A CLUSTER RANDOMISED TRIAL OF CLINICALLY-ASSISTED HYDRATION IN PATIENTS IN THE LAST DAYS OF LIFE

"CHELsea II Trial"

PROTOCOL: VERSION 1.0
(27th Jul 2022)

TRIAL REGISTRY NUMBER

International Standard Randomised Controlled Trials Number (ISRCTN) Register

Registry number: ISRCTN65858561

PROTOCOL VERSION NUMBER

Version 1 (27th July 2022)

SPONSOR

University of Surrey

Stag Hill, Guildford, Surrey GU2 7XH, United Kingdom

FUNDER

National Institute for Health Research (United Kingdom)

Grant number: NIHR131687

Approved

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature: Date:

..../...../.....

Name (please print):

.....

Position:

.....

Chief Investigator:

Signature: Date:

..../...../.....

Name: (please print):

.....

Statistician:

Signature: Date:

..../...../.....

Name: (please print):

.....

Approved

KEY TRIAL CONTACTS

Chief Investigator	Prof Andrew Davies School of Medicine, Trinity College Dublin, Dublin D2 Email: andavies@tcd.ie
Sponsor	University of Surrey Stag Hill, Guildford, Surrey GU2 7XH https://www.surrey.ac.uk
Funder	National Institute for Health Research (Department of Health and Social Care) https://www.nihr.ac.uk
Clinical Trials Unit	Surrey CTU (University of Surrey) Clinical Research Building, Egerton Road, Guildford Surrey GU2 7XP Tel: 01483 689898 Email: ctu@surrey.ac.uk
Trial Manager	Andy McClave c/o Surrey CTU (see above) Email: a.mcclave@surrey.ac.uk
Lead Statistician	Prof Simon Skene c/o Surrey CTU (see above) Email: s.skene@surrey.ac.uk
Lead Research Nurse	Melanie Waghorn c/o Surrey CTU (see above) Email: melanie.waghorn@surrey.ac.uk
Lead Health Economist	Prof Heather Gage c/o University of Surrey (see above) Email: h.gage@surrey.ac.uk

Approved

i. LIST of CONTENTS

Approved

ii. LIST OF ABBREVIATIONS

AE	Adverse Event
ADRT	Advance Directive to Refuse Treatment
CAH	Clinically-Assisted Hydration
CI	Chief Investigator
CRF	Case Report Form
CRM	Cluster Representation Mechanism
CRT	Cluster Randomised Trial
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DMEC	Data Monitoring & Ethics Committee
GCP	Good Clinical Practice
HRA	Health Research Authorisation
ICMJE	International Committee of Medical Journal Editors
IRAS	Integrated Research Application System
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials number
MAR	Missing at Random
MDT	Multidisciplinary Team
MHRA	Medicines and Healthcare products Regulatory Agency
m-RASS	Modified Richmond Agitation and Sedation Scale
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
Nu-DESC	Nursing Delirium Screening Scale
PI	Principal Investigator
PIS	Participant Information Sheet
PPI	Public and Patient Involvement
QC	Quality Control
RCT	Randomised Control Trial
R&D	Research & Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee

Approved

iii. TRIAL SUMMARY

Trial Title	A cluster randomised trial of clinically-assisted hydration in patients in the last days of life	
Internal ref. no. (or short title)	CHELsea II trial	
Clinical Phase	Phase III trial	
Trial Design	Cluster randomised trial	
Trial Participants	Patients in last days of life (< 7 days)	
Planned Sample Size	1600 participants	
Treatment duration	14 days (maximum)	
Follow up duration	n/a	
Planned trial period	October 2022-September 2024	
	Objectives	Outcome Measures
Primary	Prevalence of delirium	Nursing Delirium Screening Scale
Secondary	Level of sedation	Modified Richmond Agitation and Sedation Scale
	Prevalence of audible upper airway secretions	Clinical observation
	Prevalence of pain, shortness of breath, nausea & vomiting	Clinical observation
	Overall survival	Clinical observation
	Adverse effects (clinically-assisted hydration)	Clinical observation
	Health economic analysis	Resource utilisation
Intervention	Clinically-assisted hydration plus usual end-of-life care interventions (versus solely usual end-of-life care interventions)	
Formulation, dose, route of administration	Fluid type: 4% dextrose 0.18% sodium chloride Fluid volume: variable (weight dependent) Route of administration: intravenous or subcutaneous	

Approved

iv. TRIAL FLOW CHART

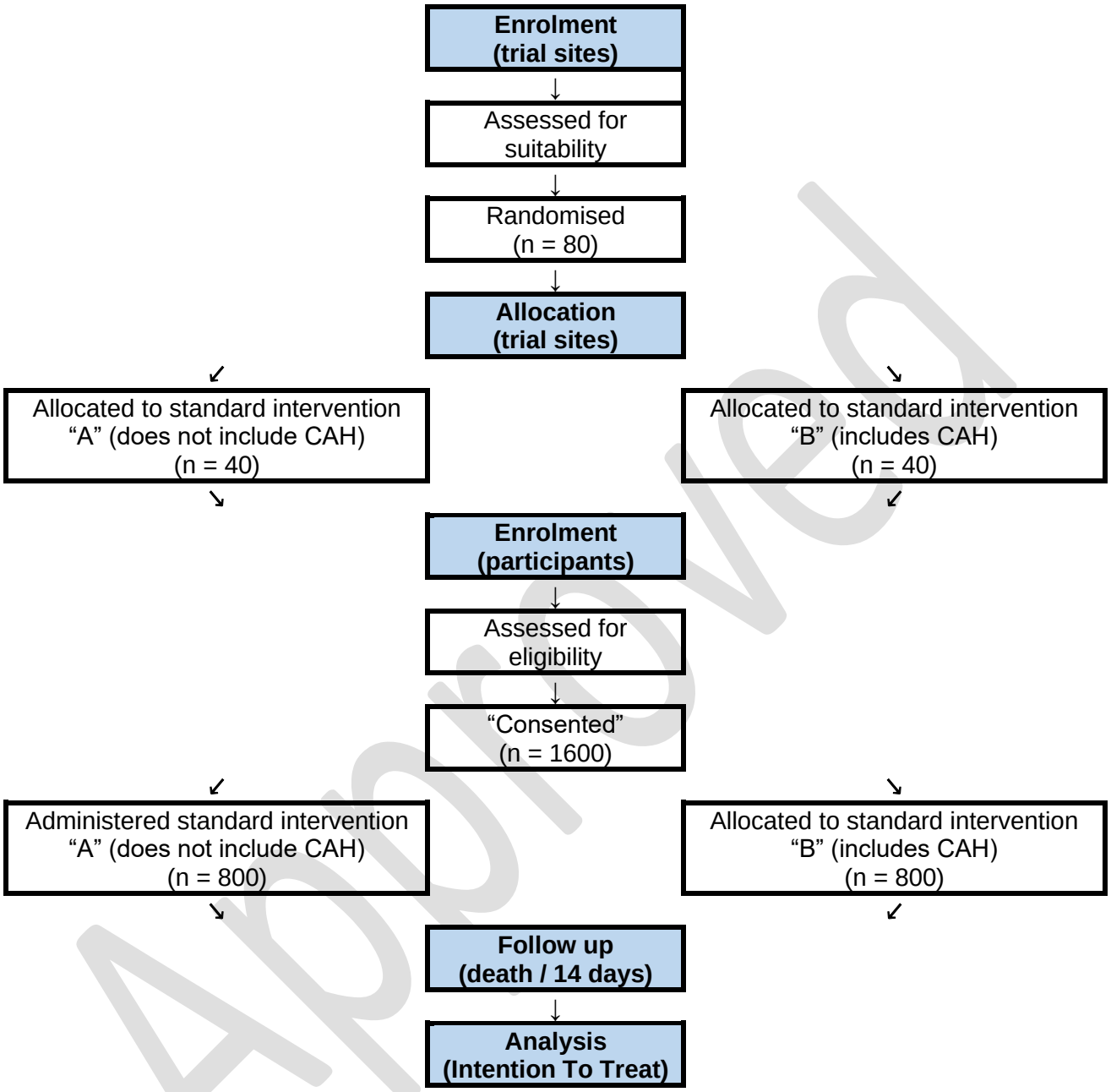

Figure 1 – Trial Flow Chart.

Approved

v. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

The trial will be coordinated by Surrey Clinical Trials Unit (based within the University of Surrey) and will be sponsored by the University of Surrey.

The trial will have a Trial Management Group (TMG), which will oversee the day-to-day management of the trial. The TMG will formally meet at least monthly (i.e., whole group), but will informally meet as often as necessary (i.e., specific members). The TMG will include Prof Davies (Chief Investigator), Prof Skene (Director of Surrey CTU), Ms Waghorn (Senior Research Nurse), Mrs Roberts (Clinical Project Manager of Surrey CTU), and dedicated Surrey CTU staff. The TMG will receive input from the Trial Steering Committee (TSC), and the Data Monitoring and Ethics Committee (DMEC) and will provide necessary feedback to the sponsor of the trial, the funder of the trial, the regulatory authorities, and the Principal Investigators (PIs)/research sites.

The trial will have a TSC, and its constitution, composition and function will follow the National Institute for Health Research (NIHR) research governance guidelines [1]. The primary role of the TSC is "to provide overall supervision for a project on behalf of the Project Sponsor and Project Funder and to ensure that the project is conducted to the rigorous standards set out in the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice". The TSC will include the following members: a) independent chair; b) independent clinician (palliative medicine consultant); c) independent statistician; d) public and patient involvement (PPI) representative(s); e) member of TMG (non-voting); f) sponsor representative (observer); g) local Cancer Research Network representative (observer). The TSC will meet at least every 6 months, and the meetings will be scheduled following the DMEC meetings (in order for the TSC to review the DMEC feedback). The TSC will provide a report for the Sponsor, the Funder, and the Project Management Group. (The report will also be sent to the PIs and the DMEC).

