendix C.

Table 43: PICO characteristics of review question

Population	• Neonates born at term, infants, children and young people (up to their 16th birthday) in hospital • Patients who need IV fluids to address existing deficits or excesses, ongoing abnormal losses, or abnormal fluid distribution including: chest tubes in place, uncontrolled vomiting, continuing diarrhoea, or externalised cerebrospinal fluid shunts
Intervention(s)	• 4-5% albumin (relevant for drains strata only) • Balanced crystalloid solutions ○ Hartmann's solution; Ringer's lactate solution; Plasma-Lyte • Isotonic sodium chloride ○ 0.9% sodium chloride • Hypotonic sodium chloride
Comparison(s)	To each other
Outcomes	**Critical** • Mortality at 28 days • Neurological compromise (return to baseline activity, ischaemic injury, cerebral oedema) • Cardiovascular compromise (blood pressure (BP)/arterial pressure, heart rate) • Other organ dysfunction, for example, renal, respiratory compromise (for rate question only) **Important** • Length of (hospital) stay • Hyperchloraemic acidosis • Quality of life • Hypoglycaemia • Hypernatraemia • Hyponatraemia
Study design	Order of preference for study designs: • Systematic reviews of randomised control trials (RCTs) which meet our PICOs • Randomised control trials Where no RCTs are available, we will consider: • Abstracts on RCTs Where no RCTs or abstracts of RCTs are available, we will consider: • Non-randomised trials: prospective or retrospective cohort studies of 50 children or more • Non-blinded, single and double-blinded trials will be included

	Where no randomised or non-randomised evidence in children is available, we will consider: • Systematic reviews of RCTs which meet our PICOs in adults • Randomised control trials in adults Where no RCTs in adults are available, we will consider: • Abstracts on RCTS in adults Where no RCTs or abstracts of RCTs in adults are available: • Non-randomised trials: prospective or retrospective cohort studies of 1000 adults or more.

8.1.2 Clinical evidence

We searched for systematic reviews, RCTs and cohort studies in children, or if not found, adults. The GDG considered that adult evidence would be relevant as the type of fluid would not differ.

One RCT in children was included in the review[22]; this is summarised in Table 44 below. Evidence from this study is summarised in the clinical evidence summary below (Table 45). See also the study selection flow chart in Appendix D, study evidence tables in Appendix G, forest plots in Appendix J, GRADE tables in Appendix I and excluded studies list in Appendix K.

Table 44: Summary of studies included in the review

Study	Intervention/comparison	Population	Outcomes	Comments
Mahajan 2012[22]	Ringer's lactate solution versus 0.9% sodium chloride	Children with acute diarrhoea and severe dehydration	Mortality; length of hospital stay	

Table 45: Clinical evidence summary: Ringer's lactate solution versus 0.9% sodium chloride

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 0.9% sodium chloride	Risk difference with Ringer's lactate solution versus 0.9% sodium chloride (95% CI)
Mortality	21 (1 study)	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	Peto OR 0.15 (0 to 7.5)	91 per 1000	76 fewer per 1000 (from 91 fewer to 338 more)
Length of hospital stay (median)	21 (1 study)	VERY LOW[a,b,d] due to risk of bias, indirectness, imprecision	–	The median length of hospital stay in the 0.9% sodium chloride group was 51 hours (IQR 36, 71) p=0.03.	The median length of hospital stay in the Ringer's lactate group was 38 hours (IQR 27,50)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
(b) 55% of patients had cholera
(c) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
(d) Median and IQR reported, could not analyse data

8.1.3 Economic evidence

8.1.3.1 Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

8.1.3.2 Unit costs

The unit costs of the IV fluids used for replacement of abnormal losses and for redistribution are presented in Table 46.

Table 46: Unit costs of IV fluids for replacement of abnormal losses and for redistribution

IV fluid	Unit cost (500 ml pre-mixed bag)[a]	Source
Isotonic crystalloids		
0.9% sodium chloride	£0.63	Department of Health Commercial Medicines Unit[11]
0.9% sodium chloride + 20 mmol potassium	£0.76	Nottingham University Hospitals NHS Trust, Pharmacy Department
Hartmann's solution (compound sodium lactate)	£0.70	Department of Health Commercial Medicines Unit[11]
Ringer's lactate solution	£0.70	Department of Health Commercial Medicines Unit[11]
Plasma-Lyte 148	1000 ml = £1.04	Nottingham University Hospitals NHS Trust, Pharmacy Department
Hypotonic crystalloids		
0.45% sodium chloride	£0.90	Department of Health Commercial Medicines Unit[20]
Non-synthetic colloid		
4.5% albumin	£33.75	Nottingham University Hospitals NHS Trust, Pharmacy Department

(a) VAT is not included in these unit costs

8.1.4 Evidence statements

8.1.4.1 Clinical

- Very-low-quality evidence from an RCT comprising of 21 participants demonstrated a clinical benefit of Ringer's lactate solution compared to 0.9% sodium chloride for mortality. The evidence was at serious risk of bias, indirectness and imprecision.
- Very-low-quality evidence from the same study of 21 participants demonstrated a clinical benefit for Ringer's lactate solution compared to 0.9% sodium chloride for length of hospital stay. The evidence was at serious risk of bias and indirectness. As medians were reported no imprecision or estimate of effect could be derived.

8.1.4.2 Economic

- No relevant economic evaluations were identified.

