

**A CLUSTER RANDOMISED TRIAL OF
ALTERNATIVE FORMS OF HYDRATION
IN CANCER PATIENTS
IN THE LAST DAYS OF LIFE
(FEASIBILITY STUDY)**

STUDY PROTOCOL

Protocol version 5: 23 February 2015

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SIGNATURE PAGE

STUDY NUMBER		
STUDY TITLE	A cluster randomised trial of alternative forms of hydration in cancer patients in the last few days of life.	
PROTOCOL VERSION / DATE	5	23 February 2015
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ABBREVIATIONS

AE	Adverse event
bd	Twice a day
CAH	Clinically assisted hydration
CI	Chief Investigator
CRF	Case report form
CRM	Cluster representation mechanism
CRT	Cluster randomised trial
EOL	End of Life
g	Gram
GMC	General Medical Council
GP	General Practitioner
hr	Hour
ICC	Intra-cluster correlation coefficient
iv	Intravenous
im	Intramuscular
in	Intranasal
kg	Kilogram
L	Litre
LCP	Liverpool Care Pathway for the Dying Patient
mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency
mL	Millilitre
mRASS	Modified Richmond Agitation-Sedation Scale
N/A	Not applicable
NCDAH	National Care of Dying Audit – Hospitals
N/K	Not known
od	Once a day
PI	Principal Investigator
po	Oral
pr	Rectal
prn	As required
qds	Four times a day

RCT	Randomised controlled trial
REC	Research ethics committee
SAE	Serious adverse event
sc	Subcutaneous
sl	Sublingual
SOP	Standard operating procedure
tds	Three times a day
TMC	Trial monitoring committee
TPN	Total parenteral nutrition

SYNOPSIS

Title

A cluster randomised trial of alternative forms of hydration in cancer patients in the last days of life (feasibility study)

Sponsor

University of Surrey

Lead Site

Royal Surrey County Hospital NHS Foundation Trust

Chief Investigator

Dr Andrew Davies (Clinical Director of Palliative Care, Royal Surrey County Hospital NHS Foundation Trust / Visiting Senior Fellow, University of Surrey)

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. The reasons for contention include: a) the lack of evidence for / against CAH; b) the disparate opinions of healthcare professionals about CAH; and c) the generally positive opinions of patients and their carers about CAH (and the generally negative opinions about withholding / withdrawing CAH).

Hypothesis

CAH during the last days of life reduces the frequency of hyperactive delirium (“terminal agitation”) in cancer patients as a result of maintenance of renal perfusion and the prevention of accumulation of toxins and drugs (i.e. prevention of dehydration).

Aims / Objectives

The aim of the definitive study is to evaluate the utility / role of CAH in cancer patients in the last days of life. The aim of the feasibility study is to answer the question “can this study (*the definitive study*) be done”.

The objectives of the feasibility study are:

- Process
 - 1). Assess the recruitment rate, i.e. number eligible patients, number recruited patients, barriers to recruitment
 - 2). Assess the retention rate
 - 3). Assess impact of trial procedures on clinical workload, i.e. completion of observation chart, undertaking mouth care / CAH

- Resources

- 1). Assess the adequacy resources to conduct the study at research centres
- 2). Assess the adequacy of resources to support the study at Surrey Clinical Research Centre

- Management

- 1). Determine other challenges for researchers / research centres
- 2). Determine other challenges for Surrey Clinical Research Centre

- Scientific

- 1). Assess safety of CAH
- 2). Determine total variability / intra-cluster correlation coefficient

Study design

A cluster randomised trial

Methodology

The study is a cluster randomised trial, and consent will be sought from the patient (whenever possible), or advice from a “personal consultee” (when the patient is unable to provide consent), or advice from a “nominated consultee” (when the patient is unable to provide consent, and there is no personal consultee).

Sites will be randomised to either “standard intervention arm A”, or “standard intervention arm B”. Patients in standard intervention arm A will be managed with continuance of oral intake (if appropriate), and regular “mouth care”. Mouth care will be performed at least every four hours, and will correspond to the investigational site’s policy / procedures for oral care in the terminal phase. Patients in standard intervention arm B will be managed with continuance of oral intake (if appropriate), regular “mouth care”, and CAH, i.e. parenteral fluids. Again, mouth care will be performed at least every four hours, and will correspond to the investigational site’s policy / procedures for oral care in the terminal phase. The parenteral fluids may be administered either intravenously or subcutaneously at the discretion of the medical and nursing team. The type of fluid to be administered will be dextrose saline (i.e. 4% dextrose, 0.18% sodium chloride), and the volume to be administered will be dependent on the patient's weight.

The primary endpoint of the definitive study is the frequency of hyperactive delirium (“terminal agitation”), and this will be assessed using the Modified Richmond Agitation and Sedation Scale (administered every four hours). Other data to be collected include the frequency of pain, respiratory secretions (“death rattle”), dyspnoea, nausea and vomiting, adverse effects from the CAH, and overall survival. In addition, data will be collected on the

use of anti-psychotic drugs, sedative drugs, analgesics, anti-secretory drugs, and other end-of-life medication.

