

Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)

SOS trial: Hyperosmolar therapy in traumatic brain injury

1. Is your project research?

☒ Yes ☐ No

2. Select one category from the list below:

- ☒ Clinical trial of an investigational medicinal product
- ☐ Clinical investigation or other study of a medical device
- ☐ Combined trial of an investigational medicinal product and an investigational medical device
- ☐ Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice
- ☐ Basic science study involving procedures with human participants
- ☐ Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology
- ☐ Study involving qualitative methods only
- ☐ Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)
- ☐ Study limited to working with data (specific project only)
- ☐ Research tissue bank
- ☐ Research database

If your work does not fit any of these categories, select the option below:

☐ Other study

2a. Is this a commercially sponsored Phase 1 or Phase 1/2a trial involving healthy volunteers?

☐ Yes ☒ No

2b. Will the study involve the use of any medical device without a CE Mark, or a CE marked device which has been modified or will be used outside its intended purposes?

☐ Yes ☒ No

2c. Please answer the following question:

Is this trial subject to advice from the Expert Advisory Group on Clinical Trials and the Commission on Human Medicine prior to authorisation from MHRA?

☐ Yes ☒ No

2d. Please answer the following question:

Is this a trial of a gene therapy medicinal product?

☐ Yes ☒ No

2e. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation? ☐ Yes ☒ No

b) Will you be taking new human tissue samples (or other human biological samples)? ☐ Yes ☒ No

c) Will you be using existing human tissue samples (or other human biological samples)? ☐ Yes ☒ No

3. In which countries of the UK will the research sites be located?(Tick all that apply)

- ☒ England
- ☒ Scotland
- ☒ Wales
- ☒ Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

- ☒ England
- ☐ Scotland
- ☐ Wales
- ☐ Northern Ireland
- ☐ This study does not involve the NHS

4. Which applications do you require?

- ☒ IRAS Form
- ☒ Medicines and Healthcare products Regulatory Agency (MHRA) – Medicines
- ☒ Confidentiality Advisory Group (CAG)
- ☐ Her Majesty's Prison and Probation Service (HMPPS)

4a. Will you be seeking data from Hospital Episode Statistics (HES) or the Secondary Uses Service (SUS)?

☐ Yes ☒ No

5. Will any research sites in this study be NHS organisations?

☒ Yes ☐ No

5a. Are all the research costs and infrastructure costs (funding for the support and facilities needed to carry out research e.g. NHS Support costs) for this study provided by a NIHR Biomedical Research Centre, NIHR Collaboration for Leadership in Health Research and Care (CLAHRC), NIHR Patient Safety Translational Research Centre or Medtech and In Vitro Diagnostic Cooperative in all study sites?

Please see information button for further details.

☐ Yes ☒ No

Please see information button for further details.

5b. Do you wish to make an application for the study to be considered for NIHR Clinical Research Network (CRN) Support and inclusion in the NIHR Clinical Research Network Portfolio?

Please see information button for further details.

☒ Yes ☐ No

The NIHR Clinical Research Network provides researchers with the practical support they need to make clinical studies happen in the NHS e.g. by providing access to the people and facilities needed to carry out research "on the ground".

If you select yes to this question, you must complete a NIHR Clinical Research Network (CRN) Portfolio Application Form (PAF) immediately after completing this project filter question and before submitting other applications. Failing to complete the PAF ahead of other applications e.g. HRA Approval, may mean that you will be unable to access NIHR CRN Support for your study.

6. Do you plan to include any participants who are children?

☐ Yes ☒ No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

☒ Yes ☐ No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

☒ Yes ☐ No

9. Is the study or any part of it being undertaken as an educational project?

☐ Yes ☒ No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

☐ Yes ☒ No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

☒ Yes ☐ No

Integrated Research Application System
Application Form for Clinical trial of an investigational medicinal product**IRAS Form (project information)**

Please refer to the E-Submission and Checklist tabs for instructions on submitting this application.

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting [Help](#).

Please define any terms or acronyms that might not be familiar to lay reviewers of the application.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
SOS trial: Hyperosmolar therapy in traumatic brain injury

Please complete these details after you have booked the REC application for review.

REC Name:
East of England – Essex

REC Reference Number:
19/EE/0228

Submission date:
10/06/2019

PART A: Core study information**1. ADMINISTRATIVE DETAILS****A1. Full title of the research:**

Sugar or Salt (SOS) trial: Hyperosmolar therapy in traumatic brain injury

A3-2. National coordinating investigator (for a multicentre trial) or principal investigator (for a single centre trial)

- ☒ National coordinating investigator
☐ Principal investigator

Given name	Gavin
Family name	Perkins
Qualification (MD...)	MB ChB, MD , FRCP , FFICM, FIMC RCS(Ed)
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** This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.*

A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.

A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?

This contact will receive copies of all correspondence from REC and HRA/R&D reviewers that is sent to the CI.

	Title Forename/Initials Surname
	Mrs Jane Prewett
Address	University of Warwick, Research & Impact Services University House, Kirby Corner Road Coventry
Post Code	CV4 8UW
E-mail	sponsorship@warwick.ac.uk
Telephone	02476522746
Fax	

A5-1. Research reference numbers. Please give any relevant references for your study:

Applicant's/organisation's own reference number, e.g. R & D (if available):	SC.14/18-19
Sponsor's/protocol number:	SC.14/18-19
Protocol Version:	1.0
Protocol Date:	31/05/2019
Funder's reference number (enter the reference number or state not applicable):	17/120/01
Project website:	https://warwick.ac.uk/sos

Registry reference number(s):

The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

International Standard Randomised Controlled Trial Number (ISRCTN):	ISRCTN16075091
ClinicalTrials.gov Identifier (NCT number):	
European Clinical Trials Database (EudraCT) number:	2019-001688-66

Additional reference number(s):

Ref.Number	Description	Reference Number
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A5-2. Is this application linked to a previous study or another current application?

☐ Yes ☒ No

Please give brief details and reference numbers.

2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.

A6-1. Summary of the study. *Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. Where the research is reviewed by a REC within the UK Health Departments' Research Ethics Service, this summary will be published on the Health Research Authority (HRA) website following the ethical review. Please refer to the question specific guidance for this question.*

Doctors need to know the best treatments for severe brain swelling after head injuries in order to improve outcomes for patients. The two main drugs that are currently used to treat brain swelling are hypertonic saline (a strong salt solution) and mannitol (a sugary solution). Both of these drugs work by reducing brain swelling which helps to reduce pressure on the brain. Currently, it is not known which drug is the most effective treatment. Both drugs have undesirable side effects (hypertonic saline causes an imbalance of salts in the blood and Mannitol can cause kidney failure). To deliver the best treatment we need to know which is most the safest and most effective.

This study is designed to work out which is the most effective treatment for brain swelling. 638 patients who have sustained a severe injury to the brain and require treatment in intensive care will take part in the study. Half the patients will receive the salty solution and half will receive the sugary solution. Which of the two treatments they receive will be decided randomly using a computer programme.

The study will compare how effective the different drugs are at reducing the pressure on the brain. It will also assess which is better at helping the patient to recover and what the side effects of treatment were. The study team will keep in contact with patients for 12 months after the study to check on how well they have recovered over time. Researchers will also calculate how much each treatment costs and compare this to how beneficial they were.

The study will take place in neurosurgical intensive care units across the UK and is expected to finish at the end of 2023.

A6-2. Summary of main issues. *Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.*

Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified and managed routinely. Others may present significant issues requiring further consideration by a REC, HRA, or other review body (as appropriate to the issue). Studies that present a minimal risk to participants may raise complex organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.

PURPOSE AND DESIGN

In writing the grant application and designing the trial, a series of meetings were held with survivors and carers of patients with previous brain injury, facilitated through Headway West Midlands. The initial meeting focused on the need for research in patients with severe traumatic brain injury, research designs and the role played by hyperosmolar therapies. There was unanimous support for the need for this research. For example, a carer at the Headway group explained "If this trial will limit deficit after a brain injury, then patients have nothing to lose".

This trial is important to conduct as it remains unclear whether there is a treatment benefit to using mannitol or hypertonic saline in the management of raised intracranial pressure, and the importance of a trial directly comparing the two treatments was highlighted in a NIHR HTA Programming Commissioning Brief (17/20).

