

BMJ Open Clinically assisted hydration in patients in the last days of life ('CHELsea II' trial): a cluster randomised trial

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To cite: Davies A, Waghorn M, Roberts M, *et al.* Clinically assisted hydration in patients in the last days of life ('CHELsea II' trial): a cluster randomised trial. *BMJ Open* 2022;**12**:e068846. doi:10.1136/bmjopen-2022-068846

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2022-068846>).

Received 01 October 2022
Accepted 03 November 2022



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ABSTRACT

Introduction Provision of clinically assisted hydration (CAH) at the end of life is one of the most contentious issues in medicine. The aim of the 'CHELsea II' trial is to evaluate CAH in patients in the last days of life. The objectives are to assess the effect of CAH on delirium, audible upper airway secretions, pain and other symptoms, and overall survival, as well as the tolerability of CAH, and the health economic impact.

Methods and analysis The study is a cluster randomised trial, involving 80 sites/clusters (mainly hospices) and 1600 patients. Sites will be randomised to an intervention, and this will become the standard of care during the trial. Intervention 'A' involves continuance of drinking (if appropriate), mouth care and usual end-of-life care. Intervention 'B' involves continuance of drinking, mouth care, usual end-of-life care and CAH, that is, parenteral fluids. The fluid may be given intravenously or subcutaneously, the type will be dextrose saline (4% dextrose, 0.18% sodium chloride) and the volume will be dependent on weight.

Participants will be assessed every 4 hours by the clinical team. The primary endpoint is the proportion of participants who develop delirium determined using the Nursing Delirium Screening Scale (using a cut-off score of ≥ 2). A mixed-effects logistic regression will be used to assess the difference in the odds of developing delirium between the interventions.

Ethics and dissemination Ethical committee approval has been granted by the Brighton and Sussex Research Ethics Committee (REC) (main REC for the UK: reference—IRAS 313640), and by the Scotland A REC (REC for adults with incapacity in Scotland: reference—22/SS/0053-IRAS-317637). The consent process follows the Mental Capacity Act: if the patient has capacity, then consent will be sought in the normal way; if the patient does not have capacity, then a personal/nominated consultee will be approached for advice about the patient entering the study. The consent process is slightly different in Scotland. The results of the trial will be published in general medical/palliative care journals, and presented at general medical/palliative care conferences.

Trial registration number ISRCTN65858561.

INTRODUCTION

Provision of clinically assisted hydration (CAH) at the end of life is one of the most

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The CHELsea II trial leads on from the CHELsea I trial (feasibility study), which achieved all of the pre-defined criteria for success.
- ⇒ The CHELsea II trial, as compared with previous randomised controlled trials, involves a clinically relevant population (ie, hydrated patients), an appropriate intervention (ie, 'maintenance' volumes of parenteral fluids) and a more relevant follow-up period (ie, until death).
- ⇒ The CHELsea II trial is adequately powered to address the primary endpoint (ie, the proportion of participants who develop delirium at any point during the trial).
- ⇒ The CHELsea II trial will mainly be undertaken in hospices, which means that the vast majority of participants will be patients with cancer (as the vast majority of hospice referrals are patients with cancer).

contentious issues in medicine, and indeed within the general population.¹ The reasons for contention include: (a) the lack of evidence for/against CAH^{2 3}; (b) the disparate opinions of healthcare professionals about CAH⁴; and (c) the generally positive opinions of patients and their carers about CAH (and generally negative opinions about withholding/withdrawing CAH).^{4 5} It is, therefore, unsurprising that the provision of CAH at the end of life is extremely variable in clinical practice (12%–88% of patients with cancer in the last week of life).⁶

The Cochrane review of medically assisted hydration (CAH) for adult palliative care patients concluded that 'there are insufficient good-quality studies to make any definitive recommendations. As a result, it is not possible to define the benefits and harms of this treatment clearly.'² The Cochrane review identified six relevant studies, although only three studies were randomised controlled trials (RCTs).^{7–9} However, none of the RCTs addressed the specific issue of the routine use

of CAH at the end of life, that is, the use of CAH to maintain hydration rather than to treat dehydration.