Sample

Inclusion criteria:

- Diagnosis of cancer
- Age \geq 18 yr
- Estimated prognosis of \leq 1 week
- Patient unable to maintain sufficient oral intake (1L / day – measured / estimated)

Exclusion criteria:

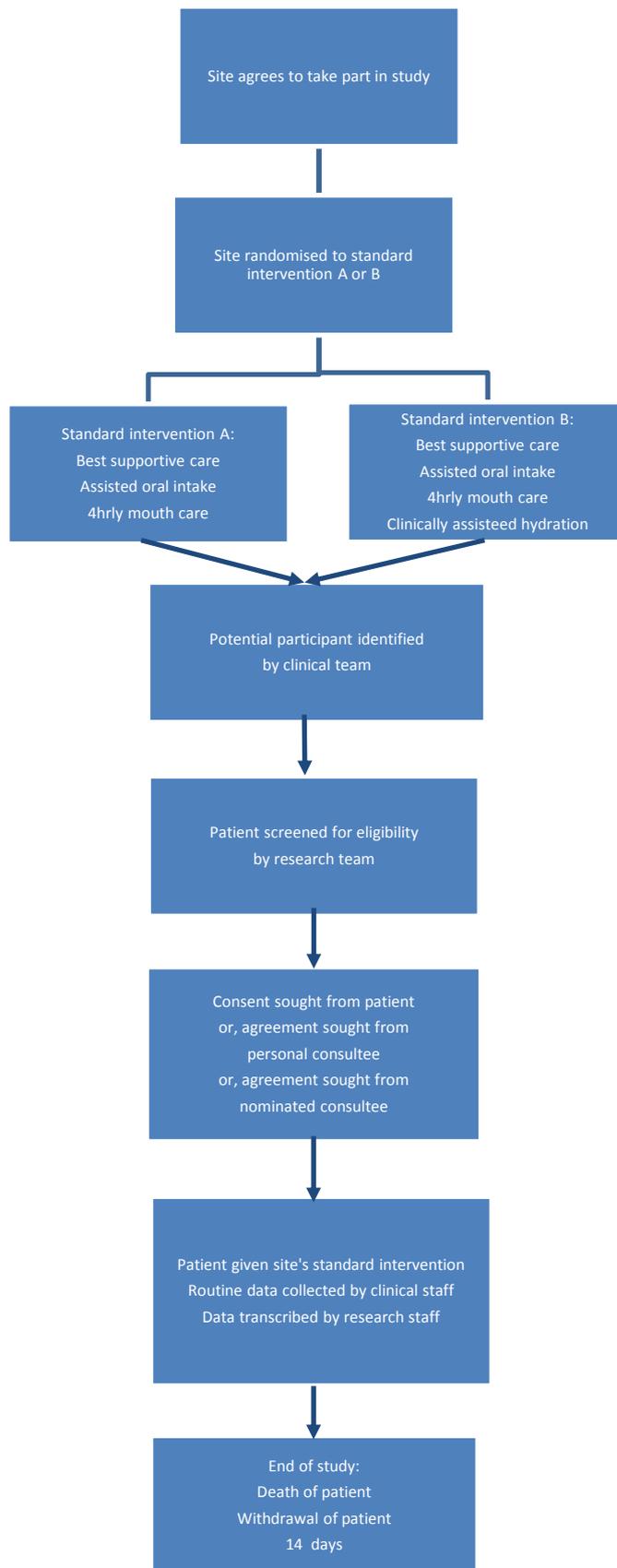
- Patient clinically dehydrated
- Patient has hyperactive delirium (“terminal agitation”) at present
- Patient has had hyperactive delirium (“terminal agitation”) in the last 24hrs
- Clinical indication for CAH (e.g. hypercalcaemia)
- Clinical contra-indication to CAH (e.g. cardiac failure)
- Clinical contra-indication to peripheral cannulation
- Intravenous fluids / subcutaneous fluids / total parenteral nutrition (TPN) / enteral feeding or fluids already being administered
- Patient likely to be transferred to another setting for end of life care (e.g. home, hospice)

Sample size

Two hundred participants

Duration

2 years (recruitment – 1 year)



Study flow diagram

1 - Introduction

1.1 - Background

The provision of clinically-assisted hydration (CAH) at the end-of-life is one of the most contentious issues in medicine [1,2], and indeed within the general population [3,4]. The reasons for contention include: a) the lack of evidence for / against CAH [5,6]; b) the disparate opinions of healthcare professionals about CAH [7]; and c) the generally positive opinions of patients and their carers about CAH (and the generally negative opinions about withholding / withdrawing CAH) [7]. It is, therefore, unsurprising that the provision of CAH at the end-of-life is extremely variable within clinical practice (i.e. 12-88% cancer patients in the last week of life) [8]. It should be noted that in this instance, CAH refers to the medical provision of parenteral fluids (i.e. intravenous, subcutaneous), and not to the medical provision of enteral fluids (e.g. administering fluids via a gastrostomy / jejunostomy).

In 2012, there were 499,331 deaths registered in England and Wales, with cancer being the most common underlying cause of death (29% total deaths) [9]. Currently, the most common place of death for cancer patients is hospital (48%), followed by home (24.5%), followed by hospice (16.4%) [10]. There is limited data on the use of CAH in hospitals, and no data on the use of CAH at home or in hospices (although the impression is that CAH is generally not available in the home setting, and is generally not utilised in the hospice setting). In 2012, the National Care of Dying Audit – Hospitals (NCDHA) reported that 16% patients continued with CAH, 28% patients discontinued CAH, and only 0.4% patients commenced on CAH, during the period they were managed on the Liverpool Care Pathway for the Dying Patient (LCP) [11]. In other words, only 16.4% patients received CAH during the period they were managed on the LCP. [Of note, 32% patients in the NCDHA had an underlying diagnosis of cancer].

The lack of provision of fluids at the end-of-life was one of the major issues raised in the recent review of the LCP (which has resulted in the planned withdrawal of the LCP in the United Kingdom) [12]. Indeed, the review notes that “most of the submissions to the Review from relatives and carers that were critical of the LCP made reference to hydration and nutrition”. The 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”. However, it also highlights that “a systematic review of all of the literature and studies evaluating the benefits of clinically assisted hydration in palliative care patients shows

no clear benefit to either length or quality of life”. Of note, the aforementioned systematic review concluded that “more evidence is needed, particularly in relation to effects of clinically-assisted hydration in patients suffering symptoms that might be strongly influenced by hydration (e.g. delirium, and symptoms of fluid overload)” [6].