At a follow-up PPI meeting we explored the use of placebo, trial outcomes and how to optimise the process for approaching, informing and consenting relatives (including the use of professional legal representative consent) and optimising follow-up. The group were uncomfortable about the inclusion of a placebo arm, and felt that the need for placebo was poorly understood by the public. The fact that doctors also seemed unwilling to include a placebo arm was also a concern. This helped shape the design of the trial for a head to head comparison of the two currently used interventions (hypertonic saline and mannitol). The Headway group also expressed a preference for outcome measures which include an assessment of disability or impairment. Survival itself was not considered sufficient as it did not include the spectrum of good and bad outcomes. The group were comfortable with the use of the GOS-E scale as something that addressed their concerns. The group were also supporting of using pre-existing information systems such as NHS Digital in order to keep follow-up to a minimum, as patients and their relatives have a lot to deal

with after a severe brain injury.

BLINDING OF TREATMENT ALLOCATION

To ensure appropriate treatment, participants must be monitored closely and investigation results known to the treating clinical staff. As patient safety is paramount, and key patient clinical parameters (urine output and serum sodium levels) monitored in TBI patients will be influenced by the IMPs, it is not possible to blind clinical staff as to the patient's treatment allocation.

We will not specifically set out to inform patients or their legal representative of the treatment allocation. We recognise however that it may become evident during the course of the patient receiving the treatment.

CONSENT

Patients who sustain a severe traumatic brain injury and develop raised intracranial pressure will be unconscious and heavily sedated in order to manage the patient's airway and to 'rest' the brain. The occurrence of a traumatic brain injury is also an unpredictable medical event. These factors mean it is not possible to consult with or obtain prospective consent directly from the patient prior to enrolling them in the trial.

If a patient develops a sustained elevation in intracranial pressure above 20mmHg this is a life-threatening emergency and urgent action is needed to prevent death and severe disability. It is therefore our assessment that in many cases it will not be reasonably practical to obtain written informed consent from a legal representative prior to enrolment in the trial, as the urgency with which treatment must be provided would not allow sufficient time to explain the nature, significant, implications and risks of the trial as is required by the Medicines for Human Use (Clinical Trials) Regulations. As enrolment will take place twenty four hours a day and seven days a week this will make it impractical to rely on timely access to a legal representative. We therefore propose to enrol patients under deferred consent using the provisions within the EU Clinical Trials Directive and the Clinical Trials Regulations (2006, No 2984).

However if a legal representative is available prior to enrolment, and there is sufficient time, then a personal or professional legal representative will be informed about the trial and written informed consent will be sought. This will only be done after an assessment of whether it is appropriate to approach the legal representative at that time.

If a personal or professional legal representative has not provided consent prior to enrolment, once the initial emergency has passed, they will be informed about the trial as soon as practicably possible and asked for written consent for the patient to continue in the trial. If the patient regains capacity while still in hospital, they will be informed about their participation in the trial and their consent for ongoing trial participation will be sought.

A poster about the trial will be displayed in hospital waiting areas and information leaflets about the trial will be made available. These will provide summary information about the trial to relatives and will signpost them to where they can find out more information.

To determine the acceptability of the proposed consent process, we consulted three different patient and public representative groups: PPI co-applicants (Malins and Muzaffar), Headway charity staff and carers, and the Clinical Research Ambassador Group (CRAG) at Heartlands hospital. All PPI representatives understood the rationale for the proposed consent process and agreed with the use of deferred consent.

RISKS, BURDENS AND BENEFITS

The risk associated with this trial is categorised as Type A i.e. no higher than the risk of standard medical care because we are testing two existing treatments. The national survey conducted as part of this study (Rowland et al, in preparation) shows that patients receive both mannitol and hypertonic saline as part of routine standard clinical management of raised ICP following severe traumatic brain injury.

Current literature and clinical expertise demonstrates equipoise as to the benefit of HTS compared to mannitol in the management of raised ICP following severe TBI. These include large meta-analyses and systematic reviews of all currently available data. Furthermore, the UK survey of clinicians involved in the management of patients with severe TBI conducted in 2018 demonstrated that both mannitol and hypertonic are used for this indication with considerable regional variation in dose, timing and indication.

As with most treatment interventions there are some potential associated risks. Patients with severe TBI are at increased risk of hypernatraemia (high levels of sodium in the blood). This may arise as a consequence of endocrine disorders associated with direct brain injury (e.g. diabetes insipidus) or as a complication of fluid and hyperosmolar therapies. Meta-analysis of randomised trials noted higher serum sodium concentration in patients treated with hypertonic saline. Whether this directly contributes to adverse outcomes is uncertain. Whilst on the ICU, serum sodium is measured routinely on blood gas samples which are taken at regular intervals. Any abnormalities can be treated accordingly and patients will stop receiving HTS if serum sodium levels rise above a certain level (155mmol/L). Acute kidney injury occurs in approximately 5% of patients with severe traumatic brain injury (EUROTHERM data). Unpublished analysis of the data from the Erythropoietin in traumatic brain injury study (NCT00987454) suggested that mannitol may be associated with a greater chance of acute kidney injury. Similar findings were observed in the

EUROTHERM study (un-published). Study participants will routinely have measurements of kidney function on a daily basis as part of routine clinical practice. Incidence of acute kidney injury (as defined by the requirement for renal replacement therapy) will be monitored and reported to the Trial Steering Committee.

Because the study involves completing questionnaires, there is a risk that the patient or their relative may find it upsetting to answer some questions about their recovery. Our trained research staff will be available to talk to patients or their relatives about any such feelings and can offer to put them in contact with professional services if they feel this would be helpful.

The burden of the research for patients and their legal representatives is expected to be minimal – completion of the follow-up questionnaire at 3 months, 6 months and 12 months will require a modest time commitment (approx. 5 minutes at 3 months, and 15 minutes at 6 months and 12 months).

Although we cannot promise any direct benefits to patients as a result of taking part in this study, it is hoped that the research will provide benefit to future patients who have a severe brain injury, as it will help doctors to know which the best treatment to give is.

CONFIDENTIALITY

Due to the emergency nature of the research, patient's personal data will need to be accessed by members of the research team (outside of the direct care team) without patient consent. A recommendation for s251 support will be sought from the Confidentiality Advisory Group. Again, all PPI groups were asked about the acceptability of this approach, and were supportive of the use of personal data without consent.

LANGUAGE BARRIERS

Due to the unpredictable nature of traumatic brain injury, patients who become eligible for the SOS trial, or their relatives, may be non-English speaking. If needed, local centres can use hospital interpreter and translator services, if available, to assist with the discussion of the study. Language Line is also available if hospital-based interpreters are not available.

3. PURPOSE AND DESIGN OF THE RESEARCH

A7. Select the appropriate methodology description for this research. Please tick all that apply:

- ☐ Case series/ case note review
- ☐ Case control
- ☐ Cohort observation
- ☐ Controlled trial without randomisation
- ☐ Cross-sectional study
- ☐ Database analysis
- ☐ Epidemiology
- ☐ Feasibility/ pilot study
- ☐ Laboratory study
- ☐ Metanalysis
- ☐ Qualitative research
- ☐ Questionnaire, interview or observation study
- ☒ Randomised controlled trial
- ☐ Other (please specify)

A8. Type of medicinal trial:

- ☐ Clinical trial of an unlicensed investigational medicinal product
- ☐ Clinical trial of a licensed medicinal product in new conditions of use (different from those in the SmPC, i.e. new

target population, new dosage schemes, new administration route, etc.)

☒ Clinical trial of a licensed medicinal product used according to the SmPC

☐ Other (please specify)

A9. Phase of medicinal trial: *(Tick one category only)*

Human pharmacology (Phase I) ☐ Yes ☒ No

Therapeutic exploratory trial (Phase II) ☐ Yes ☒ No

Therapeutic confirmatory trial (Phase III) ☒ Yes ☐ No

Therapeutic use trial (Phase IV) ☐ Yes ☒ No

A10. What is the principal research question/objective? *Please put this in language comprehensible to a lay person.*

To compare how effective mannitol (sugary solution) and hypertonic saline (salty solution) are at helping patients to recover after a traumatic brain injury where the brain swells. This will be measured at 6 months after the brain injury, using the Glasgow Outcome Scale - Extended questionnaire.