Thus, Cerchiatti *et al* included patients with evidence of dehydration (and/or renal failure), and the fluids were only given for 48 hours (and not continued until the patients' death)⁷; Bruera *et al* (2005) only included patients with evidence of dehydration, and the fluids were again only given for 48 hours (and not continued until the patients' death)⁸; and Bruera *et al* (2013) only included patients with evidence of dehydration, and the fluids were given for a variable duration, that is, 'until the patient was unresponsive, developed progressive coma or died'.⁹

These RCTs used low volumes of fluid (1 L/day), even though many of the patients were clinically dehydrated. On the basis of the National Institute for Health and Care Excellence (NICE) clinical guidance on intravenous fluid therapy in adults in hospital,¹⁰ 1 L/day would be an appropriate volume for maintenance in a non-dehydrated patient weighing only 33–40 kg, and would be an inappropriate volume for treatment in a dehydrated patient of any weight. Recommended maintenance intravenous fluid therapy is 25–30 mL/kg/day of water, with appropriate amounts of sodium, potassium, chloride and glucose.¹⁰

The CHELsea II trial is a balanced, cluster randomised trial of routine end-of-life care with CAH, versus routine end-of-life care without CAH, in patients in the last days of life. The CHELsea II trial (definitive study) leads on from the Research for Patient Benefit-funded CHELsea I trial (feasibility study),^{11 12} which achieved all of the predefined criteria for success.¹² It should be noted that the feasibility trial only included patients with cancer, but (at the request of the National Institute for Health and Care Research/relevant funding organisation) the definitive trial will also include patients with non-malignant disease.

The aim of this trial is to fully evaluate CAH in patients in the last days of life. Our hypothesis is that CAH in the last days of life reduces the prevalence of delirium (and the requirement for sedative medication), as a result of preservation of renal function, and prevention of build-up of drugs and toxins. Thus, the primary objective of this trial is to assess the effect of CAH on prevalence of delirium. The secondary objectives of this trial are to assess the effect of CAH on: (a) prevalence of audible upper airway secretions ('death rattle'); (b) prevalence of pain and other symptoms; (c) overall survival; (d) the tolerability of CAH and (e) the health economic impact of CAH.

The primary endpoint is the proportion of participants who develop delirium at any point during the trial. The Nursing Delirium Screening Scale (Nu-DESC) will be used to identify participants with delirium: it is a validated, five-item screening tool for delirium.¹³ The Nu-DESC will be completed as part of the regular 4-hour assessment of participants, and also when a participant is administered either 'as required' or regular medication

for delirium. Each item on the Nu-DESC is rated from 0 to 2 (where 0=absent and 2=severe), and a total score of ≥ 2 is indicative of delirium (although a total score of ≥ 1 has a higher sensitivity with a similar specificity).¹⁴ A cut-off of ≥ 2 is more clinically relevant (for a trial involving patients in the last days of life), and a score of ≥ 1 in domain 5/psychomotor retardation is indicative of hypoactive delirium.

METHODS

The trial start date was on 1 October 2022, and the planned end date is on 30 September 2024.

Study governance

The trial is sponsored by the University of Surrey and coordinated by the Surrey Clinical Trials Unit (based within the University of Surrey). Ethical committee approval has been granted by the Brighton and Sussex Research Ethics Committee (REC) (main REC for the UK: reference—IRAS 313640), and by the Scotland A REC (REC for adults with incapacity in Scotland: reference—22/SS/0053-IRAS-317637).

Patient and public involvement

Patient and public involvement (PPI) (ie, local PPI group, national Marie Curie Voices group) has been integral to the research programme, including supporting trial design, grant applications and trial oversight (CHELsea I trial). The CHELsea II Trial Steering Committee includes PPI representatives (who have been appointed by the National Institute for Health and Care Research).

Study design

The trial is a cluster randomised trial, where the research sites are randomised to one or other intervention. The intervention will become the standard of care at the research site and will be given to all participants unless there is a contraindication to the intervention (or an indication for the alternative intervention).

Study sites

The research sites (80 in total) will be either National Health Service (NHS) hospitals, or NHS/voluntary hospices in the four countries of UK (ie, England, Wales, Scotland, Northern Ireland). NHS hospitals will need to have a specialist palliative care team, and ideally either a palliative care inpatient unit or designated palliative care beds. NHS/voluntary hospices will need to have a palliative care inpatient unit.

Study population

Participants will be inpatients at the trial sites and will need to meet all of the inclusion criteria, and not meet any of the exclusion criteria for the trial. The clinical team will identify suitable patients, and then the research team will approach these patients or their family carers (as appropriate) to discuss the trial.