The trial will have a DMEC, and its constitution, composition and function will follow the NIHR research governance guidelines [1]. The primary role of the DMEC is "to monitor the data and make recommendations to the Trial Steering Committee on whether there are any ethical or safety reasons why the trial should not continue". The DMEC will include the following members: a) independent chair (non-medical); b) independent clinician (palliative medicine consultant); c) independent statistician; and d) independent medical ethicist. The DMEC will meet at least every 6 months, and the meetings will be scheduled before the TSC meetings (in

Approved

order for the TSC to review the DMEC feedback). The DMEC will provide a report for the TMC, the Sponsor, the Funder, and the Project Management Group. (The report will also be sent to the PIs).

1 BACKGROUND

The provision of clinically-assisted hydration (CAH) at the end-of-life is one of the most contentious issues in medicine, and indeed within the general population [2]. The reasons for contention include: a) the lack of evidence for/against CAH [3,4]; b) the disparate opinions of healthcare professionals about CAH [4]; and c) the generally positive opinions of patients and their carers about CAH (and the generally negative opinions about withholding/withdrawing CAH) [5,6] It is, therefore, unsurprising that the provision of CAH at the end-of-life is extremely variable within clinical practice (e.g., 12-88% cancer patients in the last week of life) [7].

The CHELsea II trial is a cluster randomised trial of standard end-of-life care with CAH (versus standard end-of-life care without CAH) in patients in the last days of life. The CHELsea II trial (definitive trial) leads on from the Research for Patient Benefit (RfPB) - funded CHELsea I trial (feasibility trial) [8,9], which achieved all of the pre-defined criteria for success, and especially the recruitment criterion (i.e., 200 patients from 12 trial sites in one year) [9]. It should be noted that the feasibility trial only included patients with cancer, but (on the basis of feedback from the HTA Funding Committee) the definitive trial will include patients with cancer and patients with non-malignant disease.

The Cochrane review of medically assisted hydration (aka 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” [3]. It identified 6 relevant studies, although only 3 studies were randomised controlled trials (RCTs) [10-12]. However, none of the RCTs addressed the specific issue of the routine use of CAH at the end-of-life.

Thus, Cerchietti et al (2000) included patients with evidence of dehydration (and/or renal failure), and the fluids were only given for 48 hours (and not continued until death) [10]; Bruera et al (2005) only included patients with evidence of dehydration, and the fluids were only continued for 48 hours (and not continued until death) [11]; and Bruera et al (2013) only included patients with evidence of dehydration, and the fluids were continued for a variable duration, i.e., “until the patient was unresponsive, developed progressive coma, or died” [12].

Approved

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 [13], 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)] [14].

The CHELsea II trial will uniquely address the specific issue of the "routine" use of CAH at the end-of-life: the CHELsea II trial will involve a clinically relevant population (i.e., hydrated patients), an appropriate intervention (i.e., "maintenance" volumes of parenteral fluids), a more relevant follow up period (i.e., until death), and a clinically relevant primary endpoint (i.e., delirium). Thus, the CHELsea trial will provide an evidence-base for the routine use of CAH at the end-of-life.

Delirium is one of the most common problems (25-85% patients) [14], and one of the most distressing problems [15], at the end-of-life. There are three subtypes of delirium: 1) hyperactive (agitated); 2) hypoactive (lethargic); and 3) mixed [16]. The clinical features of delirium are variable, but the two "essential concepts" are disordered attention (arousal), and disordered cognition [16]. Hyperactive delirium is associated with agitation, disorientation, delusions, and hallucinations (and is especially distressing for patients, relatives, and healthcare professionals) [15].

Dehydration is a recognised cause of delirium, and rehydration is a recommended intervention for delirium (in appropriate situations) [14]. However, the mainstay of the management is the use of antipsychotics and/or benzodiazepines [14]. Such drugs are used in ~50% patients in the last week of life [17], and although they are generally effective, they are often associated with untoward sedation (which necessarily impacts on the dying process, especially in terms of interpersonal communication).

2 RATIONALE

As discussed, the provision of CAH at the end-of-life is one of the most contentious issues in medicine. The "issue" is not new [18], and the debate primarily continues due to the lack of evidence for/against CAH [3,4]. Recently, the "issue" has received greater attention due to the widespread negative publicity about the Liverpool Care Pathway (LCP), and the subsequent Neuberger review of the LCP (which resulted in withdrawal of the LCP in the UK) [2].

Approved

The Neuberger review noted that “most of the submissions to the Review from relatives and carers that were critical of the LCP made reference to hydration and nutrition” [2]. Moreover, the Neuberger review comments that “if fluids are stopped without review over many days, death from dehydration will be inevitable, the lack of hydration having accelerated the dying process” [2]. It should be noted that the Neuberger review also highlighted concerns about the use of sedative drugs at the end-of-life (see above).

Data from recent national audits of end-of-life care in hospitals in the UK suggests that there has been an increase in the number of patients receiving CAH in the last days of life [19,20]. Thus, 29% patients were receiving CAH “at the time of the patient’s death” in 2013, whilst 43% patients were receiving CAH “in the last 24 hours before the patient’s death” in 2016 [20]. This major change in practice does not relate to any new evidence (or, indeed, any new guidance), and undoubtedly reflects the widespread negative publicity around the LCP, and specifically the negative publicity around withholding/withdrawing CAH at the end-of-life [2].

In terms of guidance, the NICE guideline on care of dying adults in the last days of life states that healthcare professionals should “discuss the risks and benefits of clinically assisted hydration with the dying person and those important to them” [21]. However, the NICE guideline highlights the lack of evidence on CAH (in order to do so): “clinically assisted hydration may relieve distressing symptoms or signs related to dehydration but may cause other problems”; “it is uncertain if giving clinically assisted hydration will prolong life or extend the dying process”; “it is uncertain if not giving clinically assisted hydration will hasten death” [21].

Thus, there has been a need for further research for some time, but recent events (and the resultant change in clinical practice despite no change in research evidence) has intensified the need for a robust (adequately powered) trial of CAH at the end-of-life. Moreover, the successful completion of the CHELsea I trial [9], which achieved all of its predetermined criteria for success, supports the undertaking of such a trial (utilising a cluster randomised trial design).

The trial will also facilitate the Consortium for Hospice and Community Research (which includes the NIHR) objective to increase the number of hospices recruiting to NIHR CRN portfolio studies [22]. Thus, the trial will recruit 1600 patients from 80 sites within the UK (predominantly inpatient hospices).

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

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

Approved

prevention of build-up of drugs and toxins. Furthermore, CAH will prevent death due to dehydration occurring before death due to the underlying disease (or its complications).

The aim of this cluster randomised trial is to fully evaluate CAH in patients in the last days of life. The primary objective is to assess the effect of CAH on prevalence of delirium. The secondary objectives are to assess the: a) effect of CAH on prevalence of audible upper airway secretions ("death rattle"); b) effect of CAH on prevalence of pain and other symptoms (shortness of breath, nausea and vomiting); c) tolerability of CAH; d) effect of CAH on survival; e) health economic impact of CAH: and f) differences in response to CAH between participants with cancer and participants with non-malignant disease.

3.1 Primary endpoint/outcome

The primary endpoint is the proportion of participants that develop delirium at any point during the trial. The Nursing Delirium Screening Scale (Nu-DESC) will be used to identify participants with delirium: the Nu-DESC is a validated, five item screening tool for delirium (Table 1) [23], which is endorsed for use at the end of life [24], and which was utilised in a recent Australian, multicentre, phase 2, CRT of a multimodal intervention to prevent delirium in participants with advanced cancer [25]. The Nu-DESC will be completed as part of the regular four hourly assessment of participants, and also when a participant is administered either "as-required" or regular medication for delirium (unless the latter relates to the regular four hourly assessment of the participant). Each "feature" on the Nu-DESC is rated from 0-2 (where 0 = absent, and 2 = severe), and a total score of >1 is indicative of delirium (although a total score of > 0 has a higher sensitivity with a similar specificity) [26]. A cut-off of > 1 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 (vs. hyperactive delirium).

3.2 Secondary endpoints/outcomes

The secondary endpoints are:

- Proportion of participants with Nu-DESC total score of > 0 at any point during the trial.
- Nu-DESC scores during trial (mean score during the trial; proportion time with score 0; proportion time with score > 0; proportion of time with score > 1).
- Time to first episode of Nu-DECSC score > 1.
- Proportion of participants that receive as-required and/or regular medication specifically for delirium at any point during the trial (data derived from drug chart).

Approved

- Time to first dose of medication for delirium (as-required or regular – data derived from drug chart).
- Modified Richmond Agitation and Sedation Scale (m-RASS) scores during trial (mean score during the trial; proportion time with score 0; proportion time with score 0 to -2 – data derived from clinical observation document). The RASS is a validated measuring tool for severity of agitation and level of sedation, and the m-RASS has been modified for/validated in patients with advanced cancer (Table 2) [27].
- Proportion of participants with audible upper airway secretions at any point during the trial ("death rattle" – data derived from clinical observation document).
- Time to first episode of audible upper airway secretions.
- Proportion of participants that receive as-required and/or regular medication specifically for audible upper airway secretions at any point during the trial (data derived from drug chart).
- Time to first dose of medication for audible upper airway secretions (as-required or regular – data derived from drug chart).
- Proportion of participants that experience pain, shortness of breath, and nausea and vomiting (and require medication for these symptoms – data derived from clinical observation document and drug chart).
- Adverse effects of CAH, e.g., peripheral oedema, pulmonary oedema, cannula site inflammation, cannula site infection. (Data derived from clinical observation document)
- Overall survival (data derived from clinical observation document). Participants that survive >14 days will continue to be followed up in order to determine their date of death.
- Participant level costs (data derived from clinical observation document and drug chart) and cost effectiveness based on reductions in the likelihood of delirium.
- Carer feedback on end-of-life care and research participation – Carers will be asked to complete a survey based on the Quality Survey developed by the National Audit of Care at the End of Life (NHS Benchmarking Network) in conjunction with the Patients Association [28]. In addition to the standard questions relating to end-of-life care, we will include specific questions about the research project. The survey will be sent out 8 weeks after the participant's death (as in the National Audit of Care at the End of Life).