1.2 - Evidence for CAH

In 2008, Good et al conducted a Cochrane systematic review of medically assisted hydration for adult palliative care patients, and concluded that “currently, there are insufficient good quality studies to make any recommendations for practice with regards to the use of medically assisted hydration in palliative care patients” [5]. Good et al identified five relevant studies [13-17], although only two studies were randomised controlled studies [15,16]. However, neither of the randomised controlled studies addressed the specific issue of the routine use of CAH at the end of life. Thus, Cerchiotti et al included patients with evidence of dehydration (and / or renal failure), and patients were given relatively low volumes of fluid (1 L / day), and the fluids were only given for 48 hr (and not continued until death) [15]. Similarly, Bruera et al only included patients with evidence of dehydration, and patients were given relatively low volumes of fluid (1 L / day), and the fluids were only continued for 48 hr (and not continued until death) [16]. It should be noted that Good et al re-searched the literature in early 2011, and although they did not find any new studies, they did identify an ongoing randomised controlled trial [18].

In 2013, Parry et al conducted a so-called rapid evidence review of the literature on pathways focused on the dying phase in end of life care and their key components, and concluded that “the current research evidence base is not sufficient to inform specific recommendations to use or not to use clinically-assisted nutrition and / or hydration” [6]. The review included the new randomised controlled trial [18], which again did not address the specific issue of the routine use of CAH at the end of life. Thus, Bruera et al only included patients with evidence of dehydration, and patients were given relatively low doses of fluid (1 L / day), and the fluids were continued for a variable duration, i.e. “until the patient was unresponsive, developed progressive coma, or died”. The conclusion of this study was that “hydration at 1 L per day did not improve symptoms, quality of life, or survival”.

The purported positive effects of CAH include the maintenance of patient comfort (e.g. prevention of thirst, prevention of dry mouth), and the maintenance of renal perfusion /

prevention of accumulation of toxins and drugs (prevention of delirium, prevention of opioid toxicity) [19]. In contrast, the purported negative effects of CAH include problems due to fluid overload (e.g. worsening of peripheral oedema, worsening of cardiac failure), and problems due to fluid-related complications (e.g. worsening of vomiting, worsening of respiratory secretions) [19]. In addition, it has been claimed that ketones and other by-products of dehydration can have positive effects on the patients' condition / symptom control (i.e. analgesic effects, sedative effects). As intimated above, there is little evidence to support / refute these effects in the general population.

It should be noted that the previous randomised controlled studies utilised relatively low volumes of fluid (i.e. 1 L/day), despite the fact that many of the patients were clinically dehydrated [15,16,18]. Moreover, there seems to be little scientific rationale for the use of 1 L / day per se [20]. The National Institute for Health and Care Excellence have developed a clinical guideline on intravenous fluid therapy in adults in hospital [21]: their recommendation for routine maintenance intravenous fluid therapy is 25-30 mL / kg / day of water (with appropriate amounts of sodium, potassium, chloride and glucose). In other words, 1 L / day would be an appropriate volume for a non-dehydrated patient weighing 33-40 kg, and would be an inappropriately low volume for a dehydrated patient of any weight. It should be noted that the subcutaneous route is a valid alternative to the intravenous route in this situation [22].

1.3 - End-of-life problems

Cancer patients may develop a range of problems in the last days of life, including delirium (aka "terminal agitation" / "terminal restlessness in the last days of life [23]), excess respiratory secretions (aka "death rattle"), urinary retention or urinary incontinence, and continuance or exacerbation of other symptoms (e.g. pain, dyspnoea, nausea and vomiting) [24].

Delirium is one of the most common problems (25-85% patients) [25], and one of the most distressing problems (for patients, relatives and healthcare professionals) [26], encountered at the end of life. There are three sub-types of delirium: 1) "hyperactive" (hyperarousal, hyperalert, or agitated); 2) "hypoactive" (hypoarousal, hypoalert, or lethargic); and 3) "mixed" [23]. The clinical features of delirium are somewhat variable, but the two "essential concepts" are disordered attention (arousal), and disordered cognition [23]. Hyperactive

delirium is often associated with agitation, disorientation, delusions and hallucinations, and is well recognised at the end-of-life. In contrast, hypoactive delirium is often associated with sedation and confusion, and is less well recognised at the end-of-life (although common) [23].

Dehydration is a recognised cause of delirium, and rehydration a recommended intervention for delirium (in appropriate situations) [25]. Nevertheless, the mainstay of the management of delirium is the use of antipsychotic and / or sedative drugs [25]. Such agents are used in ~ 50% patients in the last week of life [27], and although they are generally very effective, they are often associated with untoward sedation (which necessarily impacts on the dying process, especially in terms of interpersonal communication). It should be noted that the use of sedative drugs was another major issue raised in the recent review of the LCP (which has resulted in the planned withdrawal of the LCP in the United Kingdom) [12].

1.4 - Study rationale

The authors of the Cochrane systematic review discussed the need for further studies in this area, and highlighted the barriers to conducting such studies, including obtaining informed consent, recruitment of subjects, retention of subjects, and presence of confounders [5,28]. Our aim is to undertake a randomised controlled trial of clinically-assisted hydration in non-dehydrated cancer patients at the end of life (i.e. in the last week of life), and in an effort to overcome some of the aforementioned barriers we are proposing to undertake a cluster randomised trial, and to seek consent from the patient (whenever possible), and advice from a “personal consultee” (when the patient is unable to provide consent), or advice from a “nominated consultee” (when the patient is unable to provide consent, and there is no personal consultee) [29,30].

It should be noted that other studies involving patients at the end-of-life have adopted a cluster randomised trial design [31,32].

