Review protocol for fluid therapy for the management of DKA

ID	Field	Content
0.	PROSPERO registration number	N/ A
1.	Review title	Route of administration, type of fluid and rate and volume of rehydration for the management of diabetic ketoacidosis (DKA)
2.	Review question	In children and young people with diabetic ketoacidosis: • What is the appropriate route of fluid administration for rehydration? • What fluids (including additives) should be used for rehydration? • At what rate, including volume of fluid should children and young people be rehydrated?

3.	Objective	To determine the optimal route of administration, type of fluid (including additives) and rate and volume for rehydration in children and young people with DKA.
4.	Searches	The following databases will be searched: Clinical searches: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • DARE • MEDLINE • MEDLINE In Process • MEDLINE ePubs • Emcare Economic searches: • Econlit • Embase • HTA • MEDLINE • MEDLINE In Process

		• MEDLINE ePubs • NHS EED • Emcare Searches will be restricted by: • English language • Study designs of RCTs, SRs and observational studies will be applied • Animal studies will be excluded from the search results • Conference abstracts will be excluded from the search results • The search will be date limited to find studies from 1st June 2014 to present Other searches: • The MHRA website will be searched for reports of adverse events The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion (depending on publication date).

		The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Diabetic ketoacidosis in children and young people with type 1 and type 2 diabetes.
6.	Population	Inclusion: Children and young people with type 1 or type 2 diabetes with diabetic ketoacidosis (although the diabetes may not yet have been recognised, for example, if the child or young person is presenting for the first time with DKA) Diabetic ketoacidosis: A serious complication of diabetes. Diagnosis in children and young people who have: • Acidosis and a bicarbonate of <15 mmol/L **or** pH <7.3 and • Ketones > 3.0 mmol per litre Severity of DKA is categorised by the degree of acidosis: • **Mild DKA**: venous pH <7.3 or serum bicarbonate <15 mmol/L • **Moderate DKA**: venous pH <7.2 or serum bicarbonate <10 mml/L • **Severe DKA**: venous pH <7.1 or serum bicarbonate <5 mmol/L Definition based on the International Society for Paediatric and Adolescent Diabetes (ISPAD) 2018 consensus guideline on diabetic ketoacidosis and hyperglycaemic hyperosmolar state.

		Studies using different definitions of diabetic ketoacidosis will be included and assessed appropriately through GRADE by downgrading for indirectness. **Note:** Children and young people are defined as those younger than 18 years of age. In practice, children and young people can also be defined as aged 18 years and up to the 19th birthday when considering paediatric best practice tariffs. Studies including children and young people aged younger than 18 years and those including young people aged 18 years and up to their 19th birthday will be considered for inclusion. Exclusion: Children and young people with other forms of diabetes mellitus (for example, monogenic diabetes and cystic fibrosis-related diabetes) Studies which include a mixed population (children and young people with type 1 or type 2 diabetes) but do not report the data separately will also be included
7.	Intervention	**Route of administration:** • Oral • Intravenous

		Type of fluids:
		• Any isotonic fluid that can be taken orally
		
		• Fluids administered intravenously:
		  o Saline (sodium chloride) solution at different concentrations (e.g. 0.45% or 0.9%)
		  o Hartmann's solution
		  o Ringer's lactate solution
		• IV fluid with additives:
		  o Glucose
		  o Potassium
		  o Bicarbonate
		  o Phosphate
		
		Volume and rate of rehydration:
		• Oral:
		  o Different volumes e.g. high volume or low volume (as defined by author)
		• IV:
		  o Different rates e.g. rapid rate, fast rate or slow rate (as defined by author)
		  o Different volumes e.g. high volume or low volume (as defined by author)

8.	Comparator	**Route of administration:** • Oral vs IV

		Type of fluids:
		• Different oral fluids compared to each other*
		• Different intravenous fluids compared to each other*
		  ○ Different additives compared to each other**
		  ○ Additives compared to no additives. **
		* Rate and volume should be the same in both arms of the study.
		** Fluid regimen should be the same in both arms of the study.
		Volume and rate of rehydration:
		Oral fluids:
		• Different volumes compared to each other (low volume vs. high volume)***
		IV fluids:
		• Different rates compared to each other (e.g. slow rate vs. rapid rate) ***
		• Different volumes compared to each other (low volume vs. high volume) ***
		*** Type of fluid and route of administration should be the same in both arms of the study.