8.1.4.3 Recommendations and link to evidence

Recommendations	**26. If term neonates, children and young people need IV fluids for replacement or redistribution, adjust the IV fluid prescription (in addition to maintenance needs) to account for existing fluid and/or electrolyte deficits or excesses, ongoing losses (see the diagram of ongoing losses or abnormal distribution, for example, tissue oedema seen in sepsis.** **27. Consider isotonic crystalloids[o] that contain sodium in the range 131–154 mmol/litre for redistribution.** **28. Use 0.9% sodium chloride containing potassium to replace ongoing losses (see the diagram of ongoing losses).** **29. Base any subsequent fluid prescriptions on the plasma electrolyte concentrations and blood glucose measurements.**
Relative values of different outcomes	Mortality at 28 days, neurological compromise and cardiovascular compromise were considered to be critical outcomes. The GDG felt that it was crucial that neurological and cardiovascular compromise were specified as actual clinical outcomes (that is, cerebral oedema, vascular event) and that surrogate measures should not be considered as these are less likely to have an effect on clinical outcomes. Length of hospital stay, hyperchloraemic acidosis, quality of life, hypoglycaemia, hypernatraemia and hyponatraemia were considered important outcomes.
Trade-off between clinical benefits and harms	Limited evidence was found on the most effective fluid type for replacement and redistribution of fluids in children. One RCT was found in which Ringer's lactate solution showed reduced mortality and length of hospital stay compared to 0.9% sodium chloride; however, the sample size was very small. The GDG noted that there was 1 death in the 0.9% sodium chloride group, but the GDG considered this was unlikely to be due to the fluid type. Furthermore the study was conducted in India and 55% of the population had cholera, which was not representative of the population in UK hospitals. The GDG therefore did not have much confidence in the study's findings. Furthermore Ringer's lactate solution is not commonly used in the UK, although the GDG acknowledged that it is used in other countries. Therefore, the GDG chose to develop a recommendation based on informal consensus. The GDG felt that an isotonic crystalloid should be the preferred option for all children receiving IV fluids for redistribution and that the choice of isotonic crystalloid should be made on the basis of clinical need. The GDG noted that healthcare professionals may wish to consider the use of 0.9% sodium chloride as it is available in pre-made solutions containing different concentrations of potassium. This makes it easier to meet individual patient requirements and reduces fluid errors. Potassium is required because it is quite common in patients with ongoing losses to have a lack of potassium caused by

[o] At the time of publication (December 2015), some isotonic crystalloids with 5–10% glucose did not have a UK marketing authorisation for use in children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

	diarrhoea, vomiting or drain losses. However, the GDG acknowledged that too much potassium can lead to the development of hyperkalaemia. The GDG agreed that using pre-made solutions reduces the risks associated with adding potassium manually and noted that it is standard practice to use pre-made solutions where they exist. Furthermore, there is a risk of adding potassium in a context such as acute kidney injury and therefore it is important to check electrolytes at the outset. For perioperative redistribution losses, isotonic crystalloids that contain sodium in the range 131–154 mmol/litre were considered by the GDG to be standard practice. It is a balanced salt solution and is the closest physiologically to plasma in terms of electrolyte composition. Intraoperatively it is used not only as a maintenance fluid but also to replace third space losses and blood loss. The GDG wished to highlight that the electrolyte composition of the fluid being lost needs to be taken into account in order to ensure that the most appropriate fluid is used for replacement. Failure to do so could lead to electrolyte disturbance (see diagram of ongoing losses (see Figure 3).
Economic considerations	No economic evidence was found. The unit costs of the relevant IV fluids were presented to the GDG. It was noted that the unit costs for isotonic crystalloids (0.9% sodium chloride, Hartmann's solution, Ringer's lactate solution, Plasma-Lyte and 0.9% sodium chloride plus potassium [20–40 mmol/litre]) and hypotonic crystalloids (0.45% sodium chloride) are not largely different, and no differences in administration or monitoring costs are expected to be associated with different fluid types. The clinical evidence showed some benefit for using Ringer's lactate solution in terms of mortality and reduced length of hospital stay; however, the GDG did not feel confident in this observed difference, given the low quality and the small size of the trial. The GDG also noted that current UK practice is to use commercially prepared, premixed isotonic 0.9% sodium chloride with different potassium concentrations, tailored to the child's needs, as the first-line option for replacement. There was no reason to believe that changing this practice would be justified on clinical or economic grounds. This practice also adheres to the NPSA guidelines that recommend the use of commercially prepared, premixed IV fluids, where available, to reduce errors during preparation and the risk of infections. Preparation errors and infections are costly events; therefore the use of commercially prepared, premixed isotonic sodium chloride (0.9% solution) with potassium is likely to be the most cost-effective option.
Quality of evidence	There was limited evidence identified for the most clinically effective fluid type for replacement and redistribution. One RCT was found which compared Ringer's lactate solution to 0.9% sodium chloride. The study was very small and had a very low GRADE rating for the 2 outcomes it reported. The population differed to that of patients in UK hospitals; the setting of the study was India and 55% of the population had cholera. The evidence was downgraded if the disease type differed from that which is normally found in the UK.
Other considerations	Recommendations on the replacement of existing losses in children and young people with diabetic ketoacidosis can be found in 'Diabetes (type 1 and type 2) in children and young people' (NICE guideline NG18). The GDG identified that there may be some religious groups who choose to abstain from certain fluids (for example, Jehovah's witnesses and the use of albumin) and people who choose to abstain from the use of IV fluids because of fasting. It was identified that where there was a clinical need for the fluid and the parent/carer refused treatment, the child should become a ward of court and legally, the appropriate clinical treatment may then be given.

9 Managing hypernatraemia and hyponatraemia that develops during IV fluid administration

9.1 Introduction

IV fluid therapy in children is not without risk and electrolyte disturbances are common. This chapter will only deal with abnormalities of sodium that occur when children are receiving IV fluids.

Hypernatraemia is defined as plasma sodium greater than 145 mmol/litre. The risk of adverse events increases with the level of sodium and symptoms are usually more noticeable with sodium of over 160 mmol/litre. Clinically, signs and symptoms of either hyponatraemia or hypernatraemia can range from subtle (for example, increased thirst) to devastating (coma or death). It is therefore important to have policies in place for the monitoring of fluid input and output, serum electrolytes and central nervous system status, as early identification and treatment will improve overall outcomes.

Hyponatraemia is defined as plasma sodium less than 135 mmol/litre, usually representing an excess of water in relation to sodium in extracellular fluid. The main causes of hyponatraemia in children are:

- Administration of IV fluids in the presence of increased anti-diuretic hormone secretion. During periods of stress, (for example, pneumonia, meningitis and surgery amongst others) there is an increased secretion of ADH. This produces an increase in water retention relative to sodium.
- Administration of hypotonic IV fluids providing excessive free water.

Symptoms are most likely to occur with a plasma sodium of less than 125 mmol/litre, or if the plasma sodium has fallen rapidly, at which time the child may present with signs or symptoms of encephalopathy.

9.1.1 Management of hypernatraemia

9.1.1.1 Review question 10: What are the most clinically- and cost-effective methods to address hypernatraemia developing during IV fluid administration?

For full details see the review protocols in Appendix C.

