NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology Appraisals and Guidance Information Services

Static List Review (SLR) report

Title and TA publication number of static topic:	TA74; Pre-hospital initiation of fluid replacement therapy in trauma
Recommendation:	Recommendations 1.1, 1.2 and 1.4 in TA74 should be updated and replaced by the forthcoming NICE guideline for 'Major trauma'. That we consult on this proposal.
Rationale:	TA74 was considered for review and moved to the static list in 2007. Since this decision was taken a clinical guideline for 'Major trauma' has been referred onto the NICE work programme and will contain recommendations on the management of haemorrhage in pre-hospital and hospital settings. The draft guideline currently includes recommendations on volume resuscitation and fluid replacement in pre-hospital and hospital settings, which are directly relevant to recommendations 1.1, 1.2 and 1.4 in TA74. Rather than 2 separate pieces of NICE guidance containing similar recommendations in this setting, it would be appropriate to allow the guideline to update and replace recommendations 1 .1, 1.2 and 1.4 in TA74. Recommendations 1.3, 1.5, 1.6 and 1.7 will remain as static Technology Appraisal guidance. The clinical guideline for 'Major Trauma' should consider updating the remaining extant recommendations within TA74 at the next review consideration point following final publication.

1. Publication date:	January 2004

2. Date added to static list:	January 2007
3. Date the last searches were run:	December 2011
4. Current guidance:	This guidance covers the management of adults, children and infants with physical injuries as a result of trauma, in whom there is evidence of obvious or probable blood loss. It does not cover the management of isolated closed head injury. For the purpose of this guidance, it is assumed that basic life support and ongoing assessment of the trauma victim are taking place as appropriate. The requirement for cannulation is considered only within the context of pre-hospital intravenous fluid (IV fluid) administration. 1.1 It is recommended that in the pre-hospital management of adults and older children, IV fluid should not be administered if a radial pulse can be felt (or, for penetrating torso injuries, if a central pulse can be felt). 1.2 In the absence of a radial pulse (or a central pulse for penetrating torso injuries) in adults and older children, it is recommended that IV fluid should be administered in boluses of no more than 250 ml. The patient should then be reassessed, and the process repeated until a radial pulse (or central pulse for penetrating torso injuries) is palpable. 1.3 The administration of IV fluid should not delay transportation to hospital, but when given in accordance with 1.2 above, consideration should be given to administration en route to hospital. 1.4 It is recommended that when IV fluid is indicated in the pre-hospital setting, crystalloid solutions should be the routine choice. 1.5 There is inadequate evidence on which the Institute can base recommendations on when pre-hospital use of IV fluid in young children and infants following trauma is appropriate, or on the volumes of fluid to use. However, there is a broad consensus

	that transfer to hospital should not be delayed by attempts to administer IV fluid. 1.6 It is recommended that only healthcare professionals who have been appropriately trained in advanced life-support techniques and pre-hospital care should administer IV fluid therapy to trauma patients in the pre-hospital setting. 1.7 Training programmes for healthcare professionals should incorporate the above recommendations.
5. Research recommendations from original guidance:	5.1 It is strongly recommended that studies be undertaken to evaluate the appropriateness of pre-hospital IV fluid therapy, including consideration of specific patient groups, for example, young children and infants, and patients with blunt versus penetrating injuries. Assessment of different protocols for pre-hospital care is essential in order to improve understanding of the risks and benefits of the use of IV fluids in this setting. 5.2 Validation studies are needed to assess the suitability of the absence of a radial pulse as an indicative marker of hypovolaemia. 5.3 It is recommended that studies be undertaken to compare the efficacy of blood volume resuscitation to different blood pressures.
6. Current cost of technology/ technologies:	Sodium chloride intravenous infusion 0.9% - net price 2-mL amp = 21p; 5-mL amp = 21p; 10-mL amp = 30p; 20-mL amp = £1.04; 50-mL amp = £3.41 Gelofusine - net price 500-mL Ecobag = £4.83, 1-litre Ecobag = £9.04 Source: (BNF, July 2015)
7. Cost information from the TA (if available):	According to manufacturers' list prices, the cost of crystalloid solutions is about £1–£1.80 per 500 ml unit, compared with about £4–£16.50 per 500 ml unit for colloid solutions, excluding VAT. The list price of HyperHAES (a combination fluid comprising hypertonic saline solution and starch) is £28 per 250 ml unit, which is higher than for