A11. What are the secondary research questions/objectives if applicable? *Please put this in language comprehensible to a lay person.*

To look at the effects of mannitol and hypertonic saline on clinical and patient-centred outcomes, measured while the patient is in hospital and continuing up to 12 months after the brain injury. Researchers will also look at the costs of the two treatments and compare them to how beneficial they are in order to work out the cost-effectiveness.

A12. What is the scientific justification for the research? *Please put this in language comprehensible to a lay person.*

Over one million people a year suffer injuries to their heads which are severe enough to require them to go to hospital. The most severe injuries often result in significant brain swelling. If left untreated, this swelling causes the pressure inside the head to increase, compressing the brain and causing further brain damage. The main treatments used for severe brain swelling involve placing the patient into an artificial coma (to rest the brain), giving drugs (to reduce brain swelling) or brain surgery (to release the pressure). Even with current treatments delivered in intensive care, over half of people with severe brain injury die or are left with severe brain damage.

To improve outcomes for patients, doctors need to know the best treatments for severe brain swelling after head injuries. The two main drugs that are currently used to treat brain swelling are hypertonic saline (a strong salt solution) and mannitol (a sugary solution). Both of these drugs work by reducing brain swelling which helps to reduce pressure on the brain. Currently, it is not known which drug is the most effective treatment. Some trials have been done to investigate mannitol and hypertonic saline as treatments for reducing pressure in the brain after a traumatic brain injury, but they were very small in size and were not able to tell doctors with enough certainty whether mannitol or hypertonic saline are effective.

Several reviews have been done to look at the combined current evidence for these two treatments. These reviews found only low quality evidence that these drugs are effective, which means the Brain Trauma Foundation have not been able to recommend which treatment should be used.

This led to the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme to call for a large and well-run trial comparing mannitol and hypertonic saline to treat brain swelling after traumatic brain injury, in order to find out whether these drugs really make a difference to patient's recovery. This research is being carried out to meet the brief set by the NIHR. The aim of this study is to work out which is the safest and most effective drug to treat the swelling of the brain for future patients with traumatic brain injury.

A13. Please summarise your design and methodology. *It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.*

HYPOTHESIS

The hypothesis for the study is that the salty solution (hypertonic saline) is more effective than the sugary solution (mannitol) at reducing the pressure in the brain after a severe brain injury, through improving patient outcomes and also being more cost-effective.

OBJECTIVES

The primary objective of the trial is to compare the effectiveness of hypertonic saline and mannitol, by measuring patient's scores on the Glasgow Outcome Scale – Extended questionnaire 6 months after their brain injury.

The secondary objectives are to compare the effectiveness of hypertonic saline and mannitol on several clinical, patient-centred and economic outcomes, measured while the patient is on ICT and up until 12 months after their brain injury. These measures will assess which treatment is most clinically effective and cost-effective.

STUDY DESIGN AND METHODOLOGY

The SOS trial is a randomised controlled open-label trial comparing two standard treatments to reduce the pressure in the brain following severe traumatic brain injury. The study will take place in approximately 28 neurosurgical intensive care units across the UK.

In total, 638 patients who have sustained a severe injury to the brain and require treatment in intensive care will be invited to take part. This number of patients will allow a highly powered study (90%) which will be able to detect a difference of 13% or more in the proportion of patients who have a bad outcome compared to a good outcome following their brain injury when comparing mannitol and hypertonic saline.

Half the patients will receive the salty solution (hypertonic saline) and half will receive the sugary solution (mannitol). Which of the two treatments they receive will be decided randomly (by chance) using a computer programme. The patient will continue to receive the assigned treatment until the pressure in the skull reduces or until doctors decide the progress to the next stages of treatment.

Patients will be eligible for the study if they meet the following criteria:

- they are admitted to an intensive care unit with a traumatic brain injury (an injury to the brain which occurs after trauma to the head)
- they are aged 16 years or over
- the pressure in the brain is high (above 20mmHg) for more than five minutes despite trying initial treatments
- it's been less than 10 days since the head injury happened
- a CT scan of the brain shows damage to the brain caused by the head injury

Patients will be excluded from the trial if:

- it is thought they will not survive their injuries
- they are pregnant
- the sodium levels in their blood are high (known as severe hyponatraemia)

The study will compare how effective the different drugs are at reducing the pressure in the brain. It will also assess which was better at helping the patient to recovery and what the side effects of treatment were.

The trial will start on 1st June 2019, to allow six months of preparation and study set-up. Recruitment to the study is expected to start in December 2019 and will take approximately 3 years. Once recruitment is complete, patients will continue to be followed-up for a further six months, followed by six months of data analysis. The study is expected to finish, with results published, at the end of 2023.

CONSENT

Due to the nature of traumatic brain injury, patients who meet the criteria to be included in the SOS trial will be unconscious and sedated. This means it is not possible to get consent directly from the patient before involving them in the trial. In addition, if the pressure in the skull gets too high then this becomes a medical emergency, and treatment with either mannitol or hypertonic saline may be needed urgently. This means there may not be enough time to speak to a legal representative (a relative or friend) of the patient to get their advice on the patient's wishes before including them in the trial, as this would delay treating the patient. In situations like this, researchers are permitted to include patients in trials under 'deferred consent'. However, if there is enough time before the patient is included in the trial, then the legal representative will be informed about the trial and asked to provide written consent on behalf of the patient.

Once the initial emergency has passed, the researchers will speak to the patient's legal representative to tell them about the trial and seek their consent for the patient to continue in the trial if they have not already done so. The legal representative will be given a patient information sheet and asked to sign a written consent form. If no suitable personal legal representative is available, then a doctor who is independent of the trial will be asked to act as a professional legal representative and give consent on behalf of the patient.

In the event that the patient recovers mental capacity while in hospital, they will be informed about their involvement in the trial, given a patient information sheet and asked to sign a written consent form.

DATA COLLECTION, MONITORING AND FOLLOW-UP

Patients, or their legal representatives will be asked to complete postal questionnaires at 3 months, 6 months and 12 months after the patient's head injury. These questionnaires will tell the researchers how well the patient recovered, what their quality of life is, and any hospital and community resources they've used since being discharged.

Researchers will also calculate how much each treatment costs and compare this to how beneficial they were.

The following outcomes will be measured:

- How well the pressure in the skull is controlled while the patient is in intensive care
- Whether the patient required any other treatments to reduce the pressure in the skull and, if so, which treatments were required
- Which organs need support while the patient is in intensive care
- How many days the patient spent in critical care and in the hospital
- How well the patient's brain recovered to allow them to return to their normal life (measured using the modified Oxford Handicap Score when the patient is discharged from hospital, and using the Glasgow Outcome Scale – Extended questionnaire at 6 months and 12 months after the patient's brain injury)
- How long the patient survived (measured at hospital discharge, 3 months, 6 months and 12 months after the patient's brain injury)
- The patient's quality of life at hospital discharge, 3 months, 6 months and 12 months after their brain injury (measured using the ED-5D questionnaire).
- Any serious adverse events which occurred

Data will also be collected from the following sources for the purposes of the study:

- The patient's medical records
- The patients' GP
- NHS Digital
- Patient Episode Database for Wales (if the patient resides/is treated in Wales)
- Health and Social Care Northern Ireland (if the patient resides/is treated in Northern Ireland)
- Information Services Division Scotland (if the patient resides/is treated in Scotland)
- Intensive Care National Audit and Research Centre (ICNARC)

The quality of the trial and data will be monitored by the trial management team throughout the trial.

During the trial there will be an interim analysis part-way through patient recruitment, where an independent Data Monitoring Committee will look at the data so far. They will make a recommendation on whether it is safe and worthwhile to continue the trial. An independent Trial Steering Committee will also oversee the study to ensure patient safety and quality of the trial.

In order to reduce bias, when patients are allocated to receive either mannitol or hypertonic saline they will be matched based on certain characteristics (such as age, and severity of brain injury) to ensure that both groups are equal to begin with. Patients and legal representatives will not be aware of which treatment was given, in order to reduce any bias when completing follow-up questionnaires. Hospital staff who are assessing patient outcomes will also be unaware of which treatment the patient received, where this is possible.