Table 47: PICO characteristics of review question

Population	Neonates born at term, infants, children and young people (up to their 16th birthday) in hospital.
Intervention(s)	• Isotonic crystalloid solutions (including 0.9% sodium chloride), balanced isotonic crystalloids (for example Hartmann's solution, Ringer's lactate solution) at maintenance rate, as defined by the study • Isotonic crystalloids solutions (including 0.9% sodium chloride), balanced isotonic crystalloids (for example Hartmann's solution, Ringer's lactate solution) at above maintenance rate, as defined by the study • Isotonic crystalloid solutions (including 0.9% sodium chloride), balanced isotonic crystalloids (for example Hartmann's solution, Ringer's lactate solution) at below maintenance rate, as defined by the study • Hypotonic crystalloids solutions (including for example 0.45% sodium chloride, 0.225% sodium chloride, 0.18% sodium chloride, 5% glucose) at maintenance rate, as defined by the study • Hypotonic crystalloid solutions (including for example 0.45% sodium chloride, 0.225%

	sodium chloride, 0.18% sodium chloride, 5% glucose) at below maintenance rate, as defined by the study • Hypotonic crystalloid solutions (including for example 0.45% sodium chloride, 0.225% sodium chloride, 0.18% sodium chloride, 5% glucose) at below maintenance rate, as defined by the study • Enteral fluid therapy
Comparison(s)	To each other
Outcomes	**Critical** • Mortality at 28 days • Rate of return to normal electrolyte levels • Adverse events (for example hypovolaemia, hypervolaemia, neurological compromise, cardiac arrest) **Important** • Return to normal electrolyte levels • Length of hospital stay • Quality of life
Study design	Order of preference: • Systematic review of RCTs which meet our PICOs • Randomised control trials Where no RCTs are available, we will consider: • Abstracts on RCTs Where no RCTs or abstracts of RCTs are available, we will consider: • Non-randomised trials: prospective or retrospective cohort studies of 50 children or more • Non-blinded, single and double-blinded trials will be included Where no randomised or non-randomised evidence in children are available, we will consider: • Systematic reviews of RCTs which meet our PICOs in adults • Randomised control trials in adults

9.1.1.2 Clinical evidence

We searched for systematic reviews, RCTs and cohort studies in children, or adults if no evidence in children was available.

The GDG considered that findings from studies conducted in adults could be transferred to a child population.

No relevant clinical evidence, comparing different methods to address hypernatraemia, was identified.

9.1.1.3 Economic evidence

9.1.1.3.1 Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

9.1.1.3.2 Unit costs

The unit costs of IV fluids used for correction of hypernatraemia are presented in the table below.

Table 48: Unit costs of IV fluid therapy for the correction of hypernatraemia

IV fluid	Unit cost (500 ml pre-mixed bag)[a]	Source
Isotonic crystalloids		
0.9% sodium chloride	£0.63	Department of Health Commercial Medicines Unit[11]
Hartmann's solution (compound sodium lactate)	£0.70	Department of Health Commercial Medicines Unit[11]
Ringer's lactate solution	£0.70	Department of Health Commercial Medicines Unit[11]
Hypotonic crystalloids		
0.45% sodium chloride	£0.90	Nottingham University Hospitals NHS Trust, Pharmacy Department
0.18% sodium chloride	£2.72	Nottingham University Hospitals NHS Trust, Pharmacy Department
4% glucose + 0.18% sodium chloride	£0.59	Nottingham University Hospitals NHS Trust, Pharmacy Department
5% glucose + 0.9% sodium chloride	£0.89	Nottingham University Hospitals NHS Trust, Pharmacy Department
5% glucose + 0.45% sodium chloride	£1.20	Department of Health Commercial Medicines Unit[11]

(a) VAT is not included in these unit costs

9.1.1.4 Evidence statements

9.1.1.4.1 Clinical

- No relevant clinical evidence was identified.

9.1.1.4.2 Economic

- No relevant economic evaluations were identified.

9.1.1.5 Recommendations and link to evidence

Recommendations	**30. If hypernatraemia develops in term neonates, children and young people, review the fluid status and take action as follows:** • **If there is no evidence of dehydration and an isotonic fluid is being used, consider changing to a hypotonic fluid (for example, 0.45% sodium chloride with glucose)[p].** • **If dehydration is diagnosed, calculate the water deficit and replace it over 48 hours, initially with 0.9% sodium chloride.** • **If the fluid status is uncertain, measure urine sodium and osmolality.** • **If hypernatraemia worsens or is unchanged after replacing the deficit, review the fluid type and consider changing to a hypotonic**

[p] At the time of publication (December 2015), some hypotonic solutions did not have a UK marketing authorisation for use in children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

	solution (for example, 0.45% sodium chloride with glucose). **31. When correcting hypernatraemia, ensure that the rate of fall of plasma sodium does not exceed 12 mmol/litre in a 24-hour period.** **32. Measure plasma electrolyte concentrations every 4–6 hours for the first 24 hours, and after this base the frequency of further plasma electrolyte measurements on the treatment response.**
Relative values of different outcomes	Mortality at 28 days was considered a critical outcome that would demonstrate a potential consequence of poor fluid management. Incidence of serious adverse events (for example neurological compromise, dehydration, hypervolaemia, hypovolaemia) and rate of return to normal electrolyte levels, were also considered to be critical outcomes. These outcomes were selected as they best reflected successful administration of IV fluids in children. Quality of life, length of hospital stay and return to normal electrolyte levels were considered important outcomes.
Trade-off between clinical benefits and harms	No evidence was found for these recommendations. The recommendations were developed using informal consensus of the GDG. The GDG noted that it is important to know how high the sodium level is in children with hypernatraemia, and therefore regular monitoring of their status is required. It may not be possible to accurately know the fluid status of the child and therefore measurement of urine sodium and osmolality would be beneficial and does not cause harm to the patient. The GDG identified that term neonates, children and young people who have not been diagnosed as dehydrated were likely to have an increased sodium intake. As such, if an isotonic fluid is being administered, it may be beneficial to change to a hypotonic fluid with a lower sodium content. However, it was noted that the majority of cases of hypernatraemia were due to dehydration. A calculation of water deficit is required in order to ensure adequate replacement. It should be noted that this differs from fluid deficit, which can be assessed by change in weight. The GDG felt that this replacement should be done slowly, over 48 hours, to prevent cerebral oedema. This timing allows redistribution of the replacement fluid, preventing complications of circulatory overload or maldistribution of replacement fluids. 0.9% sodium chloride was considered to be the most effective fluid initially as isotonic fluid prevents the sodium level dropping too quickly as the plasma sodium concentration is diluted by the replacement fluids and redistribution occurs. The rate of fall in sodium levels should be monitored. However, if there is worsening or unresponsive hypernatraemia during 48 hours then a review of the fluid type should be carried out and use of a hypotonic solution considered. The GDG agreed that the rate for decreasing the serum sodium level should be no more than 12 mmol/litre per 24 hours (NPSA 2007[31]), as rapid decrease may cause harm to the child, such as cerebral oedema, convulsions or permanent brain damage. The group also felt that continued review of the serum electrolytes should be 4–6 hours for the first 24 hours, and then amended as indicated by the outcome of assessment, to ensure that the fluid is correcting the fluid imbalance, and that the decrease in serum sodium levels is not too rapid. It was acknowledged that there may be an increase in staff time for such monitoring, but the benefit in the