Approved

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, non-communicativeness, 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	

Table 1 – Nursing Delirium Screening Scale (Nu-DESC) [23].

4 TRIAL DESIGN

The trial is a cluster randomised trial (CRT), 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).

The CHELsea II trial (definitive trial) leads on from the CHELsea I trial (feasibility trial) [8,9]: the feasibility trial was conducted to ensure that the definitive trial "could be done". The CHELsea I trial achieved all of the pre-determined criteria for success [9], and so there is no rationale for major amendments to the trial protocol (i.e., trial design, trial methods).

Approved

Score	Term	Description
+4	Combative	Overtly combative, violent, and immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s) and aggressive
+2	Agitated	Frequent non purposeful movements
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous. Frequent movements, nonaggressive, in patient who is not fully alert
0	Alert or calm	
−1	Drowsy	Not fully alert but has sustained (more than 10 seconds) awakening, with eye contact to voice
−2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice
−3	Moderate sedation	Any movement (but not eye contact) to voice
−4	Deep sedation	No response to voice but any movement to physical stimulation
−5	Unarousable	No response to voice or physical stimulation

Table 2 – Modified Richmond Agitation Sedation Scale (m-RASS) [27].

We considered undertaking a “conventional” randomised controlled trial (RCT). However, RCTs are problematic in palliative care, and especially in end-of-life care [29]. Indeed, there have only been three published RCTs of CAH, and these studies recruited very small numbers of participants (i.e., 222 participants in total) [10-12]. Moreover, the principal RCT of CAH failed to meet its target for recruitment [12]. Hence, after reviewing the literature, we decided to undertake a cluster randomised trial [30,31].

CRTs are well established within palliative care [32,33], and specifically within end-of-life care [34-37] (and many other areas of medicine [30]). For example, Zimmermann et al performed a CRT of “early palliative care” in patients with advanced cancer: they “opted for cluster rather than individual randomisation...on the basis of evidence from the health services literature and advice from oncologists that it is difficult to recruit patients to be individually randomised (or not) to an intervention such as palliative care, in view of strong preconceived preferences among patients and their oncologists” [33]. A similar argument exists for CAH.

Approved

5 TRIAL SETTING

Research sites (80 in total) will be either NHS hospitals, or NHS/voluntary hospices in the four countries of the United Kingdom (i.e., England, Wales, Scotland or Northern Ireland). NHS hospitals will need to have a specialist palliative care team, and ideally either a palliative care unit or designated palliative care beds: they will need a relevant clinician willing to be the PI, and this person should ideally have experience in undertaking relevant research. NHS/voluntary hospices will need to have an inpatient unit: they will need a relevant clinician willing to be the PI, and this person should ideally have experience in undertaking similar research.

6 PARTICIPANT ELIGIBILITY CRITERIA

The target population is all patients in the last days of life that are inpatients in the research sites, and that meet the inclusion/exclusion criteria for the trial (see below).

6.1 Inclusion criteria

The inclusion criteria are:

a) any sex

b) age ≥ 18 years

c) estimated prognosis of ≤ 1 week. [Clinical opinion - MDT].

d) patient unable to maintain sufficient oral fluid intake (i.e., < 1L/day).

6.2 Exclusion criteria

The exclusion criteria are:

a) patient is dehydrated (guidance on indictors of dehydration in Appendix 5)

b) patient has a relevant Advance Directive to Refuse Treatment (ADRT)

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 as deemed by clinical team (see criteria “d”)

Approved

k) patient has clinically significant renal failure as deemed by clinical team (see criteria “d”)
l) patient has clinically significant dementia as deemed by clinical team (potential false positives on delirium screening)

Patients that are dehydrated will be eligible for inclusion after correction of dehydration has occurred.

Patients in research sites that are randomised to Standard intervention B, who are already receiving CAH, are eligible to take part in the trial (assuming they meet the other inclusion criteria). However, ongoing CAH must be given as per the protocol

7 TRIAL PROCEDURES

7.1 Recruitment

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 of the trial (see above). [All patients that meet the inclusion/exclusion criteria for the trial will be eligible for the trial].

The clinical team will identify suitable patients as part of routine clinical practice, and the research team will then approach the patient, personal consultee or nominated consultee (as appropriate) to see whether they want to take part in the trial.

Each trial site will have a screening log, which records anonymised personal data for all screened patients (i.e., initials and date of birth), this information will be obtained from the patient’s medical records. Information will also be recorded about reasons for non-participation, e.g., patient ineligible (reason stated), patient declined, personal / nominated consultee declined, other reason (reason stated): this information will be provided by the clinical team / research team (as appropriate).

7.2 Consent

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 [8,9], which was developed in accordance with the Mental Capacity Act (Figure 2) [38], and Adults with Incapacity Act (Scotland) Act 2000.

Approved

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" (i.e., 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" (i.e., independent clinician). Nominated consultees are not applicable in Scotland.

If / when a participant that 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 the 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.

Separate information sheets have been developed for participants, personal consultees, and nominated consultees. Similarly, separate consent forms have been developed for participants, personal consultees, and nominated consultees.

Trial sites will be required to develop a Cluster Representation Mechanism (CRM) to represent the interests of the cluster (and the individuals within the cluster) [30]. The CRM has the same rights as an individual participant in a normal randomised trial; the CRM has the right to withdraw the cluster from the trial if it decides that the trial is no longer in the interests of the cluster. The CRM includes a Study Gatekeeper (who is responsible for cluster as a whole, permits the cluster taking part in the trial, and monitors the continued involvement of the cluster in the trial, e.g., senior clinician), and a Trial Guardian (who is responsible for the individuals in the cluster, permits individuals to take part in the trial, and monitors the continued involvement of individuals in the trial, e.g., senior nurse). The CRM will be independent of the research team and will work to a formal document that describes the role of the CRM.

Approved

7.2.1 Additional consent provisions for use of participant data in ancillary studies

In addition to providing consent for the use of the collected clinical information in this trial, the participants or personal / nominated consultees will be asked to provide consent for the potential use of the collected clinical information (anonymised) in future studies. [Enrolment to the trial is not dependent on consent for the potential use of the collected clinical information in future studies].

7.3 The randomisation scheme

Randomisation will be undertaken 1:1 by site (cluster), to ensure balance and equal numbers in each intervention group, stratifying by home country (i.e., England, Wales, Scotland or Northern Ireland), and by type of unit (i.e., hospital or hospice). Randomisation will be undertaken by the Trial Statistician at Surrey CTU, using a blocked randomisation with separate blocks (of random length) assigned to hospitals and hospice groups within each of the home countries to ensure balance on these factors.

7.3.1 Method of implementing the randomisation/allocation sequence

A sampling frame containing all approved sites, categorised by type of unit and home country will be drawn up, and each unit matched to an allocation from the independently prepared randomisation list by the Trial Statistician. This process will ensure there can be no allocation bias.

7.4 Blinding

The trial is unblinded (to participants and researchers).

Approved

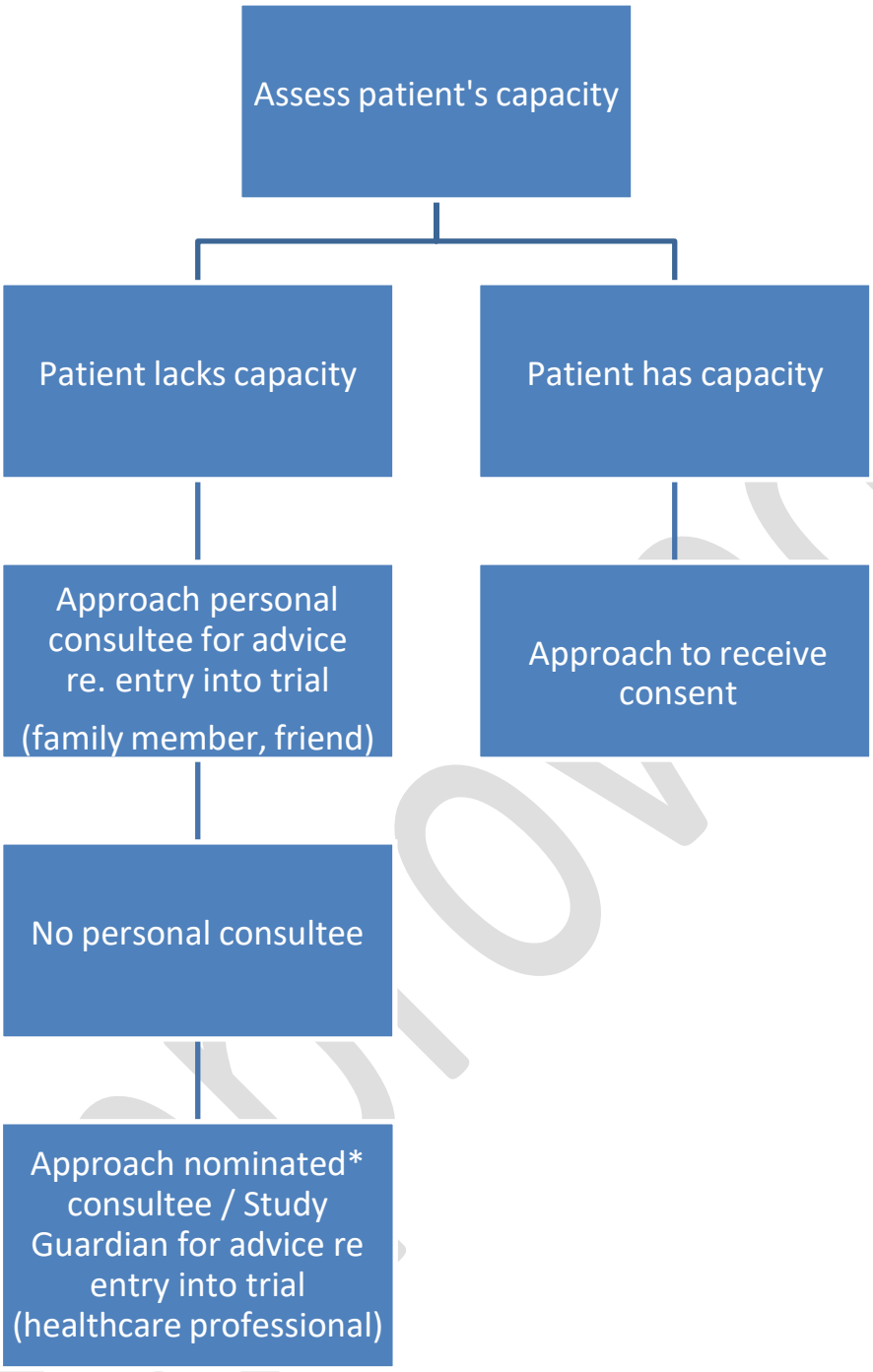

Figure 2 – Consent flow chart.