The inclusion criteria are as follows: (a) any sex; (b) age ≥ 18 years; (c) estimated prognosis of ≤ 1 week (as deemed by clinical team) and (d) patient unable to maintain sufficient oral fluid intake (< 1 L/day). The exclusion criteria are as follows: (a) patient is dehydrated (patient eligible after correction of dehydration); (b) patient has a relevant Advance Directive to Refuse Treatment; (c) clinical indication for CAH; (d) clinical contraindication to CAH; (e) contraindication to cannulation; (f) total parenteral nutrition/enteral feeding in situ; (g) patient has had delirium in last 24 hours; (h) patient has had audible upper airway secretions in last 24 hours; (i) patient likely to be transferred elsewhere for end-of-life care; (j) patient has clinically significant cardiac failure; (k) patient has clinically significant renal failure and (l) patient has clinically significant dementia.

Study interventions

Research sites will be randomised to either 'standard intervention A' or 'standard intervention B', and this will become the standard of care at the research site for the duration of this trial. These interventions represent the current standards of care in the UK. Intervention A involves: (a) continuance of oral intake—includes assistance with drinking as required; (b) regular 'mouth care'—mouth care should be performed at least every 4 hours and should correspond to the research site's usual practices; and (c) standard management of end-of-life symptoms/problems—should correspond to the research site's usual practices. Intervention B involves: (a) continuance of oral intake—as above; (b) regular mouth care—as above; (c) standard management of end-of-life symptoms/problems—as above; and (d) CAH.

The parenteral fluids may be given either intravenously (cannula present) or subcutaneously (no cannula present). Intravenous fluids must be administered using an infusion pump, and subcutaneous fluids must be administered using gravity. The type/volume of fluid administered is based on relevant NICE guidance¹⁰: the fluid to be given is dextrose saline (4% dextrose, 0.18% sodium chloride), and the volume to be given is dependent on the participant's weight. The volume of fluid is based on a figure of 25 mL/kg/day, which represents the lower limit for generic persons, and the upper limit for 'old' or 'frail' persons.¹⁰ If a recent weight is unavailable, and weighing the participant is problematic, then the clinical team may estimate the current weight.

Intravenous fluids should be administered according to the research site's usual procedures. Subcutaneous fluids should be administered according to the following guidelines: (a) site of cannula—the preferred cannula sites are the lower lateral abdomen and the upper lateral chest (rather than the upper arm or the upper leg). If the cannula needs to be changed, then an alternative site should be used; (b) type of cannula—the preferred cannula is a 24 g BD Saf-T-Intima cannula; (c) rationale for changing cannula—the decision to change/resite a cannula is at the discretion of the clinical team. Minimal

(asymptomatic) swelling is expected at the site of the cannula and is not in itself a reason to discontinue the infusion and/or resite the cannula; (d) rate of infusion—the preferred method of infusion is continuous infusion with the drop rate calculated in the usual manner.¹⁵

The decision to discontinue the CAH is at the discretion of the clinical team (rather than the research team). The CAH should be discontinued if the participant develops clinically significant adverse effects relating to the CAH, or the participant/personal consultee requests discontinuation. Minimal (asymptomatic) swelling is expected at the site of the cannula and is not in itself a reason to discontinue the infusion. If the swelling is moderate, then the cannula should be resited elsewhere. Similarly, if the infusion is not running, or the site of the cannula is inflamed, then the cannula should be resited elsewhere. The development of audible upper airways secretions ('death rattle') is also not in itself an indication to discontinue the infusion, since the development of this problem is independent of hydration status/use of CAH.^{16 17} The development of clinically significant (as determined by the clinical team) peripheral oedema and/or pulmonary oedema is an indication for discontinuation. However, mild peripheral oedema is not in itself an indication to discontinue the infusion. Thus, peripheral oedema is a common problem in patients at the end of life and is usually not related to 'overhydration'.

Study duration

The trial lasts for 14 days. However, it is expected that the majority of participants will have died within this time period (of their primary disease).

Study assessments

Participants will be reviewed every 4 hours during the trial by the clinical team and the following assessments completed: (a) Nu-DESC total score (table 1); (b) Modified Richmond Agitation and Sedation Scale score; (c) presence of audible upper airway secretions ('death rattle'); (d) presence of pain; (e) presence of shortness of breath; (f) presence of nausea and vomiting; (g) presence of adverse effects of CAH.