	controlled reduction in hypernatraemia was considered to be important.
Economic considerations	No economic evidence was found for this question. Unit costs of routinely used IV fluids for correcting hypernatraemia were presented to the GDG. The GDG noted that there were no significant differences in unit costs between fluids and no other differences such as administration or monitoring costs are expected to be associated with the fluid strategy. Therefore if one fluid strategy is deemed to be more effective than the others (that is, it reduces mortality and adverse events) then this is also likely to be cost effective. As no evidence on effectiveness was found, the recommendations were based on the GDG's expert opinion. The GDG also noted that regular monitoring of sodium levels is associated with some costs, however its benefits were considered sufficient to justify the cost.
Quality of evidence	No evidence was found for this review. The recommendation was developed using informal consensus of the GDG. Only studies on the management of hypernatraemia resulting from IV fluid administration were considered for inclusion; other situations resulting in hypernatraemia were not considered.
Other considerations	The GDG highlighted that this recommendation was intended for children who have developed hypernatraemia during IV fluid administration and that children presenting with other forms of hypernatraemia are not covered by this guideline. In term neonates, there can be an increase in hypernatraemia resulting from inadequate enteral feeding. It is rare for term neonates to have high sodium resulting from IV fluids. Instead this may result from giving too little fluid (that is, dehydration), rather than the type of fluid given. If not dehydrated their IV fluid requirements would be the same as infants and children, based on what is required for their weight. The NPSA/MHRA do not recommend the use of 0.18% sodium chloride (used in hypotonic crystalloid solutions) in children's wards and this should not be used in routine paediatric practice.[31] Recommendations on when to suspect hypernatraemia and the management of dehydration in children under 5 with diarrhoea and vomiting can be found in 'Diarrhoea and vomiting' (NICE guideline CG78). The GDG identified that there may be some religious groups who choose to abstain from certain fluids (for example, Jehovah's witnesses and the use of albumin) and people who choose to abstain from the use of IV fluids because of fasting. It was identified that where there was a clinical need for the fluid and the parent/carer refused treatment, the child should become a ward of court and legally, the appropriate clinical treatment may then be given.

9.1.2 Management of hyponatraemia

9.1.2.1 Review question 11: What are the most clinically- and cost-effective methods to address hyponatraemia developing during IV fluid administration?

For full details see the review protocols in Appendix C.

Table 49: PICO characteristics of review question

Population	Neonates born at term, infants, children and young people (up to their 16th birthday) in hospital.
Intervention(s)	• Isotonic crystalloid solutions (including 0.9% sodium chloride), balanced isotonic crystalloids (for example Hartmann's solution, Ringer's lactate solution) • Hypertonic sodium chloride • Different rates of isotonic crystalloid solutions • Different rates of hypertonic sodium chloride
Comparison(s)	To each other
Outcomes	**Critical** • Mortality at 28 days • Rate of return to normal electrolyte levels • Adverse events (for example hypovolaemia, hypervolaemia, neurological compromise, cardiac arrest) **Important** • Return to normal electrolyte levels • Length of hospital stay • Quality of life
Study design	Order of preference: • Systematic review of RCTs which meet our PICOs • Randomised control trials Where no RCTs are available, we will consider: • Abstracts on RCTs Where no RCTs or abstracts of RCTs are available, we will consider: • Non randomised trials: prospective or retrospective cohort studies of 50 children or more • Non-blinded, single and double-blinded trials will be included Where no randomised or non-randomised evidence in children are available, we will consider: • Systematic reviews of RCTs which meet our PICOs in adults • Randomised control trials in adults

9.1.2.2 Clinical evidence

We searched for systematic reviews, RCTs and cohort studies in children, or adults if no evidence in children was available.

The GDG considered that findings from studies conducted in adults could be transferred to an infant and child population.

No relevant clinical evidence, comparing different methods to address hyponatraemia, was identified.

9.1.2.3 Economic evidence

9.1.2.3.1 Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

9.1.2.3.2 Unit costs

The unit costs of IV fluids used for correction of hyponatraemia are presented in the table below.

Table 50: Unit costs of IV fluid therapy for the correction of hyponatraemia

IV fluid	Unit cost (500 ml pre-mixed bag)[a]	Source
Isotonic crystalloids		
0.9% sodium chloride	£0.63	Department of Health Commercial Medicines Unit[11]
Hartmann's solution (compound sodium lactate)	£0.70	Department of Health Commercial Medicines Unit[11]
Ringer's lactate solution	£0.70	Department of Health Commercial Medicines Unit[11]
Hypertonic crystalloids		
2.7% sodium chloride	£2.75	Nottingham University Hospitals NHS Trust, Pharmacy Department
1.8% sodium chloride	£2.97	Nottingham University Hospitals NHS Trust, Pharmacy Department
3% sodium chloride	£11.00	Nottingham University Hospitals NHS Trust, Pharmacy Department
5% sodium chloride	£2.97	Nottingham University Hospitals NHS Trust, Pharmacy Department

(a) VAT is not included in these unit costs

9.1.2.4 Evidence statements

9.1.2.4.1 Clinical

- No relevant clinical evidence was identified.

9.1.2.4.2 Economic

- No relevant economic evaluations were identified.