7.5 Baseline data

Baseline data will be collected to describe the trial population (so that comparisons can be made with other populations):

a) Age

b) Sex – female, male

c) Ethnicity

d) Primary diagnosis – cancer, non-malignant (with specific diagnosis)

e) Site of care – hospital, hospice

f) Home-country – England, Northern Ireland, Scotland, Wales

g) Type of consent – participant, personal consultee, nominated consultee

7.6 Trial assessments

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

Participants will be reviewed every four hours during the trial by the clinical team, and the following assessments completed (by the clinical team):

- Nu-DESC score (see above)
- m-RASS score (see above)
- Presence of audible upper airway secretions ("death rattle")
- Presence of pain – patient reported
- Presence of shortness of breath – patient reported
- Presence of nausea and vomiting – patient reported (nausea and vomiting), or nurse assessment (vomiting)
- Presence of adverse effects of CAH (see above)

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 (e.g., cannulae, 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 that survive >14 days will continue to be followed up in order to determine their date of death].

The clinical team will complete a trial-specific clinical observation document, which will be transcribed by the research team into the case report form (CRF). The research team will also use the participant's clinical notes and drug charts as source documents.

7.7 Long term follow-up assessments

Participants that survive >14 days will continue to be followed up in order to determine their date of death (but there will be no other trial-related assessments during this period).

Approved

ASSESSMENT	ENTRY TRIAL	DURING TRIAL (4 HOURLY ASSESSMENTS)	END TRIAL
Demographic information	√		
Regular medication	√	√	
As-required medication	√	√	
Fluid intake		√	
Urinary output		√	
NuDESC score		√	
m-RASS score		√	
Presence of audible upper respiratory secretions		√	
Presence of symptoms		√	
Adverse effects (CAH)		√	
Trial outcome			√
Overall survival			√

Table 3 – Summary of trial assessments.

7.8 Withdrawal criteria

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 / 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 that withdraw / are withdrawn will continue to be followed up in order to determine their date of death (but there will be no other trial-related assessments during this period).

The CRF will contain a section for detailing participant withdrawal. Participants that are withdrawn from the trial will not be replaced by alternative participants.

Approved

The clinical team may stop CAH (or start CAH) if clinically indicated: the clinical team will be asked to provide a reason for stopping (or starting CAH). Stopping (or starting CAH) is not synonymous with withdrawal from the trial, i.e., the participant assessments will continue until the end of the trial. (The statistical analysis will be undertaken on an intention-to-treat basis).

7.12 End of trial

The end of trial occurs when an individual participant either: a) survives for ≥ 14 days; b) dies (expected outcome); or c) is withdrawn from the trial. The end of trial occurs when the final participant reaches the end of trial (see above).

8 TRIAL TREATMENTS

The health technology being assessed is clinically-assisted hydration (CAH), i.e., parenteral fluids (intravenous/subcutaneous fluids). Currently, there is no agreed "standard of care", with some patients receiving CAH during the last days of life, whilst other patients do not receive CAH during the last days of life (but receive oral fluids, and/or regular "mouth care"). Moreover, some patients have CAH withdrawn during the last days of life.

Research sites will be randomised to either "standard intervention A" or "standard intervention B" (see below), and this will become the standard of care at the research site for the duration of this trial. The interventions represent the current typical standards of care in the UK.

8.1 Standard intervention A

Standard intervention A involves:

- Continuance of oral intake (if appropriate) - includes assistance with drinking as required.
- Regular "mouth care" - mouth care should be performed at least every four hours and should correspond to the research site's usual procedures for oral care in the terminal phase. Mouth care should be undertaken by the clinical team (but can involve carers if deemed appropriate). Mouth care should be discontinued/withheld if it causes distress/discomfort to the participant or is otherwise difficult to undertake.
- Standard management of pain and other end-of-life symptoms/problems - should correspond to the research site's usual procedures for managing relevant problems in the terminal phase.

Approved

8.2 Standard intervention B

Standard intervention B involves:

- ❖ Continuance of oral intake (if appropriate) - see above (Standard intervention A).
- ❖ Regular mouth care - see above (Standard intervention A).
- ❖ Standard management of pain and other end-of-life symptoms/problems - see above (Standard intervention A).
- ❖ CAH - see below.

The parenteral fluids may be given either intravenously (if an intravenous cannula is present), or subcutaneously (if no intravenous cannula is present). Intravenous fluids must be administered using an infusion pump, and subcutaneous fluids must be administered using gravity (and not using an infusion pump). The type/volume of fluid administered is based upon relevant NICE guidance [13]: 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 (Table 4). It should be noted that the volume of fluid is based on a figure of 25 ml/kg/day, which is the lower limit for generic participants, and the upper limit (for consideration) in “old” or “frail” participants [13]. If a recent weight is unavailable, and weighing the participant is problematic, then the clinical team may estimate the current weight.

Participant**’s weight**	**Volume of fluid**
≤ 40 kg	1 L
50 kg	1.25 L
60 kg	1.5 L
70 kg	1.75 L
≥ 80 kg	2 L

Table 4 - Volume of fluid to be administered [13].

Intravenous fluids should be administered according to the research site’s usual procedures. Subcutaneous fluids should be administered according to the following guidelines:

- ❖ 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.
- ❖ Type of cannula - the preferred cannula is a 24 g BD Saf-T-Intima cannula.

Approved

- Rationale for changing cannula - the decision to change/re-site 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 re-site the cannula.
- Rate of infusion - the preferred method of infusion is continuous infusion with the drop rate calculated in the usual manner [39].

Participants with unstable diabetes mellitus may require monitoring of blood sugars (at the discretion of the clinical team). Participants with persistently high blood sugars may require use of other fluids (at the discretion of the clinical team).

8.3 Discontinuation of CAH

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 re-sited elsewhere (not the same area). Similarly, if the infusion is not running, or the site of the cannula is inflamed, then the cannula should be re-sited 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 [40,41]. 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 “over hydration”.

8.4 Regulatory status of fluid

Dextrose saline is not deemed a drug, and the Medicines and Healthcare products Regulatory Agency (MHRA) have agreed that the trial is not a Clinical Trial of Investigational Medicinal Product (CTIMP) (and does not require a Clinical Trial Authorisation (CTA)).

Approved

8.5 Fluid supply and storage

The dextrose saline will be obtained through the trial site's normal medical supplier. The dextrose saline will be stored in the normal manner (no special conditions).

8.6 Assessment of compliance with protocol

The clinical team will record the volume of fluid prescribed, and also the amount of fluid received, in the clinical observation document. The research team will monitor the amount of fluid received and liaise with the clinical team about remedial measures if the volume of fluid received is less than the volume of fluid prescribed (i.e., < 75% total). Compliance with fluid prescription will be documented in the final trial report.

The research team will also monitor the clinical observation chart and liaise with the clinical team about remedial measures if the recording of observations is < 90% total. [In the feasibility trial, the recording of observations was 93.6%] [9]. Compliance with clinical observations will be documented in the final trial report.

9 PHARMACOVIGILANCE

9.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product or intervention has been administered, including occurrences which are not necessarily caused by or related to that product.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Approved

9.2 Operational definitions for AEs and SAEs

As the trial is being undertaken in participants in the last days of life, progression of existing problems, and development of typical end-of-life problems (e.g., delirium, audible upper airway secretions) are not considered to be AEs / SAEs (and so are not reportable). Similarly, death related to the primary disease / complication of the primary disease is not considered an SAE, nor is inpatient hospitalisation or prolongation of existing hospitalisation, because all participants will already be in a hospital or hospice.

The development of localised swelling at the site of infusion, or the requirement to re-site the cannulae are not considered AEs (and so are not reportable). Other complications of the CAH (e.g., peripheral oedema, pulmonary oedema) will be considered as AEs / SAEs (and so are reportable). Death directly related to the CAH is considered an SAE.

9.3 Recording and reporting of SAEs

All AEs will be recorded in the CRF, and SAEs must be reported to Surrey CTU, acting on behalf of the Sponsor, within 24hours. AEs / SAEs recording starts from the time the participant consents to take part in the trial. AEs will continue to be recorded / reported until the end of the trial (i.e., ≤ 14 days).

The following information will be collected about SAEs (on a specific form): a) full details in medical terms and case description; b) event duration (start and end dates, if applicable); c) action taken d) outcome e) seriousness criteria f) causality (i.e., relatedness to intervention), in the opinion of the investigator; g) whether the event would be considered anticipated. AEs will be followed up until resolved or a final outcome has occurred.

9.4 Responsibilities

Principal Investigator (PI)

1. Checking for AEs.
2. Using medical judgement in assigning seriousness, causality and whether the event/reaction was anticipated.
3. Ensuring that all SAEs are recorded and reported to Surrey CTU within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.

Approved

4. Make certain that SAEs are followed up with Surrey CTU if a record of receipt is not received within 2 working days of initial reporting.
5. Ensuring that all AEs are documented fully in the back of the CRF.

Chief Investigator (CI) / delegate

1. Clinical oversight of the safety of participants participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning the SAEs seriousness, causality and whether the event was anticipated where it has not been possible to obtain local medical assessment.
3. Review of specific SAEs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
4. Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs.

Surrey Clinical Trials Unit, acting on behalf of the Sponsor

1. Central data collection and verification of AEs and SAEs onto a database, in accordance with the trial protocol.
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
3. Reporting safety information to the independent oversight committees identified for the trial DMEC) and / or TSC) according to the Trial Monitoring Plan.