A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?

- ☒ Design of the research
- ☒ Management of the research
- ☐ Undertaking the research
- ☐ Analysis of results
- ☒ Dissemination of findings
- ☐ None of the above

Give details of involvement, or if none please justify the absence of involvement.

The grant application was informed through a series of meetings with survivors and carers of patients with previous

brain injury, facilitated through Headway West Midlands (<https://www.headway.org.uk>). The group are supportive of this trial. We discussed and decided together our joint position on the use of placebo, trial outcomes and how to optimise the process for approaching, informing and consenting relatives (including the use of professional legal representative) and optimising follow-up. Two members (Muzaffar and Malins) have committed to join the investigator team as co-applicants. Further PPI input will be provided through independent membership of the Trial Steering Committee (two members).

We will follow INVOLVE best practice guidance in our approach. We will meet with the PPI group at the start of the study and regularly thereafter to enable full involvement through the trial and have included funds to support this. The group will help keep patients and public informed through the progress of the trial and lead the dissemination of the trial findings to lay persons.

A14-2. Have you tested the acceptability of using patient identifiable data in this study without consent?

Please give details.

Yes - we conducted two PPI group meetings (one with patients and members of staff at Headway Birmingham and Solihull; one with the Clinical Research Ambassador Group at Heartlands hospital). Both groups were asked whether it is acceptable to access and use personal data without consent. Examples such as linking with NHS Digital, or obtaining information from hospital or GP records were given. Both groups agreed this would be acceptable, as long as data is held securely.

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

A15. What is the sample group or cohort to be studied in this research?

Select all that apply:

- ☐ Blood
- ☐ Cancer
- ☐ Cardiovascular
- ☐ Congenital Disorders
- ☐ Dementias and Neurodegenerative Diseases
- ☐ Diabetes
- ☐ Ear
- ☐ Eye
- ☐ Generic Health Relevance
- ☐ Infection
- ☐ Inflammatory and Immune System
- ☒ Injuries and Accidents
- ☐ Mental Health
- ☐ Metabolic and Endocrine
- ☐ Musculoskeletal
- ☐ Neurological
- ☐ Oral and Gastrointestinal
- ☐ Paediatrics
- ☐ Renal and Urogenital
- ☐ Reproductive Health and Childbirth

- ☐ Respiratory
- ☐ Skin
- ☐ Stroke

Gender: Male and female participants

Lower age limit: 16 Years

Upper age limit: No upper age limit

A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

Inclusion criteria:

- Age 16 years or over
- Admission to ICU following traumatic brain injury
- Intracranial pressure (ICP) over 20mmHg for more than 5 minutes despite stage 1 treatments
- Less than 10 days since initial head injury
- Abnormal CT scan consistent with traumatic brain injury

Exclusion criteria:

- Devastating brain injury with withdrawal of treatment anticipated in the next 24 hours
- Pregnancy
- Severe hypernatraemia (defined as serum Na >155mmol/L)

A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

- Devastating brain injury with withdrawal of treatment anticipated in the next 24 hours
- Pregnancy
- Severe hypernatraemia (serum sodium more than 155mmol/L)

RESEARCH PROCEDURES, RISKS AND BENEFITS

A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. These include seeking consent, interviews, non-clinical observations and use of questionnaires.

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Eligibility assessment	1	0	10 minutes	Principal Investigator or their delegate while the patient is on ICU
Baseline characteristics and demographics	1	0	10 minutes	Delegated member of the research team
Trial discussion and taking written informed consent from legal representative or patient	1	0	30 minutes	Principal Investigator or their delegate, hospital/discharge location
Modified Oxford Handicap score (mOHS) and EQ-5D assessment	1	0	10 minutes	Principal Investigator or delegated member of the research team, prior to hospital discharge
Follow-up questionnaires (GOS-E, EQ-5D and health economics resource use)	3	0	15 minutes	Self-completed by patient/legal representative in hospital or discharge location
GOS-E assessment by GP (if patient/legal	2	0	5	Patient's General Practitioner at GP practice

representative has not responded)

minutes

A19. Give details of any clinical intervention(s) or procedure(s) to be received by participants as part of the research protocol. *These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material. Include procedures which might be received as routine clinical care outside of the research.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days).
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Medical history	1	1	20 minutes	Clinical staff (doctor/nurse/AHP) on ICU
Best Glasgow Coma Score (GCS) prior to intubation/sedation	1	1	1 minute	Clinical staff (doctor/nurse/AHP) on ICU
CT scan	1	1	20 minutes	NHS Radiology team
Administer hypertonic saline/mannitol	>1	>1	5 minutes	Clinical staff authorised to administer IV medications
Intracranial pressure (ICP) bolt insertion	1	1	10 minutes	NHS doctor
Routine ICU monitoring	>1	>1	5 minutes	Clinical staff (doctor/nurse/AHP) on ICU

A20. Will you withhold an intervention or procedure, which would normally be considered a part of routine care?

☐ Yes ☒ No

A21. How long do you expect each participant to be in the study in total?

12 months

A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.

The risk of physical harm from taking part in the trial is not considered to be any higher than the risks of standard clinical care as we are testing two existing treatments.

There is a risk that patients or their personal legal representative may find completing the questionnaires upsetting because the questions will ask about the patient's recovery and quality of life after their injury. If we receive any communication from the patient or their legal representative that indicates they are upset or distressed we will refer them to a clinical member of the team who will be able to talk to them about these feelings and offer to put them in touch with professional services.

Completing the questionnaires will require a modest time commitment to complete. To minimise the burden for the patient or their legal representative we will keep the questionnaires as short as possible and collect as much data as possible from routine data sources such as Hospital Episode Statistics where this is feasible.

A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

☒ Yes ☐ No

If Yes, please give details of procedures in place to deal with these issues:

There is a risk that patients or their personal legal representative may find completing the questionnaires upsetting because the questions will ask about the patient's recovery and quality of life after their injury. If we receive any communication from the patient or their legal representative that indicates they are upset or distressed we will refer them to a clinical member of the team who will be able to talk to them about these feelings and offer to put them in touch with professional services.

A24. What is the potential for benefit to research participants?

The clinical benefit to patients is uncertain as we do not currently know which treatment is better. However participating in the study will provide important information on which is the most effective treatment for reducing brain swelling after a traumatic brain injury.

A25. What arrangements are being made for continued provision of the intervention for participants, if appropriate, once the research has finished? May apply to any clinical intervention, including a drug, medical device, mental health intervention, complementary therapy, physiotherapy, dietary manipulation, lifestyle change, etc.

Mannitol and hypertonic saline are given intravenously while the patient is on ICU, and are used routinely in clinical practice therefore there is no requirement for special continued provision of the intervention once the research has finished.

A26. What are the potential risks for the researchers themselves? (if any)

We do not anticipate any potential risks to researchers.

RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used? For example, identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).

At each recruiting site the Principal Investigator will ensure all relevant colleagues are aware of the study and eligibility criteria.

Identification of potential participants will involve a review of medical records of patients admitted to ICU in participating hospitals. This review will be done by the direct healthcare team or by research staff (e.g. a Research Nurse) employed by the participating hospital.

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

☒ Yes ☐ No

Please give details below:

As part of screening processes, patient's medical records will be viewed by members of research staff at participating centres in order to check whether a patient is eligible for the trial. These medical records may include patient identifiable details.

A27-3. Describe what measures will be taken to ensure there is no breach of any duty of confidentiality owed to

patients, service users or any other person in the process of identifying potential participants. *Indicate what steps have been or will be taken to inform patients and service users of the potential use of their records for this purpose. Describe the arrangements to ensure that the wishes of patients and service users regarding access to their records are respected. Please consult the guidance notes on this topic.*

Patient's medical records will be screened while the patient is on ITU, to determine whether the patient is eligible to be included in the trial. As part of this screening, patient identifiable details within the medical records may be visible. Records may be screened by the clinical care team, but in some participating centres this may be done by separate research staff who sit outside of the patient's direct care team.

Members of the clinical care and research teams will handle this data confidentially and will only use the data for the purposes of screening and recruitment to the trial.

The use of medical records is included in the transparency information in the Information Sheets for patients and legal representatives.