9.1.2.5 Recommendations and link to evidence

Recommendations	**33. If asymptomatic hyponatraemia develops in term neonates, children and young people, review the fluid status and take action as follows:** • **If a child is prescribed a hypotonic fluid, change to an isotonic fluid**

	(for example, 0.9% sodium chloride). • **Restrict maintenance IV fluids in children and young people who are hypervolaemic or at risk of hypervolaemia (for example, if there is a risk of increased ADH secretion) by either:** o **restricting maintenance fluids to 50–80% of routine maintenance needs or** o **reducing fluids, calculated on the basis of insensible losses within the range 300–400 ml/m^2/24 hours plus urinary output.** **34. Be aware that the following symptoms are associated with acute hyponatraemia during IV fluid therapy:** • **Headache.** • **Nausea and vomiting.** • **Confusion and disorientation.** • **Irritability.** • **Lethargy.** • **Reduced consciousness.** • **Convulsions.** • **Coma.** • **Apnoea.** **35. If acute symptomatic hyponatraemia develops in term neonates, children and young people, review the fluid status, seek immediate expert advice (for example, from the paediatric intensive care team) and consider taking action as follows:** • **Use a bolus of 2 ml/kg (maximum 100 ml) of 2.7% sodium chloride over 10–15 minutes.** • **Use a further bolus of 2 ml/kg (maximum 100 ml) of 2.7% sodium chloride over the next 10–15 minutes if symptoms are still present after the initial bolus.** • **If symptoms are still present after the second bolus, check the plasma sodium level and consider a third bolus of 2 ml/kg (maximum 100 ml) of 2.7% sodium chloride over 10–15 minutes.** • **Measure the plasma sodium concentration at least hourly.** • **As symptoms resolve, decrease the frequency of plasma sodium measurements based on the response to treatment.** **36. Do not manage acute hyponatraemic encephalopathy using fluid restriction alone.** **37. After hyponatraemia symptoms have resolved, ensure that the rate of increase of plasma sodium does not exceed 12 mmol/litre in a 24-hour period.**
Relative values of different outcomes	Mortality at 28 days was considered a critical outcome that would demonstrate a potential consequence of poor fluid management. Incidence of serious adverse events (for example neurological compromise, dehydration, hypervolaemia and hypovolaemia) and rate of return to normal electrolyte levels were also considered to be critical outcomes. These outcomes were selected as they best reflected

	successful administration of IV fluids in children. Patient quality of life, length of hospital stay and return to normal electrolyte levels were considered important outcomes.
Trade-off between clinical benefits and harms	No evidence was found for these recommendations. The recommendations for term neonates, children and young people were developed by consensus of the GDG. **Asymptomatic hyponatraemia:** Children receiving hypotonic solutions should be immediately changed to an isotonic solution, which has a higher sodium content, as this is more likely to restore plasma sodium levels to normal. Many children who develop asymptomatic hyponatraemia have increased anti-diuretic hormone secretion and are hypervolaemic or have the potential to develop hypervolaemia. The GDG felt that fluid restriction should be applied to these children as part of their management in restoring a normal sodium level. Asymptomatic hyponatraemia should be managed conservatively with the goal of returning sodium levels to the normal range. Sodium should not be corrected more rapidly than 0.5 mmol/hour over a 24-hour period. Rate of correction should be monitored closely with regular assessment of sodium to ensure that the rate is within acceptable limits. **Symptomatic hyponatraemia:** The GDG felt that in cases of symptomatic hyponatraemia, the condition of a child could rapidly deteriorate, causing cerebral oedema. This was considered a medical emergency which requires urgent correction with hypertonic sodium chloride regardless of biochemical sodium level. The risk of overcorrecting the sodium level (raising above 145 mmol/litre) is outweighed by the potentially devastating outcomes of neurological compromise. Rapid increase with bolus delivery of 2.7% sodium chloride, at an initial rate of 2 ml/kg, over 10–15 minutes, up to a volume of 100 ml was considered to be safe by the GDG. Sodium levels should continue to be closely monitored following administration of hypertonic solution to ensure that the correction rate is appropriate. Documentation and monitoring of key clinical symptoms and biochemical sodium levels as part of the fluid balance sheet are crucial for identification of hyponatraemia and when presented together should suggest risk of hyponatraemia and indicate treatment (see Chapter 5).
Economic considerations	No economic evidence was found for this review. Unit costs of IV fluids for correcting hyponatraemia were presented to the GDG. The GDG noted that there was no significant difference in unit costs between isotonic crystalloids. Hypertonic sodium chloride is more expensive than isotonic crystalloids but is still low cost, with the exception of sodium chloride 3% which does not have a marketing licence in the UK and has to be imported. No other differences such as administration or monitoring costs are expected to be associated with the choice of a particular fluid strategy. The GDG stressed that the use of hypertonic sodium chloride is potentially life-saving in symptomatic patients and could avert serious neurological complications, therefore it is likely to be highly cost effective. In non-symptomatic children, a more conservative management with isotonic fluids was deemed to be clinically safer and therefore cost effective. As no evidence on effectiveness was found, the recommendations were based on GDG expert opinion.

	The GDG also noted that monitoring sodium levels and osmolality is associated with some costs of healthcare professionals' time. However, these are likely to be offset by the clinical benefits as monitoring may prevent complications by suggesting that a change in management is required.
Quality of evidence	No evidence was found for this review. The recommendations were developed using GDG consensus. Only studies on the management of hyponatraemia resulting from IV fluid administration were considered for inclusion: other situations resulting in hyponatraemia were not considered.
Other considerations	The GDG identified that there may be some religious groups who choose to abstain from certain fluids (for example, Jehovah's witnesses and the use of albumin) and people who choose to abstain from the use of IV fluids because of fasting. It was identified that where there was a clinical need for the fluid and the parent/carer refused treatment, the child should become a ward of court and legally, the appropriate clinical treatment may then be given.

10 Training and education of healthcare professionals for management of IV fluid therapy

10.1 Introduction

The assessment, prescription and administration of intravenous fluids in children are complex responsibilities involving clinical and biochemical assessment and a good understanding of the principles of fluid physiology. Healthcare professionals involved require appropriate training and education to ensure that morbidity and mortality is minimised.

'Intravenous fluid therapy in adults in hospital' (NICE guideline CG174) outlined 4 issues relating to failures in education and training which contribute to poor fluid management, and these would equally apply to a paediatric setting:

1. Poor understanding of the basic principles of fluid balance and a lack of knowledge about fluid management.
2. Poor fluid balance (chart) documentation.
3. Poor interpretation of laboratory results.
4. Inadequate involvement of senior clinicians in fluid management and delegation of fluid prescription to junior members of the team.

In 2007, the National Patient Safety Agency (NPSA) highlighted the risk of fatal hyponatraemia in children receiving IV fluids and required all NHS trusts in the UK to take steps to minimise the risk. One of the stipulated actions was to "provide adequate training and supervision for all staff involved in the prescribing, administering and monitoring of intravenous infusions for children".

10.1.1 Review question 12: What skills are needed for the adequate training and education of healthcare professionals involved in prescribing and administering IV fluids?

For full details see the review protocols in Appendix C.