Trial Management Group (TMG)

The TMG will regularly review safety events and ensure onward reporting and notification to the Sponsor and oversight committees in accordance with their Terms of Reference.

9.5 Reporting urgent safety measures

If any urgent safety measures are taken, the CI / Sponsor shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant Research Ethics Committee (REC) of the measures taken and the circumstances giving rise to those measures.

Approved

10 STATISTICS AND DATA ANALYSIS

10.1 Sample size calculation

The sample size is based on a “clinically meaningful” reduction in the proportion of participants developing delirium in the CAH intervention group (versus 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 (i.e., palliative care doctors / nurses), 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 > 0 on the Nu-DESC scale) 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 intra-cluster 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).

10.2 Planned recruitment rate

Recruitment will take place over 24 months, which will require an overall recruitment rate of 67 per month (which is < 1 participant per centre/month assuming centres can be quickly opened).

The “green” criteria for progression from internal pilot to full trial at 12 months (see below) are entirely realistic based on the recruitment rate in the feasibility trial.

10.3 Statistical analysis plan

A full statistical analysis plan (SAP) will be prepared and approved in advance of the first substantive unblinded analysis of efficacy data.

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.

Approved

10.3.1 Summary of baseline data and flow of participants

Baseline data will be collected to describe the trial population (so that comparisons can be made with other populations):

a) Age

b) Sex – female, male

c) Primary diagnosis – cancer, non-malignant (with specific diagnosis)

d) Ethnicity

Baseline characteristics will be summarised by intervention group using appropriate point (e.g. proportions for binary outcomes, means or medians for continuous variables), and interval estimates.

10.3.2 Primary outcome analysis

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 (i.e., England, Wales, Scotland or Northern Ireland) and by type of unit (i.e., hospital or hospice), which were used as stratification variables in the randomisation, disease category (i.e., cancer, non-malignant disease), age (e.g., < 65 years, > 65 years), and sex (i.e., male, female). 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 take into account 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.

A sensitivity analysis for the primary outcome will be undertaken per-protocol excluding those participants who did not comply with the protocol. Compliance with the CAH regimen will be defined as receiving >75% of the prescribed fluids.

10.3.3 Secondary outcome analysis

Secondary outcomes will be handled similarly for dichotomous outcomes, including at the various thresholds for delirium on the NUDESC scale (≥1 versus ≥2). Survival and time to delirium will be assessed by Kaplan Meier plot and analysed using a Cox regression model. Where there are problems of convergence in models using random effects, centre will be

Approved

converted to a fixed effect. Intervention tolerability and adherence to the CAH procedures will be presented. Exploratory analysis (to be detailed in the SAP) will include methods accounting for the repeated observations on outcomes.

10.4 Subgroup analyses

Subgroup analyses of the primary outcome will be performed for disease category (cancer, non-malignant), age (< 65years, ≥ 65 years), and sex (female, male). Results on these strata will be reported separately and tested by inclusion of the appropriate interaction term in the analysis model.

10.5 Adjusted analysis

Analyses will be adjusted for home country (i.e., England, Wales, Scotland or Northern Ireland) and by type of unit (i.e., hospital or hospice), which were used as stratification variables in the randomisation, disease category (i.e., cancer, non-malignant disease), age (e.g., < 65 years, > 65 years), and sex (i.e., male, female) as described above.

10.6 Interim analysis and criteria for the premature termination of the trial

The statistical analysis will be undertaken at the end of the trial: there will be no planned interim analysis, although this can be requested by the DMEC if felt necessary following periodic review of the data. An internal pilot will confirm continuance of the trial according to satisfaction of recruitment targets.

The CHELsea II trial follows on from the CHELsea I trial (feasibility trial) [8,9]. Nevertheless, the CHELsea II trial will include an internal pilot, which will last for 12 months (from recruitment of the first participant). The criteria for progression from the internal pilot to the full trial are shown in Table 5. Green ("Go") would represent ≥ 75% of the initial target recruitment of 800 after 12 months; amber would represent ≥ 50% of the initial target recruitment of 800 after 12 months (which would trigger a recovery plan to ensure the overall target recruitment of 1600 after 24 months). Failure to recruit 400 participants, and/or less than 30 sites opened, and/or a recruitment rate < 2 participants/site/month would result in the trial being halted [42].

Progression criteria	**Green "Go"**	**Amber**	**Red "Stop"**

Approved

		"Action Required"	
Number of sites opened	≥ 40	≥ 30 (< 40)	< 30
Recruitment rate / site / month (at end of internal pilot)	≥ 4	≥ 3 (< 4)	< 2
Total recruitment (absolute number)	≥ 600	≥ 400 (< 600)	< 400
Total target recruitment (% sample size)	≥ 40%	≥ 25% (< 40%)	< 25%

Table 5 - Criteria for progression (from internal pilot to full trial) at 12 months.

10.7 Participant population

As described above, all analyses will be undertaken according to the intention-to-treat principle, including all observed data on participants according to their randomised allocation. A sensitivity analysis per-protocol will exclude those who did not comply with the protocol procedures.

10.8 Procedure(s) to account for missing or spurious data

Missing and spurious data will be queried, and summarised and reported following resolution. Decisions regarding inclusion or exclusion of spurious values will be taken according to the SAP. The (mixed model) analysis will be based on all observed data on individuals and will provide robust estimation under the assumption that any missing data are missing at random (MAR), ie. where missingness can be fully accounted for by variables where there is complete information. Sensitivity analysis can test this assumption, but imputation is not planned.

10.9 Other statistical considerations

Deviations from the SAP where necessary will be reported and justified.

10.10 Economic evaluation

The economic analysis will take a health care payer perspective and seek to understand the potential impact of clinically assisted hydration as it pertains to resource utilisation. A micro

Approved

costing exercise will be undertaken to estimate the cost for each participant, for each day they are in the trial. We will also calculate the total costs, and the mean total costs, for each group separately, and then compare them. Costs will initially be expressed as a cost per participant per day because participants are likely to be in the trial for varying lengths of time. Data will be extracted from the clinical records of all participants, covering routine care and treatment of end-of-life symptoms/problems (including but not limited to treatments for delirium, audible upper respiratory secretions, pain, and shortness of breath), from the point of entry to the trial to death or withdrawal. This will include the administration of clinically assisted hydration in the relevant intervention group. The cost analysis will be comprehensive in coverage and will include monitoring the full costs of all participants in both groups, including all treatments and adverse events.

Resources utilised (medications, facilities, treatment and clinical time) will be costed using nationally validated unit costs [43], the British National Formulary [44], and NHS national costs [45], supplemented by costs from finance departments as needed. Mean daily costs will be compared between the two intervention groups, and between those experiencing delirium and those that do not. 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 diagnosis (cancer, non-malignant disease), home country (England, Wales, Scotland, Northern Ireland), and centre as a random effect.

We are aware of the ongoing debate concerning the appropriateness of use of Quality Adjusted Life Years (QALYs) for decision-making in palliative care [46]. We decided that EQ-5D would not be suitable in this trial where participants are so close to death and may lack the ability to complete the measure. Hence, we will use a cost effectiveness measure as the primary outcome from the health economic analysis. This measure refers to the reduction in the proportion of participants developing delirium (an absolute rather than relative reduction) over the whole time the participant is in the trial from recruitment to death or 14 days. Whilst limiting the ability to use the results to inform decisions on resource allocation among palliative care interventions, the cost effectiveness outcomes might be used to benchmark other studies.

Where the statistical analysis finds a statistically significant difference between the intervention and control groups in the proportions of participants developing delirium (primary outcome), 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

Approved

a gamma curve. Sampling uncertainty in overall differences in cost per day between groups will be handled using generalised linear mixed models.

A formal Health Economic Analysis Plan (HEAP) will be developed.

11 DATA MANAGEMENT

11.1 Data collection tools and source document identification

The clinical team will complete a trial-specific clinical observation document, which contains the assessment tools (see above), and which is considered the primary source document. Other source documents include the participant's medical notes, and the participant's drug charts.

The research team will complete the paper CRF using information from the trial-specific clinical observation document, and the other source documents.

All source documents (and other trial documentation) will need to be retained by the trial sites for 5 years after the end of the trial.

11.2 Data handling and record keeping

All data management processes will be described in a detailed Data Management Plan, prepared by the Trial Manager/ Data Coordinator at Surrey CTU.

11.3 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections - in line with participant consent.

11.4 Archiving

At the end of the trial, Surrey CTU will archive all centrally held trial related documentation, including the trial database, securely for a minimum of 10 years. For regulatory purposes, at the end of the trial, is defined as the date of final database lock. Arrangements for confidential destruction will then be made after the 10-year period has passed. It is the responsibility of Principal Investigators (PIs) to ensure data and all essential documents relating to the trial held at site are retained for a minimum of 5 years after the end of the trial, in accordance with national legislation and for the maximum period of time permitted by the site.

Approved

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with the principles of Good Clinical Practice (GCP) and all applicable regulatory requirements (i.e., ISFs, Consent Forms, copies of CRFs).

Surrey CTU will notify sites when trial documentation held at sites may be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

Surrey CTU will facilitate the archiving / destruction of trial documents at the trial sites, if required.

12 RISK ASSESSMENT & MONITORING

12.1 Risk Assessment

This trial is classed as relatively high risk. The main risks identified are associated with the non-serious adverse effects from clinically-assisted hydration, the potential negative publicity surrounding palliative care, and the risks associated with working with hospices and NHS organisations in the post COVID environment, delays with participant recruitment and availability of skilled staff.

A robust risk management process will be followed to mitigate and manage all potential risks at each step of the trial set up.

12.2 Monitoring

A Trial Monitoring Plan will be developed by Surrey CTU and agreed by the CI and TMG and based on the trial risk assessment. This will be dependent on a documented risk assessment of the trial and will state the procedures required and anticipated frequency for monitoring.