Patients, or their legal representative, can also withdraw from further data collection from their medical records using the contact details specified in the Information Sheets.

A27-4. Will researchers or individuals other than the direct care team have access to identifiable personal information of any potential participants?

☒ Yes ☐ No

A27-5. Has prior consent been obtained or will it be obtained for access to identifiable personal information?

☐ Yes ☒ No

If No, and your application involves identifiable patient information, application should be made to the Confidentiality Advisory Group (CAG) to process identifiable information of patients in England and Wales without consent – see guidance notes.

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

☐ Yes ☒ No

A29. How and by whom will potential participants first be approached?

Patients enrolled in this trial, due to the nature of their underlying condition, will be unconscious or sedated and lack capacity to consent. We will therefore seek written consent from a personal or professional legal representative on behalf of the patient. Consent will be sought while the patient is on ICU either before the patient is enrolled (if there is sufficient time and it is deemed appropriate to do so) or as soon as practically possible once the initial emergency has passed. Consent will be taken by the Principal Investigator or by a delegated member of the research team.

If or when the patient subsequently regains capacity, they will be provided with a Patient Information Sheet and asked to provide written informed consent to continue taking part.

A30-1. Will you obtain informed consent from or on behalf of research participants?

☒ Yes ☐ No

If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

Please see Part B Section 6

If you are not obtaining consent, please explain why not.

Please see Part B Section 6

Please enclose a copy of the information sheet(s) and consent form(s).

A30-2. Will you record informed consent (or advice from consultees) in writing?

☒ Yes ☐ No

A30-3. Why is it not practicable for either the researcher's organisation, or the current holder of the information required by the researcher, to seek or obtain patient consent for proposed use of patient identifiable information?

In many cases, patient identifiable information may be processed and used before consent can be obtained from the patient or their legal representative. Patients who sustain a severe traumatic brain injury and develop raised intracranial pressure will be unconscious due to the severity of damage to the brain. Current best practice is to treat such patients with deep sedation to facilitate endotracheal intubation (protection of the airway), invasive mechanical ventilation to achieve satisfactory oxygenation and to "rest" the brain (induced coma to reduce oxygen demand). It is therefore not possible to consult with or obtain prospective consent directly from the research participant.

If a patient develops a sustained elevation in ICP >20mmHg this is a life-threatening emergency and urgent action is needed to prevent death and severe disability. It is therefore our assessment that in many cases it will not be reasonably practical to obtain written informed consent from a legal representative prior to enrolment in the trial as the urgency with which treatment must be provided would not allow sufficient time to explain the nature, significant, implications and risks of the trial as is required by the Medicines for Human Use (Clinical Trials) Regulations. As enrolment will take place twenty four hours a day and seven days a week this will make it impractical to rely on timely access to a professional legal representative. However if a legal representative is available prior to enrolment, and there is sufficient time, then a personal or professional legal representative will be informed about the trial and written informed consent will be sought. This will only be done after an assessment of whether it is appropriate to approach the legal representative at that time.

Once the initial emergency has passed, consent for continuation in the trial and continued use of patient identifiable data will be sought from the patient's legal representative (if they have not already consented). If the patient regains capacity while in hospital, they will be informed about their participation and asked for informed consent for continued data collection.

A31. How long will you allow potential participants to decide whether or not to take part?

Participants or their legal representatives will be given sufficient time to decide whether to continue to take part, if approached after enrolment. Where possible 24 hours will be provided, however it may not be possible to allow 24 hours in all situations e.g. if the legal representative is approached for consent prior to the patient being enrolled, due to the urgent need to treat the patient's condition.

A32. Will you recruit any participants who are involved in current research or have recently been involved in any research prior to recruitment?

☒ Yes
☐ No
☐ Not Known

If Yes, please give details and justify their inclusion. If Not Known, what steps will you take to find out?

Patients who are known to have participated in a Clinical Trials of Investigational Medicinal products (CTIMPs) within the preceding 90 days are not permitted to be enrolled in this trial.

After enrolment in SOS, co-enrolment to other concurrent Clinical Trials of Investigational Medicinal products (CTIMPs) is not permitted under the EU Clinical Trials Directive.

Co-enrolment to other studies will be allowed where the PIs and/or trial management teams have considered the scientific and practical implications of co-enrolment and agreed that co-enrolment is permitted, referring to UK

guidance for critical care trials and/or local standard operating procedures. The option for co-enrolment will only apply where agreement has been reached between the two studies prior to an individual participant being considered for inclusion, and this has been documented in the trial materials and site files.

A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs?(e.g. translation, use of interpreters)

We will expect local investigators to ensure that patients or their legal representatives have adequate communication. If needed, hospital interpreter and translator services will be available to assist with the discussion of the study, information sheets and consent forms. Arrangements may be made for the patient information sheets and consent forms to be available in other common languages once the English versions have been approved.

A33-2. What arrangements will you make to comply with the principles of the Welsh Language Act in the provision of information to participants in Wales?

Arrangements will be made for all written patient information to be translated into Welsh once the English versions have been approved.

A34. What arrangements will you make to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

Should there be any subsequent amendment to the final protocol, which might affect the patient's participation in the trial, then these will be discussed with the participant or legal representative and, if applicable, continuing consent will be obtained using an amended consent form.

CONFIDENTIALITY

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

Storage and use of personal data during the study

A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)?(Tick as appropriate)

- ☒ Access to medical records by those outside the direct healthcare team
- ☐ Access to social care records by those outside the direct social care team
- ☒ Electronic transfer by magnetic or optical media, email or computer networks
- ☒ Sharing of personal data with other organisations
- ☐ Export of personal data outside the EEA
- ☒ Use of personal addresses, postcodes, faxes, emails or telephone numbers
- ☐ Publication of direct quotations from respondents
- ☐ Publication of data that might allow identification of individuals
- ☐ Use of audio/visual recording devices
- ☒ Storage of personal data on any of the following:
 - ☒ Manual files (includes paper or film)
 - ☒ NHS computers
 - ☐ Social Care Service computers
 - ☐ Home or other personal computers
 - ☒ University computers
 - ☐ Private company computers

☒ Laptop computers*Further details:***A37. Please describe the physical security arrangements for storage of personal data during the study?**

Documents that are not submitted to the Sponsor (e.g. signed informed consent form) should be kept strictly confidential by the investigator. Patient identifiable data will only be transmitted to Warwick Clinical Trials Unit from participating sites via a secure online web portal, designed by the WCTU Programming Team. Access to this online web portal will be restricted to authorised members of the research team, via individual logins and IP addresses. Identifiable data will be held in a separate table within the trial database so that access can be further restricted to only individuals who require it. Any paper forms with patient identifiable information will be held in secure locked filing cabinets within a restricted access area at participating centres.

Any data received through data linkage with other organisations will be held securely in a PGP encrypted file share, with access restricted to only specific members of the trial team at Warwick Clinical Trials Unit.

A38. How will you ensure the confidentiality of personal data? Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.

All trial staff and investigators will adhere to General Data Protection Regulation (GDPR) and the Data Protection Act 2019. The University of Warwick is registered on the Data Protection Act Register.

Access to patient's personal data will be limited to the trial staff, investigators and regulatory authorities. Databases will only be accessed by authorised personnel using individual user accounts. On all trial-specific documents, other than the consent form, the participant will be referred to by the trial participant number, not by name.

Only anonymised data will be available to statisticians for data analysis.

Participants will not be identified in any trial reports or publications.

A39. Please specify whether identifiers will be held in the same database as the clinical data, or in a separate database and linked through a unique study or case number. If held separately, please specify how and at what point the separation will occur. If held in the same database, will the identifiers be encrypted? If so, specify what will be encrypted and who will continue to have access.

Patient identifiers will be held in the same database as the clinical data, but in a separate table linked through a unique study number. The trial database is encrypted and held on a secure server at the University of Warwick. Access to the table containing patient identifiable data will be restricted to members of the trial team who require access e.g. for posting follow-up questionnaires or undertaking data linkage work. Members of the trial team undertaking the analysis e.g. the statistician and health economist will not have access to the table containing patient identifiable data.

A40. Who will have access to participants' personal data during the study? Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.