	other colloids. HyperHAES is intended for single-dose administration and may be followed by standard volume-replacement therapy. Costs may vary in different settings because of negotiated procurement discounts. Source: TA74 section 3.3
8. Alternative companies:	None
9. Changes to the original indication:	The marketing authorisations for hydroxyethyl starch products were suspended in all patient populations in 2013 (Source: European Medicines Agency, 19 December 2013; see also: MHRA (2013) Hydroxyethyl starches Benefit/ Risk review). After reviewing the available evidence, the European Medicines Agency later concluded that HES should be contraindicated in critically ill patients or patients with sepsis or burns. However, HES can be used in patients with acute blood loss, where treatment with crystalloids alone is not sufficient. In order to minimise potential risks in these patients, HES solutions should not be used for more than 24 hours and patients' kidney function should be monitored after HES administration. Further information is available on the MHRA website (19 December 2014).
10. New relevant trials:	**Crystalloid Versus Hydroxyethyl Starch Trials (CHEST)** NCT00935168 Phase 3 Purpose: to determine whether patients in the Intensive Care Unit who receive fluid resuscitation with either hydroxyethyl starch (a synthetic colloid solution) or saline (a salt solution), have an increased rate of survival at 90 days. Results: Myburgh J, et al. (2012) Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care. NEJM, 367: 1901-1911.

	Scandinavian Starch for Severe Sepsis/Septic Shock Trial (6S) NCT00962156 Phase 3 Purpose: to assess the effects of HES 130/0.4 on mortality and endstage kidney failure in patients with severe sepsis Results: Perner et al. (2012) Hydroxyethyl Starch 130/0.42 versus Ringer's Acetate in Severe Sepsis. NEJM, 367: 124-134. **Ontario Prehospital Advanced Life Support (OPALS) Major Trauma Study** Results: Stiell IG, Nesbitt LP, Pickett W et al. (2008) The OPALS Major Trauma Study: impact of advanced life-support on survival and morbidity. *CMAJ: Canadian Medical Association Journal*, 178(9): 1141-1152. **Hypertonic Saline With Dextran for Treating Hypovolemic Shock and Severe Brain Injury** NCT00113685 Purpose: to evaluate the clinical outcome of patients following blunt traumatic injury with hypovolemic shock, who receive either lactated ringer's solution or hypertonic saline with dextran (HSD) resuscitation. Results: Bulger EM et al. (2008) Hypertonic resuscitation of hypovolemic shock after blunt trauma: a randomized controlled trial. *Archives of Surgery*, 143(2):139-48.

	Hypertonic Resuscitation Following Traumatic Injury NCT00316017 Purpose: to determine if hypertonic saline with and without dextran can improve overall survival in victims of trauma with shock. Status: terminated, futility & potential safety concerns Results: Bulger EM et al. (2011) Out-of-hospital hypertonic resuscitation after traumatic hypovolemic shock: a randomized, placebo controlled trial. *Archives of Surgery*, 253(3):431-441. **Field Trial of Hypotensive Versus Standard Resuscitation for Hemorrhagic Shock After Trauma (HypoResus)** NCT01411852 Purpose: to determine the feasibility and safety of hypotensive resuscitation for the early treatment of patients with traumatic shock compared to standard fluid resuscitation Status: completed, October 2014. Results available **Control of Major Bleeding After Trauma Study (COMBAT)** NCT01838863 Purpose: a prospective, randomized comparison of fresh frozen plasma versus standard crystalloid intravenous fluid as initial resuscitation fluid Status: recruiting

	Estimated completion: December 2017
11. Relevant NICE guidance (published or in progress):	**Published** Intravenous fluid therapy in adults in hospital (2013) NICE guideline CG174 Intravenous fluid therapy in adults in hospital (2014) NICE quality standard 66 Intravenous fluid therapy in adults in hospital overview (2015) NICE pathway Head injury: Triage, assessment, investigation and early management of head injury in children, young people and adults (2014) NICE guideline CG176 (replaces CG56). Head injury overview (2015) NICE pathway **In development** Intravenous fluids in children and young people in hospital. NICE guideline. Publication expected December 2015. Major trauma. NICE guideline. Publication expected February 2016 comprising: • Complex fractures: assessment and management of complex fractures • Fractures: diagnosis, management and follow up of fractures • Major trauma: assessment and management of airway, breathing and ventilation, circulation, haemorrhage and temperature control • Major trauma services: service delivery for major trauma • Spinal injury assessment: assessment and imaging, and early management for spinal injury (spinal column or spinal cord injury)