Monitoring will be initially conducted across all sites, and subsequently conducted using a risk-based approach that focuses, for example, on sites that have the highest enrolment rates, largest numbers of withdrawals, or atypical (low or high) numbers of reported adverse events.

As this is a relatively high-risk trial, the monitoring will be a combination of remote, on-site and site self-monitoring. All sites will be required to host site visits where necessary, provide information for remote monitoring when requested and put procedures in place to monitor the trial internally.

Approved

Examples of the types of information that will be monitored are listed below. Please note additional information may be monitored outside of this list should it be deemed necessary:

- The trial is conducted appropriately and in accordance with the protocol and ICH-GCP
- All staff involved in the trial have the necessary qualifications for their delegated duties and have received the necessary training
- Only eligible participants are enrolled onto the trial
- Informed consent is received and documented accurately
- All data is entered accurately, completely and promptly
- Site files are maintained and kept up to date
- Safety reporting processes are correct and within the set timeframes
- Surrey CTU is informed of any problems in a timely manner

Surrey CTU will keep a record of any recurrent issues and will notify the TMG so that they can decide whether additional training or other action at the site/sites is required.

Each site is responsible for keeping their own Investigator Site File (ISF). The Surrey CTU Trial Manager/ Data Coordinator and/or Lead Research Nurse, in conjunction with the TMG will provide the sites as necessary, with updates regarding the versions of documents that should be filed in their site files to ensure each site has the correct documentation.

If there are any concerns regarding the data integrity at a site, then Surrey CTU will provide additional training/inspections/audits at the sites as required.

If a site discovers any major issues whilst self-monitoring (GCP breaches and Protocol deviations that may affect the safety of participants or the integrity of the data), then they must immediately notify Surrey CTU, who will notify the Sponsor, University of Surrey, as soon as possible, ideally within 2 working days. This communication should be documented in their site file. If applicable, the TMG and Trial Steering Committee TSC should be notified of any significant issues. This may trigger additional monitoring requirements which may include, more frequent on-site monitoring by a member of Surrey CTU. If the level of monitoring required at a site changes during the trial, this will be documented in the monitoring plan.

Any issues raised by monitoring which may impact the integrity of the trial, will be notified to the TSC.

12.3 Audit

Surrey CTU, as delegated sponsor responsibilities, will coordinate and review the quality assurance throughout the trial through Quality Control (QC) and central monitoring and will

Approved

perform audits if required. The Sponsor (University of Surrey), funder (NIHR) and/or regulatory authorities may also audit if requested.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Good Clinical Practice

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 and applicable regulatory requirements.

13.2 Patient Data Protection

The Informed Consent Form (ICF) will incorporate wording that complies with current data protection and privacy legislation. This will be agreed in our data sharing agreement that will be in place for this trial.

13.3 Ethics and Regulatory Review

Surrey CTU, as delegated by the Sponsor, will ensure that all trial documentation has been reviewed and approved by all relevant bodies and that the following have been obtained prior to activating the trial:

- Favourable Ethics Opinion from an approved Research Ethics Committee (REC) is acquired
- Relevant local approvals (e.g., R&D approval, management approval) for all 4 home countries– England, Northern Ireland, Scotland, Wales
- ‘Adoption’ into National Institute for Health Research (NIHR) portfolio
- Health Research Authorisation (HRA) permission, obtained via the Integrated Research Authorisation System (IRAS)
- Confirmation of sponsorship
- Adequate insurance provision

Surrey CTU will be responsible for providing REC with annual reports within 30 days of the anniversary of the favourable opinion, and a final report within one year of the end of the trial.

The MHRA have confirmed that the trial is not a CTIMP (and does not require a CTA).

Approved

13.4 Informed Consent

PIs must ensure that participants (or allocated consultee where necessary) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical trials in which they volunteer to participate.

Surrey CTU, as delegated by the Sponsor, will provide the PIs with an appropriate Informed Consent Form (ICF) which will include all elements required by International Conference on Harmonisation (ICH), Good Clinical Practice (GCP) and applicable regulatory requirements. The ICF will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

PIs must:

- Provide copies of the ICFs to the participant (or allocated consultee where necessary) and written information about the trial in English (or Welsh for Welsh sites, when requested) prior to clinical trial participation. The language must be non-technical and easily understood.
- Allow time necessary for the participant (or allocated consultee where necessary) to inquire about the details of the trial.
- Obtain an ICF signed and personally dated by the participant (or allocated consultee where necessary) and by the person who conducted the informed consent discussion.
- Obtain an Independent Ethics Committees (IEC's) written approval/favourable opinion of the ICF and any other information to be provided to the participant (or allocated consultee) where necessary, prior to the beginning of the trial, and after any revisions are completed for new information.

The CI may revise the ICF whenever important new information becomes available that is relevant to the participant's (or allocated consultee's where necessary) consent. Any changes will need to be submitted to the REC as a substantial amendment. Once a favourable opinion has been obtained, the PI, or a person designated by the PI, should fully inform the participant (or allocated consultee where necessary), of all pertinent aspects of the trial and of any new information relevant to the willingness to continue participation in the trial. This communication will be documented.

The confidentiality of records that could identify participants must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements.

The consent forms must also include a statement that sponsor and regulatory authorities have direct access to the participant records. The rights, safety, and well-being of the trial

Approved

participants are the most important considerations and should prevail over interests of science and society.

13.5 Peer Review

The trial was subject to independent expert peer review as part of the NIHR grant application processes (including PPI).

13.6 Public and Patient Involvement (PPI)

PPI (i.e., local PPI group, Marie Curie Voices group) has been integral to the research programme, including supporting the trial design, the grant applications, and the trial oversight. The CHELsea II TSC will have PPI representatives (appointed by the NIHR).

Surrey CTU will apply for REC approval, and support PIs in obtaining relevant local approvals (and ensure all required approvals are obtained in a timely manner).

13.7 Protocol compliance

Protocol non-compliances are departures from the approved protocol. Participating sites will inform Surrey CTU as soon as they are aware of a possible serious breach of compliance, so that Surrey CTU can fulfil its requirement to report the breach if necessary, within the timelines specified in the UK Clinical Trials Regulations. For the purposes of this regulation a 'serious breach' is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects in the trial, or
- The scientific value of the trial.

Other deviations will be logged and dealt with appropriately. Any decisions relating to the inclusion or otherwise of such data in the analysis will be fully documented in accordance with the detailed statistical analysis plan.

13.8 Notification of Serious Breaches to GCP and/or the Protocol

A "serious breach" is a breach which is likely to effect to a significant degree – the safety or physical or mental integrity of the participants of the trial; or the scientific value of the trial.

The Regulations define 'serious breaches' as any serious breach of:

- the conditions and principles of good clinical practice in connection with that trial; or
- the protocol relating to that trial, as amended from time to time in accordance with regulations 22 to 25 of the Medicines for Human Use (Clinical Trials) Regulations 2004 and the

Approved

UK Medical Device Regulations 2002 as well as the EU Medical Device Regulation (https://www.legislation.gov.uk/)

In the event of either a serious breach of GCP or the Protocol, Surrey CTU and relevant involved parties must be notified immediately so that they can take appropriate action. The Clinical Trials regulations state that the Sponsor is required to report serious breaches to the REC, within seven days of becoming aware of the breach.

In the event that a serious breach is suspected at a site, the relevant NHS R&D Department must also be contacted so that an investigation of the concern can be undertaken as a matter of urgency.

Surrey CTU and local R&D departments can provide information on what should, or should not, be classified as a serious breach and on the practical arrangements for notifications.

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase. The sponsor will then notify the licensing authority in writing of any serious breach of the conditions and principles of GCP in connection with that trial; or the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach.

13.9 Data protection and participant confidentiality

Surrey CTU, on behalf of the Sponsor, will comply with all aspects of the UK Data Protection Act 2018. All information collected during the course of the trial will be kept strictly confidential and data will be anonymised prior to removal from the trial sites. All participants will receive a participant number which will replace the participant's name and provide anonymisation. Participants will not be identified in the results of the trial.

All trial staff will sign a confidentiality statement where they are obliged not to disclose confidential information.

Standard Operating Procedures (SOPs) are in place to cover appropriate storage, restricted access and archive/destruction arrangements of participants personal and clinical details.

All non-anonymised information (i.e., personal data that can be used to identify participants, e.g., hospital number, name, date of birth, and contact details including home address and telephone numbers) will be stored securely for 10 years after the last contact between the research team and participant according to usual Information Governance (ISO 27001) and NHS Information Governance Toolkit safeguards. All anonymised information will

Approved

be stored securely for 10 years according to University of Surrey policy. The procedures that will be followed for the collection, storage, protection, retention and destruction of all information comply with the UK Data Protection Act 2018 and the EU General Data Protection Regulation (GDPR).

13.10 Financial and other competing interests for the CI, PIs at each site and committee members for the overall trial management

A CI statement and PI statements for all sites involved will be completed prior to sites being given the green light to begin recruiting participants into the trial. This will ensure that everyone knows what their responsibilities and obligations are with regards to the trial and give them the opportunity to identify and disclose any competing interests that they might have, such as a professional interest, a proprietary interest or any other conflict of interest. Any issues that arise from this will be reported to the TSC and/or Sponsors to determine what further action is required.

All members of the TSC and DMEC will also be required to complete a Members Agreement and Potential Competing Interests Form, under their agreed terms of reference. This will again ask if members have any potential conflict of interest such as

- Stock ownership in any commercial companies involved
- Stock transaction in any commercial company involved (if previously holding stock)
- Consulting arrangements with the Sponsor and Funder (including CI for other trials)
- Ongoing advisory role to a company providing the trial intervention
- Frequent speaking engagements on behalf of the intervention
- Intellectual conflict e.g., strong prior belief in the trial intervention
- Involvement in regulatory issues relevant to the trial procedures
- Investment (financial or intellectual) or career tied up in competing products

Any issues arising will be dealt with by the Sponsor.

13.11 Indemnity

If participants or relatives believe they may have been harmed in anyway by taking part in this trial, they have the right to pursue a complaint and seek any resulting compensation through the University of Surrey which is acting as the research sponsor. Details about this are available from Surrey CTU who are running this trial on behalf of the University of Surrey.