Personal data will be accessed initially by members of the research team at participating sites, who may sit outside of the patient's direct care team, for screening, recruitment and data collection purposes. Personal data will then be entered onto the trial database via the online web portal, which will be accessed at the University of Warwick Clinical Trials Unit by members of the coordinating centre trial team. This is to allow patients, their legal representatives or their General Practitioners to be contacted to complete the follow-up questionnaires, undertake data linkage activities, oversee the quality of the study and to send trial results to patients/legal representatives once the trial is complete.

The data that will be collected, the purposes and who will have access to that data is specified in the Patient Information sheet. Statement confirming understanding of this are included on the patient and legal representative consent forms.

Storage and use of data after the end of the study

A41. Where will the data generated by the study be analysed and by whom?

The data will be analysed by statisticians at Warwick Clinical Trials Unit, University of Warwick

A42. Who will have control of and act as the custodian for the data generated by the study?

	Title Forename/Initials Surname
	Prof Gavin Perkins
Post	Chief Investigator/WCTU Director
Qualifications	MB ChB, MD , FRCP , FFICM, FIMC RCS(Ed)
Work Address	Warwick Clinical Trials Unit, University of Warwick
	Gibbet Hill Road
	Coventry
Post Code	CV4 7AL
Work Email	g.d.perkins@warwick.ac.uk
Work Telephone	02476150479
Fax	

A43. How long will personal data be stored or accessed after the study has ended?

- ☐ Less than 3 months
☐ 3 – 6 months
☐ 6 – 12 months
☐ 12 months – 3 years
☒ Over 3 years

If longer than 12 months, please justify:

Access to personal data at participating centres may be required for the purposes of sponsor audit or inspection by the regulatory authorities, and must be stored for a period of 10 years or longer if required as per WCTU Standard Operating Procedures. Please note patient identifiable data will be deleted as soon as possible once no longer required (i.e. once communication with patients/legal representatives and data linkage work is complete).

A44. For how long will you store research data generated by the study?

Years: 10
Months: 0

A45. Please give details of the long term arrangements for storage of research data after the study has ended. Say where data will be stored, who will have access and the arrangements to ensure security.

The local Principal Investigators will maintain all records and documents regarding the conduct of the study. These will be archived by the site for at least 10 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at the secure archive facilities used by WCTU. This archive shall include all trial databases and associated meta-data encryption codes. Only the trial research team will have authority to access this data if required. The records will be archived for at least 10 years from the close of the study.

INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

☒ Yes ☐ No

If Yes, please give details. For monetary payments, indicate how much and on what basis this has been determined. A £10 high street voucher will be sent to patients or their legal representative in the post with the 3 month, 6 month and 12 month postal questionnaires. Vouchers will be provided regardless of whether the questionnaire is completed or returned.

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

☐ Yes ☒ No

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

☐ Yes ☒ No

NOTIFICATION OF OTHER PROFESSIONALS

A49-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?

☐ Yes ☒ No

If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

PUBLICATION AND DISSEMINATION

A50. Will the research be registered on a public database?

The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

☒ Yes ☐ No

Please give details, or justify if not registering the research.

The trial has been registered on the ISRCTN registry and EudraCT database.

Please ensure that you have entered registry reference number(s) in question A5-1.

A51. How do you intend to report and disseminate the results of the study? Tick as appropriate:

- ☒ Peer reviewed scientific journals
- ☒ Internal report
- ☒ Conference presentation
- ☒ Publication on website

- ☐ Other publication
- ☒ Submission to regulatory authorities
- ☐ Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
- ☐ No plans to report or disseminate the results
- ☐ Other (please specify)

A52. If you will be using identifiable personal data, how will you ensure that anonymity will be maintained when publishing the results?

Participants will not be identified in any trial reports or publications.

A53. Will you inform participants of the results?

☒ Yes ☐ No

Please give details of how you will inform participants or justify if not doing so.

A summary of the trial results will be sent to participants and/or their legal representatives at the end of trial. Participants/legal representatives will be given the option of not receiving the results. A summary of the results will also be made available on the trial website at the appropriate time (following publication in a scientific journal).

5. Scientific and Statistical Review

A54. How has the scientific quality of the research been assessed? Tick as appropriate:

- ☒ Independent external review
- ☐ Review within a company
- ☒ Review within a multi-centre research group
- ☒ Review within the Chief Investigator's institution or host organisation
- ☒ Review within the research team
- ☐ Review by educational supervisor
- ☐ Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:

The trial is the beneficiary of a grant from the NIHR Health Technology Assessment (HTA) Programme. As part of the application process the scientific quality of the research has undergone independent external review. Leading experts in this field of research are co-applicants/co-investigators on the trial and have contributed to the trial protocol.

For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.

For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.

A56. How have the statistical aspects of the research been reviewed? Tick as appropriate:

- ☐ Review by independent statistician commissioned by funder or sponsor
- ☐ Other review by independent statistician
- ☐ Review by company statistician
- ☒ Review by a statistician within the Chief Investigator's institution
- ☐ Review by a statistician within the research team or multi-centre group

- ☐ Review by educational supervisor
- ☐ Other review by individual with relevant statistical expertise
- ☐ No review necessary as only frequencies and associations will be assessed – details of statistical input not required

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

	Title Forename/Initials Surname
	Prof Ranjit Lall
Department	Warwick Clinical Trials Unit, Division of Health Sciences, Warwick Medical School
Institution	University of Warwick
Work Address	Warwick Clinical Trials Unit University of Warwick, Gibbet Hill Road Coventry
Post Code	CV4 7AL
Telephone	02476574649
Fax	
Mobile	
E-mail	R.Lall@warwick.ac.uk

Please enclose a copy of any available comments or reports from a statistician.

A57. What is the primary outcome measure for the study?

The primary trial outcome will be the Extended Glasgow Outcome Score (GOS-E) at 6-months post-TBI. The GOS-E questionnaire is a global functional outcome scale incorporating assessment of functional status, independence and role participation, and is recommended as the core global outcome for TBI research (<http://comet-initiative.org/studies/details/562>). This scale is the most commonly used global outcome measure in published research on TBI and can be reliably collected through a structured questionnaire/interview. The eight outcome categories are:

- Death
- Vegetative state (unable to obey commands)
- Lower severe disability (dependent on others for care)
- Upper severe disability (independent at home and outside the home but with some physical or mental disability)
- Lower moderate disability
- Upper moderate disability
- Lower good recovery (able to resume normal activities with some injury related problems)
- Upper good recovery (no problems)

A58. What are the secondary outcome measures?(if any)

1. ICP control (during period of monitoring on ICU)
2. Progression to stage 3 therapies
3. Which stage 3 therapies were required
4. Organ support requirements during ICU
5. Critical care length of stay
6. Hospital length of stay
7. Modified Oxford Handicap Score (mOHS) at hospital discharge
8. GOS-E at 12m
9. Survival at hospital discharge, 3m, 6m and 12m
10. Quality of life (EQ-5D-5L) at hospital discharge, 3m, 6m and 12m
11. Serious Adverse events
12. Costs and within-trial and lifetime cost-effectiveness from an NHS and personal social services (PSS) perspective.

A59. What is the sample size for the research? How many participants/samples/data records do you plan to study in

total? If there is more than one group, please give further details below.

Total UK sample size: 638
Total international sample size (including UK): 638
Total in European Economic Area: 638

Further details:

A60. How was the sample size decided upon? If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.

The planned size of this trial is 638 patients. This is based on a superiority hypothesis of a difference between the two interventions, using 90% power, a significance level of 5% with a dropout/withdrawal rate of 6%. In order to detect a treatment reduction of 13% (63.5% to 50.5%) in the proportion of patients having a worse neurological outcome (GOS-E: dead, vegetative state, lower severe disability, upper severe disability) compared to better outcome (GOS-E: lower moderate disability, upper moderate disability, lower good recovery, upper good recovery) between mannitol and hypertonic saline, 319 patients would be required on each arm.