1.5 – Study hypothesis

Our hypothesis is that CAH during the last few days of life reduces the frequency of hyperactive delirium (“terminal agitation”) in cancer patients as a result of the maintenance of renal perfusion and the prevention of accumulation of toxins and drugs (i.e. prevention of dehydration).

2 - Aim and objectives

2.1 - Aim

The aim of the definitive study is to evaluate the utility / role of CAH in cancer patients in the last days of life. The aim of the feasibility study is to answer the question “can this study (*the definitive study*) be done”?

2.2 - Objectives

The objectives of the definitive study are to:

- 1). Assess the effect of CAH on the frequency of hyperactive delirium ("terminal agitation")
- 2). Assess the effect of CAH on the frequency of pain
- 3). Assess the effect of CAH on the frequency of respiratory secretions ("death rattle")
- 4). Assess the effect of CAH on the frequency of dyspnoea
- 5). Assess the effect of CAH on the frequency of nausea and vomiting
- 6). Assess the effect of CAH on survival
- 7). Assess the tolerability of CAH
- 8). Assess the health economic impact of CAH

The objectives of the feasibility study are [33]:

▪ Process

- 1). Assess the recruitment rate, i.e. number eligible patients, number recruited patients, barriers to recruitment
- 2). Assess the retention rate
- 3). Assess the impact of trial procedures on clinical workload, i.e. completion of observation chart, undertaking mouth care / CAH

▪ Resources

- 1). Assess the adequacy of resources to conduct the study at research centres
- 2). Assess the adequacy of resources to support the study at Surrey Clinical Research Centre

▪ Management

- 1). Determine other challenges for researchers / research centres
- 2). Determine other challenges for Surrey Clinical Research Centre

▪ Scientific

- 1). Assess the safety of CAH
- 2). Determine total variability / intra-cluster correlation coefficient

3 - Criteria for success

The following criteria will be used to determine the success of the feasibility study (and so progression to the definitive study):

- 1). Recruitment - 200 patients from 12 centres in 1 year
- 2). Retention - $\geq 67\%$ participants complete the study
- 3). Adherence to study procedures - $\geq 67\%$ nursing observations are completed on the observation charts
- 4). Safety of study interventions - $\leq 50\%$ participants have CAH discontinued due to treatment-related adverse events

The possible outcomes of the feasibility study are:

- 1). Feasibility study deemed a success, and definitive study undertaken with no change to the protocol (subject to funding)
- 2) Feasibility study deemed a success, but definitive study undertaken with changes to the protocol (subject to funding)
- 3). Feasibility study deemed a failure, and definitive study not undertaken

4 - Study methodology

4.1 - Study design

The study will be a cluster randomised trial (CRT) rather than a conventional randomised controlled trial: a CRT is one where “clusters of people, or intact social units, rather than individuals are randomised to intervention and control groups and outcomes are measured on individuals within those clusters” [34].

The authors of the Cochrane systematic review of medically-assisted hydration for adult palliative care patients concluded that “currently, there are insufficient good quality studies to make any recommendations for practice with regards to the use of medically assisted (*clinically-assisted*) hydration in palliative care patients” [5]. Moreover, they discussed the need for further studies in this area, and highlighted the barriers to conducting such studies, including obtaining informed consent, recruitment of subjects, retention of subjects, and presence of confounders [5,28]. Indeed, the most recently published conventional randomised controlled trial of CAH in palliative care patients failed to recruit its target sample size of 150 patients, despite the study being conducted in 6 sites, and despite the study running for over 4 years (50 months) [18].

In an attempt to overcome the aforementioned barriers, a number of researchers have (successfully) undertaken CRTs in palliative care [35,36], and specifically in end-of-life care [31,32]. Zimmermann et al performed a CRT of “early palliative care” in patients with advanced cancer: they commented that 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” [36]. Similarly, Fowell et al performed a crossover study of the effectiveness of anti-emetics in syringe drivers in dying patients: the focus of this study was on obtaining consent (rather than the effectiveness of anti-emetics), and the influence of individual randomisation (using Zelen’s design) versus cluster randomisation [31]. During the individual randomisation phase of the study 24% patients consented to participate in the study, whilst during the cluster randomisation phase of the study 54% patients consented to participate in the study.

On the basis of the repeated failures to complete conventional RCTs at the end-of-life, and the recent successes in completing CRTs at the end of life, we have decided to undertake a CRT (involving a transparent consent process). All of the study sites have a standard regimen in terms of hydration at the end of life, and although the study sites are willing to be potentially randomised to an alternative regimen, the study sites were unanimous in stating that it would be difficult to recruit patients to a conventional RCT due to patient, carer and healthcare professional’s opinions about CAH (as in the study of early palliative care) [7,36]. Thus, patients may be reluctant to consent to a study where there is the possibility of receiving one of two interventions, but less reluctant to consent to a study where there is the inevitability of receiving one intervention (and in effect they are consenting to the use of their personal information). In addition, if the study site has a standard regimen, then it is less likely that patients will be given the “wrong” intervention, and the staff will be proficient / confident in giving their standard regimen.

Another advantage of performing a CRT is the formation of cluster representation mechanism (CRM), which is independent of the research team, and which represents the interests of the cluster (and the individuals within the cluster). As many of the patients will lack capacity at the start of the study, and almost all the remaining patients will lose capacity during the

study, the CRM provides additional oversight of the study (from both an ethical, and a research governance perspective). The CRM is discussed in more detail in the next section.

The CRT design was developed in conjunction with the Research Design Service South East (University of Surrey), and has been endorsed by the peer reviewers involved in the successful grant application to Research for Patient Benefit Programme (of the National Institute for Health Research).

It should be noted that RCTs are considered to be the “gold standard”, and clinical practice will only change as a result of high quality evidence from new RCTs, and will not change as a result of low quality evidence from additional observational (uncontrolled) studies.