The clinical team will also record the participant's fluid intake (oral, CAH) and medications/other interventions provided to the participant (and the indications) during the trial. Data on usage of CAH paraphernalia (eg, cannulas, giving sets), and paraphernalia relating to other interventions, will also be recorded (to support the health economic analysis). Overall survival (from the time of randomisation) will be recorded. Participants who survive > 14 days will continue to be followed up in order to determine their date of death.

ANALYSIS

Sample size

The sample size is based on a 'clinically meaningful' reduction in the proportion of participants developing

Table 1 Nursing Delirium Screening Scale¹³

Features and description	Symptom rating
1. Disorientation Verbal or behavioural manifestation of not being oriented to time or place or misperceiving persons in the environment	0—absent 1—present but not severe 2—severe
2. Inappropriate behaviour Behaviour inappropriate to place and/or for the person; e.g., pulling at tubes or dressings, attempting to get out of bed when that is contraindicated, and the like	0—absent 1—present but not severe 2—severe
3. Inappropriate communication Communication inappropriate to place and/or for the person; e.g., incoherence, noncommunicativeness, nonsensical or unintelligible speech	0—absent 1—present but not severe 2—severe
4. Illusions/hallucinations Seeing or hearing things that are not there; distortions of visual objects	0—absent 1—present but not severe 2—severe
5. Psychomotor retardation Delayed responsiveness, few or no spontaneous actions/words; e.g., when the patient is prodded, reaction is deferred and/or the patient is unarousable	0—absent 1—present but not severe 2—severe
Total score	

delirium in the CAH intervention group (vs the non-CAH intervention group): a figure of 10% was deemed to be appropriate by the clinicians involved in the trial, and this figure was supported by clinical colleagues and members of the local PPI group.

To demonstrate a reduction of 10% in the proportion of participants developing delirium (defined as having a score of ≥ 2 on the Nu-DESC) would require 1038 evaluable participants with 90% power and at a significance level of 0.5. The calculation assumes the incidence of delirium in the non-CAH intervention group of 60% (as observed in the feasibility trial). To account for clustering in the responses of participants within centres of size 20, the sample size will be inflated by 1.475 using an estimate of the intracluster correlation of 0.025 (as observed in the feasibility trial). A further allowance of 5% for attrition suggests that 80 centres will be required (delivering 1600 participants).

Statistical analysis

The initial analysis will be undertaken at the end of the trial: there will be no planned interim analysis. However, an internal pilot will monitor recruitment, to ensure that the trial is meeting its pre-agreed targets for recruitment (and if not, either initiate remedial measures/stop the trial).

All analyses will be conducted according to the intention-to-treat principle in accordance with the randomised

intervention. A sensitivity analysis will be performed per protocol for the primary outcome, including only those participants who completed the trial in accordance with the approved protocol.

The primary analysis will use a multilevel regression approach, which recognises the hierarchical nature of the data, and participants nested within centres (clusters). A mixed-effects logistic regression will be used to assess the difference in the odds of delirium (defined as a Nu-DESC score ≥ 2 at any point during the trial observation period) between intervention groups, using intervention group as a covariate and adjusting for home country (England, Wales, Scotland, Northern Ireland) and by type of unit (hospital, hospice), which were used as stratification variables in the randomisation, disease category (cancer, non-malignant disease), age (< 65 years, ≥ 65 years) and sex (female, male). Centre will be included as a random effect, to allow for correlation in outcomes within clusters. A significance level of 5% will be used to judge significance for the primary outcome measure. The analysis will consider different 'times at risk' by adding an offset term of log (observed days to delirium) to the model, effectively adjusting the binomial denominator to reflect the number of 'trials' in each participant.

Health economic analysis

The economic analysis will take a healthcare payer perspective and seek to understand the potential impact of CAH as it pertains to resource utilisation.

A micro-costing exercise based on clinical records will be undertaken to estimate the cost for each patient, for each day they are in the study. We will also calculate the total costs and the mean total costs, for each group, and then compare them. Costs will initially be expressed as a cost per patient per day because patients are likely to be in the trial for varying lengths of time. Resources used (facilities, clinical time, treatment and medications) will be costed using nationally validated unit costs, supplemented by costs from finance departments as needed. Differences in cost per day between groups will be explored using mixed-effects models, recognising the cluster nature of randomisation, with intervention assignment as a covariate, adjusting for home country, disease category and centre as a random effect.