Table 51: PICO characteristics of review question

Population and setting	All healthcare professionals involved in IV fluid administration and prescription to neonates born at term, infants, children and young people (up to their 16th birthday) in hospital. Relevant to an NHS setting.
Topic of interest	To qualitatively synthesise which components healthcare professionals think they require in training and education in order to administer and prescribe IV fluids to children
Context (specific aspects of interest – for example, the themes we are hoping to get opinions on)	These will be determined by the qualitative data found. Specific focus includes: • Body surface area versus body weight • Recognition and treatment of hyponatraemia • Recognition and treatment of hypoglycaemia • Fluid overload in children • Calculation of fluid balance
Study design	Study types: • Qualitative studies including questionnaires

This review aimed to qualitatively synthesise which components healthcare professionals think they require in training and education in order to administer and prescribe IV fluids to children.

10.1.2 Clinical evidence

We searched for qualitative studies in children.

The GDG thought that most components of education and training were already included in the adult guideline, therefore this review focused specifically on areas where training and education requirements for the management of babies and children would differ from that of adults.

10.1.3 Economic evidence

10.1.3.1 Published literature

No relevant economic evaluations were identified. See also the economic article selection flow chart in Appendix E.

10.1.4 Evidence statements

10.1.4.1 Clinical

- No relevant clinical evidence was identified.

10.1.4.2 Economic

- No relevant economic evaluations were identified.

10.1.5 Recommendations and link to evidence

Recommendations	**38. For guidance on training and education for healthcare professionals involved in prescribing and delivering IV fluid therapy, see the training and education section in 'Intravenous fluid therapy in adults' (NICE guideline CG174).**
Relative values of different outcomes	Outcomes were determined by the themes that would emerge from the qualitative review. The GDG pre-specified areas relating specifically to IV fluid administration in children which may require different training and education from those of adults. These included: the use of body surface area and body weight for calculating IV fluid requirements, recognition and treatment of hyponatraemia, recognition and treatment of hypoglycaemia, fluid overload in children and calculation of fluid balance.
Trade-off between clinical benefits and harms	No evidence was identified in relation to the specific training and education of health professionals working with children, therefore the recommendations were based on informal consensus. The GDG felt that the recommendations relating to the training and education of healthcare professionals in 'Intravenous fluid therapy in adults in hospital' (NICE guideline CG174) were also applicable to the training and education needs of healthcare professionals prescribing and administering IV fluids in children and young people. The GDG considered that, given the lack of available evidence to suggest otherwise, the training requirements for issues relevant to children were likely to be included in generic training of healthcare professionals.

Economic considerations	No economic evaluations were identified. The GDG believed that all the guideline recommendations will need to be implemented through training and quality assurance mechanisms. In the medium to longer term, the training should be incorporated into the undergraduate training curriculum. In the short-term there will be some costs incurred in training current staff to the required standard. However, costing this is not straightforward due to the following: 1) The required training course could be delivered by many different means (including e-learning), some of which may not incur much staff time. 2) Improving practice, through implementation of the guideline recommendations, should offset these costs (for example by preventing complications). Therefore there is an interaction between training and all the other recommendations in the guideline.
Quality of evidence	No evidence was identified for this question.
Other considerations	The GDG identified that there were some areas in which training and education of healthcare professionals in the prescription and administration of IV fluids may be beneficial. In particular, the GDG felt that the signs and symptoms of cerebral oedema caused by acutely developing hyponatraemia are under-recognised by healthcare professionals. Recognition of these is essential so that treatment of this life-threatening medical emergency can be initiated immediately. This can only be achieved by a robust education and training programme aimed at all healthcare professionals involved in the management of children. Additionally, since the NPSA alert in 2007, glucose-containing IV fluids with lower concentrations of glucose have become standard clinical practice. It is essential that healthcare professionals involved in the care of children receiving IV fluids have received training in the identification and treatment of hypoglycaemia. The GDG also felt that the calculation of fluid balance in children is complex and requires an understanding of normal developmental physiology of children and the changes that occur with illness. Educational programmes underpinning these requirements are essential for best practice to be achieved. However, given the lack of evidence identified, the GDG did not choose to develop specific recommendations in these areas, as it was felt that these areas were covered by the recommendations in 'Intravenous fluid therapy in adults in hospital' (NICE guideline CG174).

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12 Acronyms and abbreviations

Acronym or abbreviation	Description
ADH	Antidiuretic hormone
BCS	Blantyre coma score
BMI	Body mass index
BNF	British National Formulary
BP	Blood pressure
CI	Confidence intervals
CPDA	Citrate-phosphate-dextrose-adenosine
CPB	Cardiopulmonary bypass
CSW	Clinical support worker
ECF	Extracellular fluid
ED	Emergency department
FBC	Full blood count
GCS	Glasgow coma scale
GDG	Guideline Development Group
GRADE	Grading of recommendations assessment, development and evaluation
HES	Hydroxyethyl starch
ICF	Intracellular fluid
ICU	Intensive care unit
IQR	Interquartile range
IV	Intravenous
JVP	Jugular venous pressure
LETR	Linking evidence to recommendations
MID	Minimally important differences
Na	Sodium
NCGC	National Clinical Guideline Centre
NICE	National Institute for Health and Care Excellence
NICU	Neonatal intensive care unit
NPSA	National Patient Safety Agency
OECD	Organisation for Economic Co-operation and Development
OR	Odds ratio
ORT	Oral replacement therapy
PICO	Population Intervention Comparison Outcomes
PICU	Paediatric intensive care unit
PRBC	Packed red blood cells
QALYS	Quality-adjusted life-years
RCT	Randomised controlled trial
RR	Risk ratio (relative risk)
SIADH	Syndrome of inappropriate antidiuretic hormone secretion
TBW	Total body water
WHO	World Health Organisation

13 Glossary

Term	Definition
Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Acidosis	Accumulation (increase) of acid within the blood and other body tissues. Occurs with a pH of less than 7.35.
Albumin	See colloids
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Arm (of a clinical study)	Subsection of individuals within a study who receive one particular intervention, for example placebo arm.
Association	Statistical relationship between 2 or more events, characteristics or other variables. The relationship may or may not be causal.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Bias	Influences on a study that can make the results look better or worse than they really are. (Bias can even make it look as if a treatment works when it does not.) Bias can occur by chance, deliberately or as a result of systematic errors in the design and execution of a study. It can also occur at different stages in the research process, for example, during the collection, analysis, interpretation, publication or review of research data. For examples see selection bias, performance bias, information bias, confounding factor, and publication bias.
Bolus	A volume of fluid given quickly
Carer (caregiver)	Someone who looks after family, partners or friends in need of help because they are ill, frail or have a disability.
Child	29 days to under 12 years
Clinical effectiveness	How well a specific test or treatment works when used in the 'real world' (for example, when used by a doctor with a patient at home), rather than in a carefully controlled clinical trial. Trials that assess clinical effectiveness are sometimes called management trials. Clinical effectiveness is not the same as efficacy.
Clinician	A healthcare professional who provides patient care. For example, a doctor, nurse or physiotherapist.
Cochrane Review	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration).
Cohort study	A study with 2 or more groups of people – cohorts – with similar characteristics. One group receives a treatment, is exposed to a risk factor or has a particular symptom and the other group does not. The study follows their progress over time and records what happens. See also observational study.
Colloids	A solution which is administered intravenously and acts as a volume expander. It is composed of particles which are not capable of passing through a semipermeable membrane. Examples of colloids include albumin, starches and gelatin. Colloids can be synthetic (containing naturally-produced proteins such as albumin or haemoglobin) and non-synthetic (containing synthetically-derived colloid particles such as hydroxyethyl starches).
Confidence interval (CI)	There is always some uncertainty in research. This is because a small group