4.2 - Cluster representation mechanism

Study sites will be required to develop a CRM to represent the interests of the cluster (and the individuals within the cluster) [34]. The CRM has the same rights as an individual patient in a normal randomised trial; the CRM has the right to withdraw the cluster from the study if it decides that study 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 study, and monitors the continued involvement of the cluster in the study, e.g. senior clinician), and a Study Guardian (who is responsible for the individuals in the cluster, permits individuals to take part in the study, and monitors the continued involvement of individuals in the study, 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.

4.3 - Consent process

The study involves patients in the last week of life, and it is anticipated that many of the potential participants will be unable to provide informed consent (due to impaired cognition / impaired consciousness).

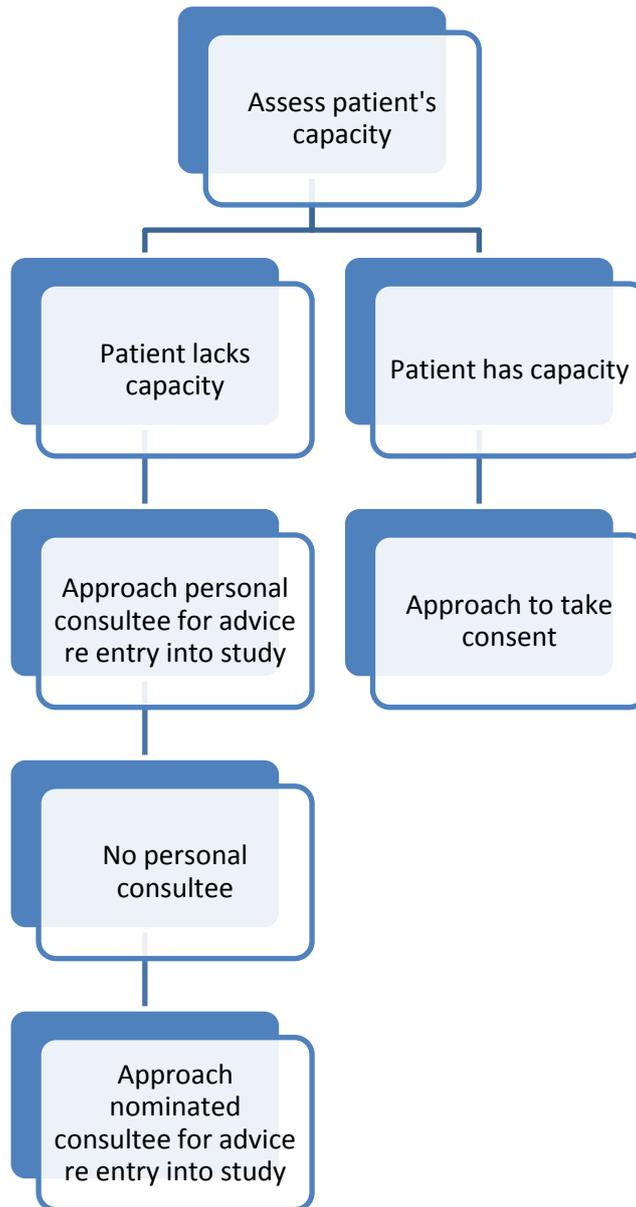
As the study is not a clinical trial of an investigational medicinal product (CTIMP), the study comes under the remit of the Mental Capacity Act [29,30].

If the patient is deemed to have capacity by the clinical team, then consent will be sought from the patient in the normal manner by the research team. Moreover, we will attempt to

seek “advanced” consent (i.e. attempt to seek consent from patients before they become eligible for the study / before they become unable to give consent). Advanced consent has been utilised in a previous end-of-life care study in the United Kingdom [37], but now must be ratified by either a personal consultee or a nominated consultee (see below) [29].

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 re the patient entering the study [29,30]. In this study, the personal consultee could be a relation of the person, or a friend of the person. The personal consultee will be given an information sheet about the study, given the opportunity to ask questions about the study, and asked whether in their opinion the patient would have any objection to taking part in the study.

If the patient is deemed not to have capacity, and no personal consultee is available, then a nominated consultee will be approached for advice re the patient entering the study [29,30]. In this study, the nominated consultee will be the Study Guardian (who is independent of the research team).



Summary of “consent” process for study

5 - Study participants

5.1- Study sites

This study will be carried out in NHS hospitals and NHS / voluntary sector hospices in the United Kingdom. The number of sites in the feasibility study will be twelve (four hospitals, eight hospices); the number of sites in the definitive study will be determined from the analysis of the feasibility study.

5.2 - Study population

The number of participants in the feasibility study will be 200 (see statistical considerations); the number of participants in definitive study will be determined from the analysis of the feasibility study.

Participants will be inpatients at the study sites, and meet all of the inclusion criteria, and none of the exclusion criteria, of the study (see below).

5.3 - Inclusion criteria

- Diagnosis of cancer
- Age \geq 18 yr
- Estimated prognosis of \leq 1 week
- Patient unable to maintain sufficient oral intake (1L / day – measured / estimated)

5.4 - Exclusion criteria

- Patient clinically dehydrated
- Patient has hyperactive delirium (“terminal agitation”) at present
- Patient has had hyperactive delirium (“terminal agitation”) in the last 24hrs
- Patients with a relevant advance directive to refuse treatment
- Clinical indication for clinically-assisted hydration (e.g. hypercalcaemia)
- Clinical contra-indication to clinically-assisted hydration (e.g. cardiac failure)
- Clinical contra-indication to peripheral cannulation
- Intravenous fluids / subcutaneous fluids / total parenteral nutrition (TPN) / enteral feeding or fluids already being administered
- Patient likely to be transferred to another setting for end of life care (e.g. home, hospice)

5.5 - Recruitment process

Potential participants will be highlighted to the research team by the clinical team; the research team will then screen the patient for eligibility to enter the study, and, if appropriate, obtain “consent” for the patient to enter the study. The details of patients that failed the screening process, or that were not “consented” to the study, will be recorded in the site’s screening log.