Approved

Also, all participants of the NHS, have the right to pursue a complaint through the usual NHS process. Note that the NHS has no legal liability for non-negligent harm. However, if participants are harmed and this is due to someone's negligence, they may have grounds for a legal action against NHS but the participant may have to pay their own legal costs.

The participants of non-NHS HSC organisations (the hospices) have the right to pursue a complaint through the usual processes put in place by each organisation.

13.12 Amendments

The trial protocol and related documents and procedures will not be changed without the mutual agreement of the CI, Sponsor and Surrey CTU.

Any 'substantial' protocol amendment(s) (meaning that it could have a significant impact on the safety or physical or mental integrity of the participants, the scientific value of the trial, or the conduct or management of the trial) must be submitted to the REC and the NHS R&D prior to its implementation.

For non-substantial changes that do not affect the safety or validity, e.g., an administrative change, the Ethics Committee must be notified. The amendment will be forwarded to the REC for their information, and the changes implemented immediately, unless otherwise instructed by the sponsor or REC.

In the case of changes consisting of urgent safety measures to protect the trial subjects, the sponsor should inform the REC as soon as possible after these measures have been implemented.

In the case of any non-substantial protocol amendments, it may be necessary to notify all sites. This will be decided on a case-by-case basis. In the case of any substantial protocol amendments, it will be necessary to notify all sites.

Surrey CTU will coordinate and prepare all necessary amendments.

13.13 Access to the final trial dataset

The CI, Trial Manager Data Coordinator, Statistician, and other members of the Trial Team at University of Surrey will have full access to the trial data. Following the predefined analyses on response to treatment, requests for access to trial data will be considered, and approved in writing where appropriate, after formal application to the TSC. Considerations for approving access are documented in the TSC Terms of Reference.

Approved

14 DISSEMINATION

14.1 Dissemination policy

The TMG will develop a trial dissemination policy and identify an appropriate writing committee for each planned output. The results of the trial will be published in high-impact general medical/palliative care journals and presented at major international/national medical/palliative care conferences.

14.2 Authorship eligibility guidelines and any intended use of professional writers

The International Committee of Medical Journal Editors (ICMJE) criteria for authorship will be utilised for all trial outputs. (Professional writers will not be utilised to produce trial outputs).

Approved

15 REFERENCES

[1]. National Institute for Health Research. Research Governance Guidelines; 2019. https://www.nihr.ac.uk/documents/research-governance-guidelines/12154

[2]. Neuberger J, Aaronovitch D, Bonset T et al. More care, less pathway. A review of the Liverpool Care Pathway; 2013. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/212450/Liverpool_Care_Pathway.pdf

[3]. Good P, Richard R, Syrmis W et al. Medically assisted hydration for adult palliative care patients. Cochrane Database of Systematic Reviews 2014, Issue 4. Art. No.: CD006273.DOI: 10.1002/14651858.CD006273.pub3.

[4]. Kingdon A, Spathis A, Brodrick R et al. What is the impact of clinically assisted hydration in the last days of life? A systematic literature review and narrative synthesis. BMJ Support Palliat Care 2020 [Online ahead of print].

[5]. del Rio MI, Shand B, Bonati P et al. Hydration and nutrition at the end of life: a systematic review of emotional impact, perceptions, and decision-making among patients, family, and health care staff. Psychooncology 2012; 21: 913-21.

[6]. Bukki J, Unterpaul T, Nubling G et al. Decision making at the end-of-life – cancer patients' and their caregivers' views on artificial nutrition and hydration. Support Care Cancer 2014; 22: 3287-99.

[7]. Raijmakers NJ, van Zuylen L, Costantini M et al. Artificial nutrition and hydration in the last week of life in cancer patients. A systematic literature review of practices and effects. Ann Oncol 2011; 22: 1478-86.

[8]. Davies A, Waghorn M, Boyle J et al. Alternative forms of hydration in cancer patients in the last days of life: study protocol for a randomized controlled trial. Trials 2015; 16: 464.

[9]. Davies AN, Waghorn M, Webber K et al. A cluster randomised feasibility trial of clinically assisted hydration in cancer patients in the last days of life. Palliat Med 2018; 32: 733-43.

[10]. Cerchietti L, Navigante A, Sauri A et al. Hypodermoclysis for control of dehydration in terminal-stage cancer. International Journal of Palliative Nursing 2000; 6: 370-4.

[11]. Bruera E, Sala R, Rico MA et al. Effects of parenteral hydration in terminally ill cancer patients: a preliminary study. J Clin Oncol 2005; 23: 2366-71.

[12]. Bruera E, Hui D, Dalal S et al. Parenteral hydration in patients with advanced cancer: a multicenter, double-blind, placebo-controlled randomized trial. J Clin Oncol 2013; 31: 111-8.

Approved

[13]. National Institute for Health and Care Excellence. Intravenous fluid therapy in adults in hospital; 2013 (updated 2017).
http://guidance.nice.org.uk/CG174

[14]. Breitbart W, Friedlander M. Confusion / delirium. In: Bruera E, Higginson IJ, Ripamonti C, von Gunten C, editors. Textbook of Palliative Medicine. London: Hodder Arnold; 2006. p. 688-700.

[15]. Leonard M, Agar M, Mason C et al. Delirium issues in palliative care settings. Journal of Psychosom Res 2008; 65: 289-98.

[16]. Breitbart W, Chochinov HM, Passik SD. Psychiatric symptoms in palliative medicine. In: Hanks G, Cherny NI, Christakis NA, Fallon M, Kaasa S, Portenoy RK, editors. Oxford Textbook of Palliative Medicine, 4th edition. Oxford: Oxford University Press; 2010. p. 1453-82.

[17]. Sykes N, Thorns A. Sedative use in the last week of life and the implications for end-of-life decision making. Arch Intern Med 2003; 163: 341-4.

[18]. Anonymous. Terminal dehydration. Lancet 1986; 327: 306.

[19]. Marie Curie Palliative Care Institute Liverpool. National Care of Dying Audit – Hospitals (NCDAH). Round 3. Generic Report 2011/2012.
http://www.pcil.org.uk/media/16537/ncdah%20generic%20report%202011-2012%20final.doc%2017.11.11.pdf

[20]. Royal College of Physicians. End of life care audit – dying in hospital: national report for England 2016; 2016.
https://www.rcplondon.ac.uk/projects/outputs/end-life-care-audit-dying-hospital-national-report-england-2016

[21]. National Institute for Health and Care Excellence. Care of dying adults in the last days of life; 2015.
https://www.nice.org.uk/guidance/ng31

[22]. National Institute for Health Research website:
https://www.nihr.ac.uk/news/nihr-shines-a-spotlight-on-hospice-and-community-research/11396

[23]. Gaudreau J, Gagnon P, Harel F et al. Fast, systematic, and continuous delirium assessment in hospitalized patients: the Nursing Delirium Screening Scale. J Pain Symptom Manage 2005; 29: 368-75.

[24]. Hosker CM, Bennett MI. Delirium and agitation at the end of life. BMJ 2016; 353: i3085.

Approved

[25]. Hosie A, Phillips J, Lam L et al. A multicomponent nonpharmacological intervention to prevent delirium for hospitalized people with advanced cancer: a phase ii cluster randomized waitlist controlled trial (the PRESERVE pilot study). J Palliat Med 2020; 23: 1314-22.

[26]. Jeong E, Park J, Lee J. Diagnostic test accuracy of the Nursing Delirium Screening Scale: a systematic review and meta-analysis. J Adv Nurs 2020; 76: 2510-21.

[27]. Benitez-Rosario MA, Castillo-Padros M, Garrido-Bernet B et al. Appropriateness and reliability testing of the modified Richmond Agitation-Sedation Scale in Spanish patients with advanced cancer. J Pain Symptom Manage 2013; 43: 6: 1112-9.

[28]. NHS Benchmarking Network website:
https://www.nhsbenchmarking.nhs.uk/nacel

[29]. Grande GE, Todd CJ. Why are trials in palliative care so difficult? Palliat Med 2000; 14: 69-74.

[30]. Medical Research Council. Cluster randomised trials: methodological and ethical considerations. London: MRC; 2002.

[31]. Fayers PM, Jordhoy MS, Kaasa S. Cluster randomized trials. Palliat Med 2001; 16: 69-70.

[32]. Currow DC, Abernethy AP, Shelby-James TM et al. The impact of conducting a regional palliative care clinical study. Palliat Med 2006; 20: 735-43.

[33]. Zimmermann C, Swami N, Krzyzanowska M et al. Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. Lancet 2014: 383: 1721-30.

[34] Jordhoy MS, Fayers P, Saltnes T et al. A palliative care intervention and death at home: a cluster randomised trial. Lancet 2000; 356: 888-93.

[35]. Fowell A, Johnstone R, Finlay IG et al. Design of trials with dying patients: a feasibility study of cluster randomisation versus randomised consent. Palliat Med 2006; 20: 799-804.

[36]. Costantini M, Ottonelli S, Canavacci L et al. The effectiveness of the Liverpool care pathway in improving end of life care for dying cancer patients in hospital. A cluster randomised trial. BMC Health Serv Res 2011; 11: 13.

[37]. Beernaert K, Smets T, Cohen J et al. Improving comfort around dying in elderly people: a cluster randomised controlled trial. Lancet 2017; 390: 125-34.

[38]. Her Majesty's Government. Mental Capacity Act 2005.
http://www.legislation.gov.uk/ukpga/2005/9/pdfs/ukpga_20050009_en.pdf

[39]. Anonymous. How fast should the drops drip? Nursing Made Incredibly Easy! 2004; 2: 60-62.

Approved

[40]. Ellershaw JE, Sutcliffe JM, Saunders CM. Dehydration and the dying patient. J Pain Symptom Manage 1995; 10: 192-7.

[41]. Morita T, Hyodo I, Yoshimi T et al. Incidence and underlying etiologies of bronchial secretions in terminally ill cancer patients: a multicenter, prospective, observational study. J Pain Symptom Manage 2004; 27: 533–9.