Term	Definition
	of patients is studied to predict the effects of a treatment on the wider population. The confidence interval is a way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. The CI is usually stated as '95% CI', which means that the range of values has a 95 in a 100 chance of including the 'true' value. For example, a study may state that 'based on our sample findings, we are 95% certain that the 'true' population blood pressure is not higher than 150 and not lower than 110'. In such a case the 95% CI would be 110 to 150. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment – often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).
Control group	A group of people in a study who do not receive the treatment or test being studied. Instead, they may receive the standard treatment (sometimes called 'usual care') or a dummy treatment (placebo). The results for the control group are compared with those for a group receiving the treatment being tested. The aim is to check for any differences. Ideally, the people in the control group should be as similar as possible to those in the treatment group, to make it as easy as possible to detect any effects due to the treatment.
Creatinine	A waste product produced by the body during muscle metabolism and normally excreted in urine. If the creatinine level increases in the blood, this may indicate decreased kidney function.
Critical postnatal adaptation phase	Cardiopulmonary adaptation after birth. Characterised by a fall in pulmonary vascular resistance and pulmonary artery pressure with a rise in pulmonary blood flow associated with contraction of the extracellular fluid compartment.
Crystalloids	A solution which is administered intravenously and acts as a volume expander. It is composed of particles which are capable of passing through a semipermeable membrane. Examples of crystalloids include 0.9% sodium chloride and Ringer's lactate solution. Crystalloids can be divided into the following groups based on their tonicity: isotonic, hypertonic and hypotonic.
Dehydration	Depletion of body water and, to varying degrees, electrolytes.
Dextran	See colloids
Dextrose	See crystalloids
Economic evaluation	An economic evaluation is used to assess the cost effectiveness of healthcare interventions (that is, to compare the costs and benefits of a healthcare intervention to assess whether it is worth doing). The aim of an economic evaluation is to maximise the level of benefits – health effects – relative to the resources available. It should be used to inform and support the decision-making process; it is not supposed to replace the judgement of healthcare professionals. There are several types of economic evaluation: cost–benefit analysis, cost–consequences analysis, cost-effectiveness analysis, cost–minimisation analysis and cost–utility analysis. They use similar methods to define and evaluate costs, but differ in the way they estimate the benefits of a particular drug, programme or intervention.
Effect (as in effect measure, treatment effect, estimate of effect, effect size)	A measure that shows the magnitude of the outcome in one group compared with that in a control group. For example, if the absolute risk reduction is shown to be 5% and it is the outcome of interest, the effect size is 5%. The effect size is usually tested, using statistics, to find out how likely it is

Term	Definition
	that the effect is a result of the treatment and has not just happened by chance (that is, to see if it is statistically significant).
Effectiveness	How beneficial a test or treatment is under usual or everyday conditions, compared with doing nothing or opting for another type of care.
Electrolyte	Ions in solution that acquire the capacity to conduct electricity.
Euvolaemia	Term implying that the individual described appears to have a normal circulating blood volume within their body.
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals or patients).
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Fluid balance chart	A record of a patient's fluid intake, output and balance. This may or may not be combined with a fluid prescription chart.
Fluid prescription chart	A record of IV fluid prescriptions administered to a patient. This may or may not be combined with a fluid balance chart.
Fluid resuscitation	The replacement of bodily fluid lost through pathological processes
Follow-up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Gold standard	A method, procedure or measurement that is widely accepted as being the best available to test for or treat a disease.
GRADE, GRADE profile	A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile.
Harms	Adverse effects of an intervention.
Hartmann's solution	A balanced isotonic crystalloid solution containing potassium. For further information, see Table 6. Also known as compound sodium lactate.
Health economics	Study or analysis of the cost of using and distributing healthcare resources.
Heterogeneity or Lack of homogeneity	The term is used in meta-analyses and systematic reviews to describe when the results of a test or treatment (or estimates of its effect) differ significantly in different studies. Such differences may occur as a result of differences in the populations studied, the outcome measures used or because of different definitions of the variables involved. It is the opposite of homogeneity.
Hyperchloraemia	Increased chloride level in the blood
Hyperglycaemia	Increased glucose level in the blood
Hyperkalaemia	Increased potassium level in the blood
Hypernatraemia	Increased sodium level in blood
Hyperoncotic	Increased oncotic pressure of blood plasma
Hypertonic	In the context of a human body cell, a hypertonic solution is one with a higher concentration of solutes outside the cell than inside the cell. When a cell is immersed in a hypertonic solution, water will flow out of the cell to balance the concentration of solutes.
Hypervolaemia	Term implying that the individual described appears to have increased