6 - Study interventions

6.1 - Standards of care

The interventions utilised within this trial represent current standards of care within clinical practice (see introduction). Sites will be randomised to either “standard intervention arm A” or “standard intervention arm B”, and this will become the standard of care within the site for the duration of this trial.

6.2 - Standard intervention arm A

Standard intervention arm A involves:

- Continuance of oral intake (if appropriate)
- Regular “mouth care”
- Standard management of pain and other symptoms in the terminal phase

Mouth care should be performed at least every four hours, and should correspond to the participating sites policy / procedures for oral care in the terminal phase. Mouth care should be discontinued if it causes distress / discomfort to the patient.

6.3 - Standard intervention arm B

Standard intervention arm B involves:

- Continuance of oral intake (if appropriate)
- Regular “mouth care”
- Standard management of pain and other symptoms in the terminal phase
- Clinically-assisted hydration, i.e. parenteral fluids

Mouth care should be performed at least every four hours, and should correspond to the participating sites policy / procedures for oral care in the terminal phase. Mouth care should be discontinued if it causes distress / discomfort to the patient.

The parenteral fluids may be administered either intravenously or subcutaneously at the discretion of the medical and nursing team [22]. The type of fluid to be administered is dextrose saline (i.e. 4% dextrose, 0.18% sodium chloride), and the volume to be administered will be dependent on the patient's weight [21]:

Patient's weight	Volume of fluid
< 45 kg	1L / 24hr
45-60 kg	1.5 L / 24hr
> 60 kg	2 L / 24hr

6.4 - Intravenous fluids

Intravenous fluids should be administered according to the investigational site's policy / procedures.

6.5 - Subcutaneous fluids

Subcutaneous fluids should be administered according to the following guidelines [22]:

a) Site of cannula

– the recommended sites are the lateral lower abdomen, the upper anterior chest, the upper posterior chest, and the upper leg.

– some authors recommend that the site is alternated after each litre of fluid; the decision to alternate the site is at the discretion of the medical and nursing team.

b) Type of cannula

– it is suggested that a 22g or 24g plastic cannula is used, although a similar gauge metal “butterfly” needle (or similar device) may be used.

c) Change of cannula

– the decision to remove / re-site the cannula is at the discretion of the medical and nursing team.

d) Infusion method

– the fluid should be administered via gravity using a standard intravenous giving set connected to the cannula: the fluid should not be administered via an infusion pump.

– the fluid can be administered as either a continuous infusion (i.e. over 24hr), or an intermittent infusion (e.g. over 8hr)

e) Infusion rate

– it is suggested that a maximum infusion rate of 1L / 4hr is used.

– the infusion rate will be set as drops per minute (calculated by the nursing team, and dependent on the volume of fluid, infusion time, and type of giving set).

7 - Study assessments

7.1- Screening

At screening, the researcher will assess eligibility to enter study (i.e. inclusion / exclusion criteria), and record demographic data, cancer diagnosis, significant concurrent medical history, current regular medications, recent blood test results (if available; if < 1 week), current oral intake, and urinary continence (or presence of catheter). The data will be obtained from the participant's medical records (paper or electronic), and the participant's drug chart(s); these documents are considered source documents in this study. [If there are no recent blood test results then this section should be left blank; there is no compulsion to undertake a blood test for the purposes of the study].

7.2 - Treatment period (day 1 to death / withdrawal / day 14)

During the treatment period, the researcher will record the 4 hrly agitation scores (see below), 4hrly symptom occurrences, change in regular medications, use of as required (prn) medications, oral intake, urinary continence, and (if appropriate) parenteral fluids administered, adverse events relating to parenteral fluids, and requirements for re-cannulation. The data will be obtained from the participant's observation chart, and the participant's drug chart(s); these documents are considered source documents in this study.

7.3 - End of study (death / withdrawal / day 14)

The researcher will record the participant's outcome, including the date of death / withdrawal, and the reason for withdrawal (if appropriate).

7.4 - Overview of study assessments

ASSESSMENTS	Screening	Treatment period (daily assessments)	End of study
Inclusion / exclusion criteria	√		
Consent	√		
Demographic data	√		
Cancer diagnosis	√		
Concurrent medical history	√		
Regular medication	√	√	
Oral intake	√	√	
Urinary continence	√	√	
4 hrly Modified Richmond Agitation & Sedation Scale scores		√	
4hrly symptom occurrences		√	
As required medication		√	
Oral intake		√	
Urinary continence		√	
Parenteral fluids administered		√	
Adverse events		√	
Cannulation problems		√	
Participant outcome			√

7.5 - Observation chart

The observation chart (standardised) will be completed by the clinical team, and the data transcribed onto the case report form by the research team. The observation chart is considered a source document in this study.

Patients will be reviewed at least every 4 hours, and an assessment made as to whether or not certain symptoms are present, i.e. hyperactive delirium (“terminal agitation”), pain, excess respiratory secretions (“death rattle”), nausea and vomiting, dyspnoea, and urinary continence. Agitation will be given a score (see below), but the other symptoms will simply be recorded as present or absent.

7.6 - Modified Richmond Agitation–Sedation Scale

The primary outcome of the definitive study will be the frequency of hyperactive delirium (“terminal agitation”), and this will be assessed using the modified Richmond Agitation and Sedation Scale (mRASS) (Appendix 4) [37]. The m-RASS is a numerical scale that includes

four levels of agitation: +1 = “restless”; +2 = “agitated”; +3 = “very agitated”; and +4 = “combative”. The mRASS will be an integral part of the observation chart. The original / unmodified RASS has been recommended for use in Palliative Care [38,39], although the tool does not appear to have been validated / tested for reliability in a palliative care population. However, the mRASS has recently been successfully validated (face validity) / tested for reliability (inter-rater reliability) in a palliative care population [37].