9.	Types of study to be included	• Systematic reviews and RCTs • Comparative prospective observational studies ○ If no comparative prospective observational studies are identified, comparative retrospective observational studies will be included.
10.	Other exclusion criteria	• Non-English language studies

		• Conference abstracts
11.	Context	This review is part of an update of the NICE guideline on diabetes (type 1 and type 2) in children and young people: diagnosis and management. This guideline covers children and young people (younger than 18 years) with type 1 and type 2 diabetes. This guideline will also cover all settings in which NHS care is received or commissioned.
12.	Primary outcomes (critical outcomes)	• Mortality • Incidence of cerebral oedema (this could cause morbidity or mortality), to include participants with symptoms or signs suggestive of cerebral oedema (for example, development of unconsciousness) provided these are reported as being related to cerebral oedema Note: Core outcome sets were explored however none were identified for this population. Important follow up points: • During treatment (first hour, 24 hours, 48 hours) • After recovery from DKA (up to a week, 3 months or 6 months post discharge or recover) For further information on how data will be analysed see Section 16.
13.	Secondary outcomes (important outcomes)	• Time to resolution of dehydration • Rate of change of blood glucose concentration or resolution of hyperglycaemia • Resolution of acidosis/ resolution of ketosis • Serum chloride concentration • Serum sodium concentration • Healthcare utilisation (for example, duration of admission, requirement for ventilation [as a proxy for severity of DKA or presence of cerebral oedema]) • Acute cases of renal failure

		• Neurologic status - decline in neurological status measured using validated scores such as the Glasgow Coma Scale score (e.g. magnitude of decline or the duration of time in which GCS was less than 14) • IQ (assessed using validated scales such as the Wechsler Preschool and Primary School Scale of Intelligence short form) Note: Core outcome sets were explored however none were identified for this population.
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. This review will make use of the priority screening functionality within the EPPI-reviewer software. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. Randomised control trials (individuals or cluster) will be assessed using the Cochrane risk of bias tool 2.0.

		Assessment of observational studies will be dependent on study design. Cohort studies will be assessed using the Cochrane ROBINS-1 tool.

16.	Strategy for data synthesis	For details please see section 6 of Developing NICE guidelines: the manual
		
		Both RCTs and comparative observational studies will be included in the review. When conducting GRADE, RCT evidence will start as high quality evidence while comparative observational evidence will start as moderate quality evidence.
		
		Meta-analysis will be conducted where appropriate.
		
		Evidence will be stratified ~~grouped~~ in the following categories:
		
		• Type 1 diabetes
		
		• Type 2 diabetes
		
		Furthermore, outcomes in these categories will be stratified into the following time-points:
		
		• During treatment:
		  ○ first hour
		  ○ 24 hours
		  ○ 48 hours
		• After recovery from DKA and patient discharge:
		  ○ Up to a week post discharge or recovery from DKA
		  ○ 3 months post discharge or recovery from DKA (or the one nearest to 3 months if multiple time-points are given)

		○ 6 months post discharge or recovery from DKA (or the one nearest to 6 months if multiple time-points are given) Studies which include a mixed population (children and young people with type 1 or type 2 diabetes) but do not report the data separately will also be included and will be assessed appropriately through GRADE by downgrading for indirectness. These studies will also be analysed separately to studies including children and young people with type 1 or type 2 diabetes. Additionally, a definition of ketoacidosis has been provided but studies using different definitions will be included and assessed appropriately through GRADE by downgrading for indirectness. Specific definitions have not been provided for different rates (e.g. rapid, fast or slow rate) or volumes (e.g. high or low volume). Definitions provided by the authors will be included and pooled together in the meta-analysis.

17.	Analysis of sub-groups	For all three questions results will be stratified by the following subgroups where possible:
		• Age:
		  ○ Children under 5s
		  ○ School age children (5-12 years)
		  ○ Adolescents (>12 years)
		• Recognised diabetes (defined as a child known to have diabetes mellitus)
		• First presentation of diabetes (e.g. if the child or young person is presenting for the first time with DKA)
		• Severity of DKA(based on ISPAD definition (see Section 6))
		
		For question examining the rate and volume of fluid administration:
		• results will be stratified by type of fluid.
		
		For question examining type of fluid:
		• results will be stratified by rate and volume of fluid
		
		If heterogeneity is present, a random effects (RE) model will be adapted.

18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic

		☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	6/12/19		
22.	Anticipated completion date	16/12/20		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☐	☐
		Piloting of the study	☐	☐

		selection process		
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	**5a. Named contact** Guideline Updates Team		

		5b Named contact e-mail Diabetesupdate@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE)
25.	Review team members	From the Guideline Updates Team: • Dr Caroline Mulvihill • Ms Shreya Shukla • Mr Gabriel Rogers • Mr Thomas Jones • Ms Sarah Glover
26.	Funding sources/sponsor	This systematic review is being completed by the Centre for Guidelines which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part

		of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10158
29.	Other registration details	None
30.	Reference/URL for published protocol	None
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Diabetic ketoacidosis, rehydration, fluid therapy, volume, rate, cerebral oedema, children, young people
33.	Details of existing review of same topic by same authors	None

34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	
36.	Details of final publication	www.nice.org.uk