	Quality and Productivity Topics Colloids versus crystalloids for fluid resuscitation in critically ill patients. Published: December 2011. Cost and risk management in critical care: reducing the use of colloids. Provided by: City Hospitals Sunderland NHS Foundation Trust. Published: January 2013.
12. Relevant safety issues:	After reviewing the available evidence, the European Medicines Agency concluded that HES should be contraindicated in critically ill patients or patients with sepsis or burns. However, HES can be used in patients with acute blood loss, where treatment with crystalloids alone is not sufficient. In order to minimise potential risks in these patients, HES solutions should not be used for more than 24 hours and patients' kidney function should be monitored after HES administration. Further information is available on the MHRA website (19 December 2014).
13. Any other additional relevant information or comments:	Perel P Roberts I, Ker K (2013) Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database of Systematic Reviews*, 2013 Issue 2. Art. No.: CD000567. Mutter TC et al (2013) Hydroxyethyl starch (HES) versus other fluid therapies: effects on kidney function. *Cochrane Database of Systematic Reviews*, 2013 Issue 7. Art. No.: CD007594. Bunn F, Trivedi D (2012) Colloid solutions for fluid resuscitation. *Cochrane Database of Systematic Reviews*, 2012 Issue 7. Art. No.: CD001319. National Confidential Enquiry into Patient Outcome and Death (2007) Trauma. Who cares? Association of Paediatric Anaesthetists of Great Britain and Ireland (2007) Consensus

	guideline on perioperative fluid management in children.
14. Technical Lead comments and recommendation:	There have been a number of developments relevant to the area of pre-hospital initiation of fluid replacement therapy in trauma since TA74 was placed onto the static list in 2007. This has included new evidence in related areas. NICE is also developing a clinical guideline on major trauma, which will contain recommendations on the management of haemorrhage in pre-hospital and hospital settings. The following will discuss the impact of these new developments. Draft recommendations for the forthcoming NICE clinical guideline on major trauma (final publication expected February 2016) are due to be released at the same time as the Technology Appraisal Static List Review. The draft guideline includes recommendations on volume resuscitation and fluid replacement in pre-hospital and hospital settings, which are directly relevant to recommendations 1.1, 1.2 and 1.4 in TA74. Currently, recommendation 1.1 in TA74 states that IV fluid should not be administered if a radial pulse can be felt (or, for penetrating torso injuries, if a central pulse can be felt) and recommendation 1.2 states that in the absence of a radial pulse (or a central pulse for penetrating torso injuries) IV fluid should be administered in boluses of no more than 250 ml. Recommendation 1.2 further states that the patient should then be reassessed, and the process repeated until a radial pulse (or central pulse for penetrating torso injuries) is palpable. Recommendation 1.4 states that when IV fluid is indicated in the pre-hospital setting, crystalloid solutions should be the routine choice. The clinical guideline on major trauma is proposing that in pre-hospital settings, volume resuscitation should be titrated to maintain a palpable central pulse (carotid of femoral), and crystalloids should only be used to replace fluid volume in patients with active bleeding if blood products are not available. The draft guideline also contains recommendations on the ratio of plasma to be used to replace fluid volume in adults and children. Several Cochrane reviews were identified which considered the technologies in TA74: Perel et al. (2013) compared colloids with crystalloids for fluid resuscitation in critically ill

	patients; Mutter et al. (2013) considered the effect of hydroxyethyl starches on kidney function compared to other fluid resuscitation therapies in different patient populations; and Bunn et al. (2012) compared different colloid solutions in patients thought to need volume replacement. The studies found no evidence that colloids reduced the risk of death when compared with crystalloids, and noted that colloids are considerably more expensive. Further, the reviews found that the use of hydroxyethyl starches (HES) may increase the risk of acute kidney injury, renal replacement therapy or mortality. These studies may have less relevance to TA74 in light of the NICE draft clinical guideline recommendation that crystalloids should only be used to replace fluid volume in patients with active bleeding if blood products are not available In 2013 the MHRA produced an assessment report 'Hydroxyethyl starches benefit/ risk review'. It noted the results of 2 large randomised controlled trials comparing HES with crystalloid for critically ill patients in the intensive care setting: the '6S' trial (Perner et al., 2012) comparing 6% HES with Ringer's acetate for people with severe sepsis in intensive care (n=798), and the 'CHEST' trial (Myburgh et al., 2012) comparing 6% HES with 0.9% sodium chloride fluid resuscitation for people in intensive care (n=7000). For the HES arms, there was an increased requirement for renal replacement therapy (p=0.04 both trials) and the 6S trial reported a statistically significantly higher mortality at day 90 (p=0.03). The MHRA assessment report also noted the results of 3 meta-analyses (including Perel et al. 2013) of HES compared with crystalloids. On the basis of the available evidence, the MHRA concluded that the use of HES, when compared with crystalloids, offered no additional clinical benefit, and was associated with an increased risk of mortality, renal replacement therapy or renal failure, as well as other serious adverse reactions in patients with sepsis and in the critically ill. It noted that these risks could present in patient populations other than those identified in the report, and therefore it suspended the marketing authorisations for HES products in all patient populations. After reviewing the available evidence, the European Medicines Agency later concluded that HES should be contraindicated in critically ill patients or patients with sepsis or burns. However, HES can be used in patients with acute blood loss,