It should be noted that patients with pain / other problems may appear agitated, and so a diagnosis of hyperactive delirium (“terminal agitation”) must be validated by the clinical team’s use of an appropriate anti-psychotic or sedative drug to treat delirium (“terminal agitation”).

7.7 - Recording of oral intake / CAH

The oral intake, and (if appropriate) use of / problems relating to parenteral fluids will also be recorded in the observation chart (e.g. need to change cannula).

7.8 - Change in CAH status

If a participant’s method of hydration changes during the treatment period (on clinical grounds), then data should continued to be collected until the end of study.

7.9 - Process evaluation

A process evaluation will be undertaken in parallel to the feasibility study using a framework developed for cluster randomised trials [40] (based on the so-called RE-AIM framework [41]): data will be derived from routine research governance / trial monitoring (quantitative data), and additional / independent assessments (quantitative data, qualitative data). Thus, Principal Investigators from all units will be asked to complete a specifically developed questionnaire about the study processes at 1, 3 and 12 months after the start of the study (primarily quantitative data). In addition, clinical staff from 50% units (randomly selected) will be asked to participate in focus groups about the study processes at 3-6 months after the start of the study (qualitative data).

The framework involves:

A. Processes involving clusters

- Recruitment of clusters: how are cluster supplied and recruited? Who agrees to participate? Why do clusters agree to participate? Method – data collected by research team.
- Delivery to clusters: what intervention is actually delivered to each cluster? Is it the intended cluster? Method – study monitoring.
- Response of clusters: how is the work of the intervention and trial implemented in and adopted by clusters? Method – study monitoring, Principal Investigator questionnaires, focus groups.

B. Processes involving target population

- Recruitment and reach of individuals: who actually receives the intervention in each setting? Are they representative? Method – study monitoring, Principal Investigator questionnaires, focus groups.
- Delivery to individuals: what intervention is delivered in each cluster? Or what behaviour change has occurred because of the intervention? Method – study monitoring, Principal Investigator questionnaires, focus groups.
- Response of individuals: how does the target population respond? Method – study monitoring, Principal Investigator questionnaires, focus groups.

C. Maintenance

- How and why are these process sustained over time (or not)? Method – study monitoring, Principal Investigator questionnaires, focus groups.

D. Unintended Consequences

- Change in other outcomes (not effectiveness) which may be perverse, harmful or beneficial? Method – study monitoring, Principal Investigator questionnaires, focus group.

8 - End of study / trial

8.1 - End of study (individual participant)

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

8.2 - End of trial

The end of trial occurs when the final participant reaches the end of study (see above).

9 - Trial monitoring

9.1 - Study documentation

The PI has the responsibility for ensuring that the study documentation are properly maintained to ensure the smooth running of the study (i.e. site file, source documents).

Source documents must be retained for at least 10yrs after the end of trial.

9.2 - Monitoring visits

A monitor from the Sponsor will visit the sites on a regular basis to ensure Good Clinical Practice, and especially compliance with the protocol; the monitor will inspect the site file, check the recruitment / screening log, and check the source documents (which should be made available to the monitor).

9.3 - Trial Monitoring Committee

The study will have a Trial Monitoring Committee (TMC), which will consist of an independent Chairperson (retired Chaplain), the Chief Investigator, the Clinical Trial Unit Lead, the Lead Research Nurse, the Statisticians, the Ethical Advisor, patient / carer representatives, and one of the Principal Investigators. The TMC will meet one month after the start of the study, and then once a quarter (until the end-of-study report has been completed). The TMC will review all aspects of the study, particularly any safety issues (see below).

10 - Safety monitoring

10.1 - Adverse events

An adverse event (AE) is defined as any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

As the study is being undertaken in patients in the last days of life, progression of existing problems, and development of routine end of life problems (e.g. hyperactive delirium /

“terminal agitation”, excess respiratory secretions / “death rattle”) are not considered to be a SAE.

All AEs (and SAEs) will be documented in the CRF, and reviewed by the CI / TMC.

10.2 - Serious adverse events (SAE)

A SAE is defined as any adverse event, adverse reaction or unexpected adverse reaction that:

- a) results in death;
- b) is life-threatening;
- c) requires hospitalisation or prolongation of existing hospitalisation;
- d) results in persistent or significant disability or incapacity; or
- e) consists of a congenital anomaly or birth defect.

As the study is being undertaken in patients in the last days of life, death due to cancer / complication of cancer is not considered to be a SAE. However, death or a life threatening condition related to the study intervention is considered a SAE (and so is immediately reportable to the Sponsor).

See above re recording of SAEs.

11 - Ethical considerations

The study will be conducted in accordance with the Declaration of Helsinki, and the International Conference on Harmonisation (ICH) guidance on Good Clinical Practice (GCP).

11.1 - Ethical approval

The study will need prior (to initiation of the study) approval from the University of Surrey ethics committee and an independent research ethics committee (REC). Furthermore, amendments to the protocol will also need prior approval from the REC. The REC will also require timely safety reporting (including an annual safety report), an annual progress report, and eventually an end-of-study report.

11.2 - Ethical issues relating to CAH

The provision of clinically-assisted hydration (CAH) at the end-of-life is one of the most contentious issues in medicine [1,2], and indeed within the general population [3,4]. The reasons for contention include: a) the lack of evidence for / against CAH [5,6]; b) the disparate opinions of healthcare professionals about CAH [7]; and c) the generally positive

opinions of patients and their carers about CAH (and the generally negative opinions about withholding / withdrawing CAH) [7].