Given the concerns about the appropriateness of the use of quality-adjusted life years in palliative care, a cost-effectiveness approach will be adopted. Where the statistical analysis finds a significant difference between the intervention and control groups in the proportions of patients developing delirium, the economic evaluation will express the result as the cost per 1% reduction in the likelihood of an event. Uncertainty in input costs will be handled parametrically, sampling from a gamma curve. Sampling uncertainty in overall differences in cost per day between groups will be handled using generalised linear mixed models.

Ethics

The trial will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki, and are consistent with the ICH-GCP (International Council for Harmonisation of technical requirements for pharmaceuticals for human use - Good Clinical Practice) and applicable regulatory requirements.

Consent processes

The trial involves patients in the last week of life, and it is anticipated that many potential participants will be unable to provide informed consent. Moreover, all participants are expected to lose capacity during the trial. Informed consent will be required for all participants. The consent process that is being proposed for this trial is the same as used in the feasibility trial,^{11 12} which was developed in accordance with the Mental Capacity Act.¹⁸

If the patient is deemed to have capacity by the clinical team, then consent will be sought from the patient in the normal way by the research team. Of note, consent is not being sought for receiving the intervention (which will be the standard of care at the trial site), but for the use of routine clinical information collected during end-of-life care. If the patient is deemed not to have capacity, then a 'personal consultee' (ie, someone who has a role in caring for the person who lacks capacity or is interested in that person's welfare but is not doing so for remuneration or acting in a professional capacity) will be approached for advice about the patient entering the trial. In this trial, the personal consultee could be a relative of the person or a friend of the person. If the patient is deemed not to have capacity, and no personal consultee is available, then a 'nominated consultee' will be approached for advice about the patient entering the trial. In this trial, the nominated consultee will be the so-called 'study guardian' (ie, independent clinician).

If/when a participant who has consented to participate in the trial loses capacity, then a personal or a nominated consultee will be approached for advice about the participant continuing in the trial. Completion of another consent form will not be required, but agreement for the participant to remain in the trial must be recorded in the clinical notes. If a participant regains capacity during the trial, and was entered into the trial on the approval of a personal or a nominated consultee, then they must provide verbal or written (if appropriate) consent to remain in the trial.

It should be noted that the consent process is somewhat different in Scotland in that a 'welfare attorney', 'welfare guardian' or nearest relative will be able to consent to a person entering the trial, but that a nominated consultee (or similar) cannot provide advice about a person entering the trial.

Safety aspects

The clinical team may stop CAH (or start CAH) if clinically indicated: the clinical team will be asked to provide a reason for the decision. Stopping (or starting CAH) is not

synonymous with withdrawal from the trial, that is, the routine clinical assessments will continue until the end of the trial.

Withdrawal

Participants may withdraw from the trial at any point and do not have to give a reason for withdrawal. Withdrawal from the trial will not affect the care provided to the participant. Similarly, personal or nominated consultees may withdraw the participant from the trial at any point: personal consultees do not have to give a reason for withdrawal, but nominated consultees will be asked to provide a reason for withdrawal. Again, withdrawal from the trial will not affect the care provided to the participant. Participants who withdraw/are withdrawn will continue to be followed up in order to determine their date of death (but there will be no trial-related activities during this period).

DISSEMINATION

The Trial Management Group will develop a dissemination policy during the initial stages of the project. The results of the trial will be published in high-impact general medical and palliative care journals, and presented at major general medical and palliative care conferences.

Data deposition/curation

Standard operating procedures (SOPs) are in place to cover storage, access, archiving, and destruction of participants' personal and clinical information. These SOPs fully comply with the UK Data Protection Act 2018 and the European Union General Data Protection Regulation.

Requests for access to trial data will be considered, after formal application to the Trial Management Group/study sponsor (following completion of primary statistical analysis/publication of primary journal articles).

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Acknowledgements The authors would like to acknowledge the other NIHR grant co-applicants: Dr Barry Laird (University of Edinburgh), Professor Simon Noble (Cardiff University), Ms Jo Thompson (Royal Surrey NHS Foundation Trust), Dr Clare White (Northern Ireland Hospice) and Dr Kath Webber (Royal Surrey NHS Foundation Trust).

Contributors AD wrote the first draft of the protocol (with MW), with SSS writing the statistics section, HG writing the health economics section and MR writing the governance sections. All of the authors contributed to subsequent drafts of the protocol, and all of the authors approved the final version of the protocol.

Funding The CHELSEA II trial is funded by the National Institute for Health and Care Research (NIHR) in the UK (Health Technology Assessment Programme (NIHR131687)).

Disclaimer The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; peer reviewed for ethical and funding approval prior to submission.

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