The sample size was informed with the following evidence:

- The GOS-E is an 8-point ordinal scale (1= death and 8=upper good recovery). In studies carried out in traumatic brain injury patients, this scale is often used as a dichotomous outcome, with GOS-E categories 1-4: poor versus 5-8: good. In calculating the sample size for an ordinal scale, there is a requirement for a proportional odds over the categories. Currently, there is some indication of the violation of this proportional odds assumption (in the Rescue ICP study) and for this reason the sample size using the ordinal approach will have limitations. In light of this, for our purposes the GOS-E has been dichotomised in the conventional way. In addition to this the binary approach is a more conservative approach and analysis using the ordinal categories, will only increase the statistical power of the study.
- The proportion of patients with unfavourable neurological outcome on the mannitol arm range from 37%-70% across trials in patients with TBI. For our trial, we have taken the worse outcome as 63.5% which is representative of the larger trial samples as illustrated in the Rescue ICP study (60% in the mannitol arm) and EURO THERM trial (63.5% in the mannitol arm).
- The clinically important difference ranges from 10% to 20%. Our clinically important reduction of proportion of patients with an unfavourable neurological outcome fits in with an achievable sample size as well as aiming to minimise the difference that would be considered relevant.
- Loss of follow-up in UK critical care trials is often low (<3%). The EURO THERM trial reported a 1% withdrawal rate and the drop-out rate for the Rescue ICP study was 6%. Many of the studies report no withdrawal rates. In line with the Rescue ICP study, we have estimated a drop-out rate of 6% in the SOS Trial.

A61. Will participants be allocated to groups at random?

☒ Yes ☐ No

If yes, please give details of the intended method of randomisation:

We will use a computerized allocation-concealed minimization randomisation system, created by the Warwick Clinical Trials Unit (WCTU), with the allocation generated per participant in a 1:1 ratio. The randomization will be stratified by site and predicted probability of an unfavourable outcome at six months (calculated using age, pupillary response and documented Glasgow Coma Scale motor score at intubation using the IMPACT calculator)

A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

The main statistical analysis will be using intention-to-treat, which will include all randomly assigned patients, unless they have withdrawn their consent specifically with regards to using their data. We will carry out a complier average causal effect (CACE) analysis to address the issue of non-compliance.

For the primary analysis, the proportion of patients with good versus bad outcome of the 6-month GOS-E questionnaire will be compared between the two intervention arms using the logistic regression model. This analysis will be adjusted for key clinically important co-variables. Odds ratios and 95% confidence intervals will be presented.

As secondary analysis, we will assess the ordinal nature of the Both unadjusted and adjusted (for key clinically important co-variables) odds ratios (and 95% confidence intervals) will be presented. In addition to this, appropriate ordinal regression models will be computed, to the ordered 8-point GOS-E questionnaire using appropriate ordinal regression models. The models will depend on the assumptions satisfied: if the proportional odds assumption is satisfied we will fit the proportional odds model, otherwise we will fit the non-proportional odds model. Stacked bar charts will be used to display the ordinal GOS-E questionnaire data.

A further exploratory analysis to assess the impact of missing outcome data on the GOS-E questionnaire will be examined using multiple imputation techniques.

Survival status to 30 days will be examined in a similar way to the binary GOS-E questionnaire. In addition to this survival status over the course of the study (3, 6 and 12 months) and to time to discharge (ICU and hospital) will be assessed using Kaplan-Meier plots. The survival curves will be assessed using the log-rank test (unadjusted) and the Cox-proportional Hazards model (adjusted). In addition to this, we will assess the bad neurological outcome (GOS-E: 1-5) against the good neurological outcome (GOS-E: 6-8) using similar methods as stated above.

Continuous variables will be examined using linear regression models and summarized using mean, standard deviation, median and range values. Categorical data will be assessed using logistic regression models and summarized using the number of patients and proportions. Where appropriate, 95% confidence intervals will be presented with the appropriate point estimates. In order to obtain more insight into the primary outcome, Bayesian methods will be used taking various informative from the literature.

6. MANAGEMENT OF THE RESEARCH

A63. Other key investigators/collaborators. Please include all grant co-applicants, protocol co-authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.

	Title	Forename/Initials	Surname
	Dr	Tonny	Veenith
Post	Consultant and Honorary Senior Lecturer		
Qualifications	MBBS, MRCP(UK), FRCA, EDIC, FFICM		
Employer	University Hospitals Birmingham NHS Foundation Trust		
Work Address	Queen Elizabeth Hospital Birmingham		
	Mindelsohn Way		
	Edgbaston, Birmingham		
Post Code	B15 2GW		
Telephone	01213712777		
Fax			
Mobile			
Work Email	Tonny.Veenith@uhb.nhs.uk		

	Title	Forename/Initials	Surname
	Professor	Danny	McAuley
Post	Professor of Intensive Care Medicine		
Qualifications	Fellow - Medicine, Diploma - Intensive Care Medicine, MD - Medicine, Member - Medicine, MB ChB - Medicine		
Employer	Queen's University Belfast		
Work Address	Queen's University Belfast		
	University Road		
	Belfast		
Post Code	BT7 1NN		
Telephone	02890635794		
Fax			

Mobile
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Title Forename/Initials Surname
Professor Ranjit Lall

Post Professor of Clinical Trials

Qualifications PhD

Employer University of Warwick

Work Address Warwick Clinical Trials Unit, University of Warwick
Gibbet Hill Road
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Post Code CV4 7AL

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Fax

Mobile

Work Email R.Lall@warwick.ac.uk

Title Forename/Initials Surname
Professor Mark Wilson

Post Professor of Brain Injury, Consultant Neurosurgeon

Qualifications PhD, MB BChir, BSC

Employer Imperial College Healthcare NHS Trust

Work Address St Mary's Hospital
Praed Street
London

Post Code W2 1NY

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Fax

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Work Email mark.wilson19@nhs.net

Title Forename/Initials Surname
Professor James Mason

Post Professor of Health Economics

Qualifications MSc, D Phil, BSc

Employer University of Warwick

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Gibbet Hill Road
Coventry

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Telephone 02476151853

Fax

Mobile

Work Email J.Mason@warwick.ac.uk

Title Forename/Initials Surname
Professor Peter Andrews

Post Consultant in Anaesthetics and Critical Care

Qualifications MD

Employer The University of Edinburgh, NHS Lothian
 Work Address Western General Hospital
 Crewe Road South
 Edinburgh
 Post Code EH4 2XU
 Telephone 01315371666
 Fax
 Mobile
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Title Forename/Initials Surname
 Professor Peter Hutchinson
 Post NIHR Research Professor in Neurosurgery
 Qualifications FMedSci, FRCS, PHD, MBBS, BSc
 Employer University of Cambridge
 Work Address Department of Clinical Neurosciences, Level 3
 A Block, Box 165
 Cambridge Biomedical Campus, Cambridge
 Post Code CB2 0QQ
 Telephone 01223336946
 Fax
 Mobile
 Work Email pjah2@cam.ac.uk

Title Forename/Initials Surname
 Mr Angelos Kolias
 Post Clinical Lecturer in Neurosurgery
 Qualifications
 Employer University of Cambridge
 Work Address Department of Clinical Neurosciences, Level 3
 A Block, Box 165
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 Post Code CB2 0QQ
 Telephone
 Fax
 Mobile
 Work Email angeloskolias@gmail.com

Title Forename/Initials Surname
 Dr Matthew Rowland
 Post Clinical Lecturer
 Qualifications D Phil, MBBS
 Employer University of Oxford, Nuffield Department of Clinical Neurosciences
 Work Address Level 6, West Wing
 John Radcliffe Hospital
 Oxford
 Post Code OX3 9DU
 Telephone 01865 223058
 Fax
 Mobile

Work Email matthew.rowland@ndcn.ox.ac.uk

Title Forename/Initials Surname
Mr Andrew Malins

Post Volunteer Patient and Public representative

Qualifications N/A

Employer

Work Address

Post Code

Telephone

Fax

Mobile

Work Email afmga@aol.com

Title Forename/Initials Surname
Mr Jameel Muzaffar

Post Volunteer Patient and Public representative

Qualifications N/A

Employer

Work Address

Post Code

Telephone

Fax

Mobile

Work Email jameel.muzaffar@hyms.ac.uk

A64. Details of research sponsor(s)

A64-1. Sponsor

SP2

Status: ☐ NHS or HSC care organisation

Commercial status: ☐ Non-Commercial

☒ Academic

☐ Pharmaceutical industry

☐ Medical device industry

☐ Local Authority

☐ Other social care provider (including voluntary sector or private organisation)

☐ Other

If Other, please specify:

Contact person

Name of organisation University of Warwick
Given name Jane
Family name Prewett
Address Research and Impact Services, University House, University of Warwick
Town/city Coventry
Post code CV4 8UW
Country UNITED KINGDOM
Telephone 02476575732
Fax
E-mail sponsorship@warwick.ac.uk

Legal representative in the European Economic Area for the purpose of this trial

A legal representative must be appointed for a clinical trial of an investigational medicinal product if the sponsor is not established within the European Economic Area (EEA) (see article 19 of Directive 2001/20/EC). If this applies, please enclose evidence that the legal representative is established within the EEA and has accepted the role of legal representative.