In some instances there is a clear indication for giving CAH (e.g. a patient with opioid toxicity), whilst in other instances there is a clear indication for not giving CAH (e.g. a patient with cardiac failure). Currently, however, it is impossible to make a best interests decision for the majority of patients (due to the lack of evidence) [39]. Hence, there is an urgent need / ethical necessity to undertake research to define the role of CAH in the last days of life (and indeed the role of mouth care in the last days of life).

11.3 - Ethical issues relating to interventions

The study interventions are both routinely used in clinical practice, and so all of the patients will receive a “standard intervention” (and not an experimental treatment, or a placebo treatment).

It should be noted that the exclusion criteria will include patients that are dehydrated (and so require CAH), patients with another indication for CAH, and patients with a contra-indication to CAH. Furthermore, patients in standard intervention arm A that develop an indication for CAH may be started on parenteral fluids at the discretion of the clinical team. Equally, patients in standard intervention arm B that develop a contra-indication to CAH may be discontinued from parenteral fluids at the discretion of the clinical team.

11.4 - Ethical issues relating to consent

The study involves patients in the last week of life, and it is anticipated that many of the potential participants will be unable to provide informed consent (due to impaired cognition / impaired consciousness).

As the study is not a clinical trial of an investigational medicinal product (CTIMP), the study comes under the remit of the Mental Capacity Act [29,30]. Consent will be sought from the patient (whenever possible), or advice from a “personal consultee” (when the patient is unable to provide consent), or advice from a “nominated consultee” (when the patient is unable to provide consent, and there is no personal consultee). In this study the personal consultee will be a relation or friend of the patient, and the nominated consultee will be the Study Guardian.

Patient / consultee information sheets have been developed for the study: there is one for study sites randomised to standard intervention A, and one for study sites randomised to standard intervention B, so that patients / consultees are fully aware of the intervention to be given. Patient consent forms / consultee declaration forms have also been developed for the study.

12 - Regulatory considerations

12.1 - Medicines and Healthcare products Regulatory Agency

The Medicines and Healthcare products Regulatory Agency (MHRA) have reviewed the study, and deemed that “the study does not come under the definition of a clinical trial of an Investigational Medicinal Product (IMP)”.

12.2 - Data Protection Act

The study will conform to the Data Protection Act (and related legislation); all data will be treated as confidential, and data will be anonymised prior to removal from the study site.

13 - Statistical considerations

13.1 - Statistical support

Statistical support is being provided by the statisticians attached to the Research Design Service South East (based at the University of Surrey).

13.2 - Sample size

Twelve sites (four hospitals, eight hospices) will be involved in the feasibility study, and these will be randomised to either standard intervention A, or standard intervention B. There will be a separate randomisation process for the hospitals and the hospices. The target is to recruit 200 participants from the twelve sites within a period of one year; the end of the trial will occur when either 200 participants have been recruited, or the trial has been ongoing for one year (and inadequate numbers of participants have been recruited).

13.3 - Analysis

A “case” of hyperactive delirium is considered to be a participant that scores +2 to +4 on the mRASS [37], and is treated by the clinical team with an appropriate anti-psychotic or sedative drug to treat hyperactive delirium (“terminal agitation”). Participants who do not fall

into this category will be considered as “non-case”. This dichotomous outcome will be used as the primary endpoint for the analysis.

The analysis evaluating the difference in proportions of participants experiencing hyperactive delirium between the two interventions will be a logistic regression with the occurrence of hyperactive delirium as the dependent variable and interventions (A or B), cluster, and cluster type (hospital or hospice) as explanatory variables. The analysis will be based on the Intention-to-Treat (ITT) population, and will furnish estimates of the proportion of subjects suffering from hyperactive delirium for each intervention together with an estimate of the coefficient of variation of true proportions between clusters within each intervention arm. The latter of these estimates is an important requirement for determining the sample size aspect of a future cluster randomised study designed with adequate power to evaluate the impact of the intervention including CAH [42]. It is judged that recruitment of 200 participants in twelve clusters in the feasibility study will provide a realistic estimate.

The logistic regression analysis will allow the testing of the hypothesis of no difference in the proportion of hyperactive delirium experienced between groups treated by either intervention. The intervention including CAH will be considered an improvement on the other intervention, in this and any future definitive study, only if the proportion of hyperactive delirium sufferers is reduced by at least 20%.

It is considered unlikely that this statistical analysis of the feasibility study will be able to test this hypothesis with sufficient power, but its results, together with learnings from other aspects of the study management, will be used to design a definitive study.

From a statistical perspective, the estimates of the proportion of subjects suffering hyperactive delirium for each intervention, and the coefficient of variation of true proportions between clusters within each intervention, obtained from the feasibility study, will be used to determine the number of clusters and sample size necessary to detect a difference of 20% in the proportion of hyperactive delirium sufferers between the interventions with 80% power using a two-sided 5% significance level. This calculation will form part of the design of the definitive study.

Should the number of clusters and sample size in the feasibility study retrospectively be found to provide the necessary power to test the hypothesis, the statistician will provide this information to the study team as input into their decision as to whether a definitive study is required.

14 - Conditions for modifying the protocol

The feasibility study may result in changes to the protocol for the definitive study, or the protocol may need to be amended during the period of the feasibility study.

Any changes to the protocol must be agreed by the Trial Monitoring Committee, and approval must be obtained from the Sponsor, and the REC before the changes are implemented.

15 - Finance

The study is being funded by a grant from the Research for Patient Benefit Programme (of the National Institute for Health Research).

16 - Insurance

The study will be underwritten by the Sponsor; the study sites will be required to have insurance cover for undertaking clinical research.

17 - End of study report / publications

At the end of the study, a study report will be written, and submitted to the funder, the Sponsor, the REC, and the Principal Investigators.

The results of the study will be published in an appropriate medical journal and presented at appropriate medical conferences.

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Appendix 1

Modified Richmond Agitation-Sedation Scale [38]

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, non aggressive 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