Term	Definition
	circulating blood fluid volume within their body
Hypoalbuminaemia	Decreased albumin level in blood serum
Hypoglycaemia	Decreased glucose level in the blood
Hypokalaemia	Decreased potassium level in the blood
Hyponatraemia	Decreased sodium level in the blood
Hypotonic	In the context of a human body cell, a hypotonic solution is one with a lower concentration of solutes outside the cell than inside the cell. When a cell is immersed in a hypotonic solution, water will flow into the cell to balance the concentration of solutes.
Hypovolaemia	Term implying that the individual described appears to have decreased circulating blood fluid volume within their body
Hypovolaemic shock	An emergency condition in which severe blood and fluid loss mean that the heart is unable to pump enough blood to the body. This can cause organs to stop working.
Iatrogenic	Relating to illness caused by medical examination or treatment
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of effect.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Indirectness	The available evidence is different to the review question being addressed, in terms of PICO (population, intervention, comparison and outcome).
Inotropes	Drugs affecting muscle contraction, especially heart muscle
Insensible water loss	The amount of fluid lost on a daily basis from the lungs, skin, respiratory tract, and water excreted in the faeces.
Intervention	In medical terms this could be a drug treatment, surgical procedure, diagnostic or psychological therapy. Examples of public health interventions could include action to help someone to be physically active or to eat a more healthy diet.
Intraoperative	The period of time during a surgical procedure.
Isotonic	In the context of a human body cell, an isotonic solution is one which has the same solute concentration as the cell.
Length of stay	The total number of days a participant stays in hospital.
Meta-analysis	A method often used in systematic reviews. Results from several studies of the same test or treatment are combined to estimate the overall effect of the treatment.
Neonate	Infants aged 28 days and under (born at term)
Observational study	Individuals or groups are observed or certain factors are measured. No attempt is made to affect the outcome. For example, an observational study of a disease or treatment would allow 'nature' or usual medical care to take its course. Changes or differences in one characteristic (for example, whether or not people received a specific treatment or intervention) are studied without intervening. There is a greater risk of selection bias than in experimental studies.
Odds ratio	Odds are a way to represent how likely it is that something will happen (the probability). An odds ratio compares the probability of something in one group with the probability of the same thing in another. An odds ratio of 1 between 2 groups would show that the probability of the event (for example a person developing a disease, or a treatment working) is the same for both. An odds ratio greater than 1 means the event is more

Term	Definition
	likely in the first group. An odds ratio less than 1 means that the event is less likely in the first group. Sometimes probability can be compared across more than 2 groups – in this case, one of the groups is chosen as the 'reference category', and the odds ratio is calculated for each group compared with the reference category. For example, to compare the risk of dying from lung cancer for non-smokers, occasional smokers and regular smokers, non-smokers could be used as the reference category. Odds ratios would be worked out for occasional smokers compared with non-smokers and for regular smokers compared with non-smokers. See also confidence interval and risk ratio (relative risk).
Oedema	Excessive fluid in/around cells
Oliguria	Reduced secretion of urine
Outcome	The impact that a test, treatment, policy, programme or other intervention has on a person, group or population. Outcomes from interventions to improve the public's health could include changes in knowledge and behaviour related to health, societal changes (for example, a reduction in crime rates) and a change in people's health and wellbeing or health status. In clinical terms, outcomes could include the number of patients who fully recover from an illness or the number of hospital admissions, and an improvement or deterioration in someone's health, functional ability, symptoms or situation. Researchers should decide what outcomes to measure before a study begins.
P value	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that one seems more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance) it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Perioperative	The period from admission through surgery until discharge, encompassing the preoperative and postoperative periods.
Plasma-Lyte	See crystalloids
Point-of-care testing	Laboratory testing or analyses performed in the clinical setting by non-laboratory healthcare professionals
Polyuria	Excessive excretion of urine
Postoperative	Pertaining to the period after patients leave the operating theatre, following surgery.
Power (statistical)	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Preoperative	The period before surgery commences.
Primary care	Healthcare delivered outside hospitals. It includes a range of services provided by GPs, nurses, health visitors, midwives and other healthcare professionals and allied health professionals such as dentists, pharmacists and opticians.
Prospective study	A research study in which the health or other characteristic of participants is monitored (or 'followed up') for a period of time, with events recorded as

Term	Definition
	they happen. This contrasts with retrospective studies.
Quality of life	See 'Health-related quality of life'.
Quality-adjusted life year (QALY)	A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health. QALYS are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality of life score (on a scale of 0 to 1). It is often measured in terms of the person's ability to perform the activities of daily life, freedom from pain and mental disturbance.
Randomisation	Assigning participants in a research study to different groups without taking any similarities or differences between them into account. For example, it could involve using a random numbers table or a computer-generated random sequence. It means that each individual (or each group in the case of cluster randomisation) has the same chance of receiving each intervention.
Randomised controlled trial (RCT)	A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug or treatment. One group (the experimental group) receives the treatment being tested; the other (the comparison or control group) receives an alternative treatment, a dummy treatment (placebo) or no treatment at all. The groups are followed up to see how effective the experimental treatment was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.
RCT	See 'Randomised controlled trial'.
Redistribution	This refers to the internal redistribution of water and electrolytes across the intracellular and extracellular compartments, which can lead to the development of tissue oedema and the sequestering of fluid within body cavities. This may occur during sepsis, critical illness, or following major surgery.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Review question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Ringer's lactate solution	See crystalloids
Risk ratio (relative risk)	The ratio of the risk of disease or death among those exposed to certain conditions compared with the risk for those who are not exposed to the same conditions (for example, the risk of people who smoke getting lung cancer compared with the risk for people who do not smoke). If both groups face the same level of risk, the relative risk is 1. If the first group had a risk ratio of 2, subjects in that group would be twice as likely to have the event happen. A risk ratio of less than one means the outcome is less likely in the first group. Risk ratio is sometimes referred to as relative risk.
Sensitivity	How well a test detects the thing it is testing for. If a diagnostic test for a disease has high sensitivity, it is likely to pick up all cases of the disease in people who have it (that is, give a 'true positive' result). But if a test is too sensitive it will sometimes also give a positive result in people who don't have the disease (that is, give a 'false positive'). For example, if a test were developed to detect if a woman is 6 months

Term	Definition
	pregnant, a very sensitive test would detect everyone who was 6 months pregnant, but would probably also include those who are 5 and 7 months pregnant. If the same test were more specific (sometimes referred to as having higher specificity), it would detect only those who are 6 months pregnant, and someone who was 5 months pregnant would get a negative result (a 'true negative'). But it would probably also miss some people who were 6 months pregnant (that is, give a 'false negative'). Breast screening is a 'real-life' example. The number of women who are recalled for a second breast screening test is relatively high because the test is very sensitive. If it were made more specific, people who don't have the disease would be less likely to be called back for a second test but more women who have the disease would be missed.
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study. Multi-way simple sensitivity analysis (scenario analysis): 2 or more parameters are varied at the same time and the overall effect on the results is evaluated. Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (for example, Monte Carlo simulation).
Stakeholder	An organisation with an interest in a topic that NICE is developing a clinical guideline or piece of public health guidance on. Organisations that register as stakeholders can comment on the draft scope and the draft guidance. Stakeholders may be: • manufacturers of drugs or equipment • national patient and carer organisations • NHS organisations • organisations representing healthcare professionals.
Systematic review	A review in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. It may include a meta-analysis.
Tachycardia	Increased heart rate
Tachypnoea	Rapid breathing
Young people	13 to under 16 years