[42]. Herbert E, Julious SA, Goodacre S. Progression criteria in trials with an internal pilot: an audit of publicly funded randomised controlled trials. Trials 2019; 20: 493.

[43]. Curtis LA, Burns A. Unit costs of health and social care 2020; 2020.
https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2020/

[44]. British Medical Association / Royal Pharmaceutical Society. British National Formulary 80; 2020.
https://www.bnf.org/

[45]. NHS England / NHS Improvement. 2018/19 National Cost Collection data; 2020.
https://www.england.nhs.uk/national-cost-collection/

[46]. Wichmann AB, Adang EM, Stalmeier PF et al. The use of Quality-Adjusted Life Years in cost-effectiveness analyses in palliative care: Mapping the debate through an integrative review. Palliat Med 2017; 31: 306-22.

[47]. Armstrong LE, Kavouras SA, Walsh NP, Roberts WO. Diagnosing dehydration? Blend evidence with clinical observations. Curr Opin Clin Nutr Metab Care 2016; 19: 434-8.

Approved

16. APPENDICES

Appendix 1 - Trial management / responsibilities

Surrey CTU is coordinating the trial on behalf of the sponsor and other collaborators and has been delegated the following responsibilities

(Large X is for main/primary responsibility and small x's are for input/other responsibility):

Trial Task	Surrey CTU	CI	Sites	Comments/Clarification
Trial Management and Monitoring	x	x	X	Central monitoring by Surrey CTU, in conjunction with CI, assisted by sites self-monitoring. Review committee will have overall oversight.
Protocol and Amendments	X	x	x	Surrey CTU will coordinate, in conjunction with CI, and obtain approvals and disseminate to sites
Participant Information Sheet/Informed Consent Form management	x		X	Central monitoring by Surrey CTU – regular request of logs, assisted by sites self-monitoring
CRF design and management	X			A database will be set up in Promasys to capture the data collected on paper. Surrey CTU will design this CRF.
Translations	X		x	Welsh translations are required. Surrey CTU will arrange this and ask for assistance from all Welsh sites to check back translation of documents.
Regulatory process *(if applicable i.e if trial is a CTIMP/ATIMP)*				N/A
Investigator selection	X	x		Surrey CTU will discuss necessary requirements with CI to collate a full list of selection requirements
Site Initiation	X	x	x	Surrey CTU will manage all elements of site initiation and opening.
Ethics committee process	X	x	x	Surrey CTU will coordinate, in conjunction with CI, and obtain approvals and disseminate to sites for local assessment
Trial registrations	X			Surrey CTU will obtain on behalf of trial
Management of Intervention	x	X	x	Sites will manage intervention

Approved

Trial specific training	X			Surrey CTU will provide overall trial training for sites including data collection and administration of clinically-assisted hydration for intervention arm.
Provision of trial supplies e.g., CRFs, Lab Kits other consumables	X			Surrey CTU will coordinate the trial and provide paper CRFs for data collection.
Trial Master File (TMF) set-up maintenance	X			Surrey CTU will maintain electronic and hard copy of TMF
Reporting of Progress	X	x		Surrey CTU will manage and submit all progress reports including Annual Safety Reports, with the CI reviewing and approving where necessary
Investigator Site File (ISF) set-up and maintenance	x		X	Surrey CTU will disseminate documentation once approved to sites. Surrey CTU will require sites to keep ISF up to date and will request self-assessment of this from sites as part of central monitoring.
Safety reporting and management	X	x	x	Surrey CTU will be central point of contact for the trial. Sites will notify Surrey CTU if any safety issues occur.
Database Development	X			Surrey CTU will set up a database in Promasys® for both intervention and standard of care arm data collection.
Randomisation	X			The Trial Statistician at Surrey CTU will undertake the randomisation, using a blocked randomisation.
Quality Control/Monitoring	X	x	x	Surrey CTU will review data received and entered Promasys® and perform central monitoring with assistance from sites. Surrey CTU will produce regular reports on compliance for TMG meetings for review.
Quality Assurance/Audit	X			Surrey CTU, as delegated sponsor responsibilities, will coordinate and review the quality assurance throughout the trial through QC and central monitoring and will perform audits if required. The funder (NIHR) and/or regulatory authorities may also audit if requested.
Data Management	X			Surrey CTU will co-ordinate data management to ensure conformity for analysis. Surrey CTU will provide Promasys® database for data collection.
Data Protection	X			Surrey CTU will manage and comply with all aspects of current Data Protection legislation and SOPs

Approved

Statistical analysis and report	X			Surrey CTU is responsible for writing the Statistical Analysis Plan (SAP) and will perform the analysis at the end of the trial.
Report writing and publications	X	X	x	The report writing will be a collaboration of Surrey CTU and CI, with contributions from PIs at sites.
Storage and archiving of TMF	X			Surrey CTU is responsible for storage and archiving of TMF
Storage and archiving of ISF			X	Sites are responsible for storage and archiving of ISF under the direction of PI's.

Approved

Appendix 2 – Trial Sites

2.1 Site/ Investigator Selection

The trial will be conducted in UK hospitals and hospices with adequate resources to carry out the trial procedures and assessments.

The trial sponsor has overall responsibility for site and investigator selection and has delegated this role to Surrey CTU. To participate in the CHELsea II trial, investigators and trial sites must fulfil a set of criteria that have been agreed by the CHELsea II Trial Management Group (TMG).

The Chief Investigator (CI) leading the trial is Professor Andrew Davies, a palliative care specialist based at The School of Medicine, Trinity College Dublin.

2.2 Required local documentation prior to SIV

- CV of PI
- Confirmation of relevant training
- Signed delegation log
- Local R&D Approval

2.3 Procedure for initiating/opening a new site

The trial manager will be responsible for the site initiations, along with the lead research nurse, on confirmation from the Sponsor.

Sites accepted by the TMG as suitable to recruit to the trial will be issued with the CHELsea II Investigator Site File (ISF) documentation to use when applying for Site-Specific Approval, a copy of this protocol, and other relevant trial documentation.

On receipt of the signed Investigator Agreement, approved delegation of responsibilities log, staff contact details and any further documentation requested by Surrey CTU written confirmation will be sent to the site PI, copying in the Research Nurse / Coordinator. The Trial Manager or delegate will notify the PI in writing of the plans for site initiation, which will include training on all aspects of the trial including the informed consent process, safety reporting, aspects of GCP where necessary, and data entry. A list of activated sites may be obtained from the Trial Manager. Investigators will not be permitted to screen patients until the site has been formally activated in writing by Surrey CTU.

Approved

The site must conduct the trial in compliance with the protocol which was given favourable opinion by the REC.

2.4 Principal Investigator Qualifications and Agreements

Principle Investigators (PIs) for this trial will be suitably qualified and experienced. At each participating site, trial-related procedures will be carried out by the PI, or another suitably qualified delegate. Investigators should be able to demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period (i.e., they regularly treat the target population).

Investigators must be willing to sign a Surrey CTU Investigator Agreement to comply with the trial protocol, confirming their specific roles and responsibilities relating to the trial, and that their site is willing and able to comply with the requirements of the trial. It is the responsibility of the investigator to:

- Identify local Research & Development (R&D) contacts
- Confirm they have appropriate qualifications by providing their CV and an up-to-date GCP certificate (from within the last two years, or as specified by their Trust guidelines)
- Comply with the principles of GCP
- Permit site monitoring and audit as necessary by providing access to source data and other trial related documentation as required
- Maintain a delegation of responsibilities log which lists all members of staff that have been delegated significant trial-related duties at the site and their contact details.
- Conduct the trial in compliance with the approved protocol by signing the protocol compliance agreement
- Document and explain any deviation from the approved protocol, and communicate this to the trial team at Surrey CTU using documentation supplied during site initiation training

Approved

Appendix 3 – Safety Reporting Flow Chart

ADVERSE EVENT

Not Serious

Adverse Event (AE)

Any untoward medical occurrence in a participant to whom a medicinal product or intervention has been administered, including occurrences which are not necessarily caused by or related to that product.

Site Responsibilities

Check for AEs

Record all AEs in CRF immediately

Surrey CTU Responsibilities

Collect and verify all AEs onto trial database

Serious

Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence that: Results in death, is life threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity and/ or consists of a congenital anomaly or birth defect

Site Responsibilities

Record all SAEs in CRF and complete SAE form

PI to assess seriousness, causality and anticipation of event

Send completed SAE form, via email, to Surrey CTU immediately (within at least 24 hours), as per safety management plan

Surrey CTU Responsibilities

Send sites confirmation of SAE receipt within 2 days

Collect and verify all SAEs onto trial database

Assign unique SAE number and inform site

Report safety information to CI

Inform PIs from all sites

Report safety information to Trial Monitoring Committee

Obtains review of SAEs by CI in accordance with Risk Assessment

Appendix 4 – Amendment history

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made

Approved

Appendix 5 – Indicators of dehydration

Currently, there are no universally accepted diagnostic criteria for dehydration [47]: table 6 shows the "accuracy" of different indicators of dehydration, and none of these indicators reach the threshold for "high" accuracy. In this study, the clinical team will make the decision whether the patient is dehydrated or not, and this decision should be based on the presence / absence of those indicators with a medium, or medium to high, accuracy.

Indicator	**"Accuracy"**
Symptoms	
Thirst	Medium
Signs	
Postural hypotension - ≥ 20 mmHg	Medium to high
Reduced systolic BP (seated) - ≤ 100 mmHg	Medium to high
Dark urine	Medium
Dry mucous membranes	Low
Dry eyes (absence of tears)	Low
Reduced skin turgor	Low
Sunken eyes	Low
Laboratory investigations	
Blood urea nitrogen / creatinine ratio - ≥ 20	Medium to high
Blood osmolality - > 300 mmol/kg	Medium to high
Serum sodium – high	Medium
Mean corpuscular volume – high	Medium
Urine specific gravity - ≥ 1.025	Medium to high
Urine osmolality - ≥ 800 mmol/kg	Medium to high

Table 6 – Indicators of dehydration [47].

Approved