	where treatment with crystalloids alone is not sufficient. Further information is available on the MHRA website. Several studies were identified that considered intravenous fluid administration, including 'HypoResus' (2013) and OPALS (Stiell et al., 2008). HypoResus was a randomised field trial (n=191) in the pre-hospital and emergency room setting. It compared 'standard' resuscitation (defined as intravenous fluids given as rapidly as possible with 2 litres of normal saline fluid given as an initial bolus) with hypotensive resuscitation (either no fluids, or, if a radial pulse was not detected, 250 ml of normal saline fluids given only as necessary) in people with haemorrhagic shock following trauma. The primary outcome, the total volume of early crystalloid given, showed that those in the standard resuscitation group received 2.04 litres (95% confidence interval [CI] 1.76-2.32) and those in the controlled resuscitation group received 1.04 litres (95% CI 0.75 to 1.34). There was no statistically significant difference in the primary mortality outcome, blunt and penetrating trauma 24 hour mortality (odds ratio [OR] =0.39, 95% CI 0.12-1.25), and the secondary mortality outcome, penetrating trauma only 24 hour mortality (OR =1.92, 95% CI 0.19 to 19.11). However, the hypotensive group had a statistically significantly lower incidence of blunt trauma only 24 hour mortality (OR=0.17, 95% CI 0.03 to 0.92). There was also data on adverse events which showed that 8.42% of those in the 'standard' resuscitation group, and 18.75% of those in the hypotensive group, experienced adverse events (no statistical analysis presented). Whilst these results are not limited to the pre-hospital setting and are therefore not directly relevant to TA74, they suggest that a controlled approach to resuscitation, as recommended in TA74, may be more clinically effective, although with possibly a higher incidence of adverse events. 'OPALS' (Stiell et al., 2008) was a large observational before and after study that compared a basic life support programme (n=1373) with an advanced life support programme (n=1494, where additional advanced interventions included administration of pre-hospital IV fluid) for adults who had experienced a major trauma. The results generally showed that there were no differences in mortality and morbidity for the basic

	and advanced life support programmes, other than in people with impaired consciousness (Glasgow coma scale less than 9) who experienced worse outcomes with advanced life support (p=0.02). As the advanced life support programme contains additional interventions other than intravenous fluid therapy, the findings are not directly relevant to TA74. However, the study conducted logistic regression analyses for individual interventions, comparing survivors with non-survivors. It found that, for those who received intravenous fluid administered at the scene, there was no statistically significant difference in survival (adjusted OR 0.8, 95% CI 0.4–1.4). Several studies compared different fluid types. For example, two randomised controlled trials by Bulger et al (2008, 2011) compared pre hospital treatment with hypertonic infusions (7.5% hypertonic saline and 6% dextran 70 [HSD] or 7.5% hypertonic saline) with isotonic infusion (lactated ringer or 0.9% saline) in patients with trauma and hypotension. Both RCTs had to be terminated after interim analyses because of futility and safety concerns. An a priori subgroup analysis in one trial suggested patients with massive blood loss who required 10U or more of packed cell volume experienced better acute respiratory distress syndrome (ARDS) free survival with hypertonic infusion (Bulger et al, 2008). However, generally no statistically significant results were found in the intention to treat populations. No new studies have been identified from the literature that addressed the research recommendations in TA74 on children and young people in the pre-hospital setting. However there is information either available or forthcoming for young children in the hospital setting. The Association of Paediatric Anaesthetists of Great Britain and Ireland (APA) (2007) has developed consensus guidelines on perioperative fluid management in children. Additionally, NICE currently has a clinical guideline in development for IV fluid therapy for children and young people in a hospital setting, which is expected to be published in December 2015. Both of these pieces of guidance are relevant at the point at which the setting for TA74 ends. In terms of ongoing studies, the COMBAT study will compare fresh frozen plasma with

	standard crystalloid intravenous fluid as initial resuscitation fluid in severely injured trauma patients during ambulance transfer. Study competition is expected in 2017. **Conclusion** As noted there have been several developments in the area of fluid therapy. In the literature, most developments do not impact on the main focus of TA74, which is the setting for the initiation of fluid replacement therapy. However, NICE is currently developing a guideline on major trauma, which will contain recommendations for the pre-hospital setting on volume resuscitation and the type of fluid replacement that should be used. Therefore, it is proposed that the new recommendations in the forthcoming NICE major trauma guideline should update recommendations 1.1, 1.2 and 1.4 in TA74.

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Appendix 1 – explanation of options

Options	Consequence	Selected – 'Yes/No'
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the [specify STA or MTA] process.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline.	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	Yes (recs 1.1, 1.2 and 1.4)
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes (recs 1.3, 1.5, 1.6 and 1.7)