Legal representative**Contact person**

Name of organisation
Given name
Family name
Address
Town/city
Post code
Country
Telephone
Fax
E-mail

SP3

Status: ☒ NHS or HSC care organisation

☐ Academic

☐ Pharmaceutical industry

☐ Medical device industry

☐ Local Authority

☐ Other social care provider (including voluntary sector or private organisation)

☐ Other

If Other, please specify:

Commercial status: Non-Commercial

Contact person

Name of organisation University Hospitals Birmingham NHS Foundation Trust

Given name	Clark
Family name	Crawford
Address	Research & Development, University Hospitals Birmingham NHS Foundation Trust, Heritage Building
Town/city	Queen Elizabeth Hospital, Edgbaston, Birmingham
Post code	B15 2TH
Country	UNITED KINGDOM
Telephone	
Fax	
E-mail	R&D@uhb.nhs.uk

Legal representative in the European Economic Area for the purpose of this trial

A legal representative must be appointed for a clinical trial of an investigational medicinal product if the sponsor is not established within the European Economic Area (EEA) (see article 19 of Directive 2001/20/EC). If this applies, please enclose evidence that the legal representative is established within the EEA and has accepted the role of legal representative.

Legal representative**Contact person**

Name of organisation

Given name

Family name

Address

Town/city

Post code

Country

Telephone

Fax

E-mail

A64-2. Please explain how the responsibilities of sponsorship will be assigned between the co-sponsors listed in A64-1

Please see Division of Responsibilities document enclosed with application

A65. Has external funding for the research been secured?

Please tick at least one check box.

- ☒ Funding secured from one or more funders
- ☐ External funding application to one or more funders in progress
- ☐ No application for external funding will be made

What type of research project is this?

- ☒ Standalone project
- ☐ Project that is part of a programme grant
- ☐ Project that is part of a Centre grant

☐ Project that is part of a fellowship/ personal award/ research training award

☐ Other

Other – please state:

Please give details of funding applications.

Organisation National Institute for Health Research
Address Evaluation, Trials and Studies Coordinating Centre
 University of Southampton, Alpha House
 Enterprise Road, Southampton
Post Code SO16 7NS
Telephone 02380595586
Fax
Mobile
Email netscomms@nihr.ac.uk

Funding Application Status: ☒ Secured ☐ In progress

Amount: £1,337,958.97

Duration

Years: 4

Months: 6

If applicable, please specify the programme/ funding stream:

What is the funding stream/ programme for this research project?

A66. Has responsibility for any specific research activities or procedures been delegated to a subcontractor (other than a co-sponsor listed in A64-1) ? Please give details of subcontractors if applicable.

☐ Yes ☒ No

A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

☐ Yes ☒ No

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.

A68-1. Give details of the lead NHS R&D contact for this research:

 Title Forename/Initials Surname
 Dr Sarah Pountain
Organisation Heartlands Hospital, University Hospitals of Birmingham
Address Research and Development Office, MIDRU
 Heartlands Hospital

Birmingham
Post Code B9 5SS
Work Email sarah.pountain@heartofengland.nhs.uk
Telephone 0121 424 3631
Fax
Mobile

Details can be obtained from the NHS R&D Forum website: <http://www.rdforum.nhs.uk>

A68-2. Select Local Clinical Research Network for NHS Organisation identified in A68-1:

West Midlands

For more information, please refer to the question specific guidance.

A69-1. How long do you expect the study to last in the UK?

Planned start date: 01/06/2019

Planned end date: 01/12/2023

Total duration:

Years: 4 Months: 6 Days: 0

A69-2. How long do you expect the study to last in all countries?

Planned start date: 01/06/2019

Planned end date: 01/12/2023

Total duration:

Years: 4 Months: 6 Days:

A70. Definition of the end of trial, and justification in the case where it is not the last visit of the last subject undergoing the trial ⁽¹⁾

The trial will end once all data collection is complete. This is likely to be after the last visit of the last subject as data linkage with external organisations may extend past this date.

A71-1. Is this study?

☐ Single centre

☒ Multicentre

A71-2. Where will the research take place? (Tick as appropriate)

☒ England

☒ Scotland

☒ Wales

☒ Northern Ireland

☐ Other countries in European Economic Area

Total UK sites in study 28

Does this trial involve countries outside the EU?

☐ Yes ☒ No

A72. Which organisations in the UK will host the research? Please indicate the type of organisation by ticking the box and give approximate numbers if known:

- | | |
|---|----|
| <input checked="" type="checkbox"/> NHS organisations in England | 23 |
| <input checked="" type="checkbox"/> NHS organisations in Wales | 1 |
| <input checked="" type="checkbox"/> NHS organisations in Scotland | 3 |
| <input checked="" type="checkbox"/> HSC organisations in Northern Ireland | 1 |
| <input type="checkbox"/> GP practices in England | |
| <input type="checkbox"/> GP practices in Wales | |
| <input type="checkbox"/> GP practices in Scotland | |
| <input type="checkbox"/> GP practices in Northern Ireland | |
| <input type="checkbox"/> Joint health and social care agencies (eg community mental health teams) | |
| <input type="checkbox"/> Local authorities | |
| <input type="checkbox"/> Phase 1 trial units | |
| <input type="checkbox"/> Prison establishments | |
| <input type="checkbox"/> Probation areas | |
| <input type="checkbox"/> Independent (private or voluntary sector) organisations | |
| <input type="checkbox"/> Educational establishments | |
| <input type="checkbox"/> Independent research units | |
| <input type="checkbox"/> Other (give details) | |

Total UK sites in study: 28

A73-1. Will potential participants be identified through any organisations other than the research sites listed above?

☐ Yes ☒ No

A74. What arrangements are in place for monitoring and auditing the conduct of the research?

Site initiation visits will be conducted for all participating centres to provide protocol procedural training.

A monitoring plan will be produced in line with the level of risk identified in the risk assessment. Appropriate WCTU staff members shall carry out central monitoring of trial data on an ongoing basis. Data being recorded on the eCRF allows assessment of protocol compliance. The TMG will regularly assess serious adverse event data and protocol non-compliances.

On-site monitoring visits will be conducted as necessary and according to the monitoring plan for the trial. All trial related documents will be made available on request for monitoring and/or audit by WCTU, UHB and for inspection by the MHRA and other relevant bodies. The PI will allow the WCTU direct access to relevant source documentation for verification of data entered onto the eCRFs. Trial data and evidence of monitoring and systems audits will be made available for inspection by the regulatory authority as required.

A75-1. What arrangements will be made to review interim safety and efficacy data from the trial? Will a formal data monitoring committee or equivalent body be convened?

An independent Data Monitoring Committee will be convened, and they will meet at least annually throughout the trial. The timing and frequency of the interim analyses will be discussed and agreed with the Data Monitoring Committee members and a detailed Statistical Analysis Plan (SAP) will be written by the trial statistician and approved by the DMEC prior to any interim analysis. It is anticipated that no more than one formal interim analysis will take place during the course of the study.

If a formal DMC is to be convened, please forward details of the membership and standard operating procedures to the Research Ethics Committee when available. The REC should also be notified of DMC recommendations and receive summary reports of interim analyses.

A75-2. What are the criteria for electively stopping the trial or other research prematurely?

We will formalise the statistical stopping criteria using the O'Brien and Fleming stopping rules. In making a decision to terminate the clinical trial, the Data Monitoring Committee will use the statistical evidence as guidance to their decision making and will be also presented with a 95% confidence interval of the treatment difference.

A76. Insurance/ indemnity to meet potential legal liabilities

Note: in this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland

A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? Please tick box(es) as applicable.

Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.

- ☒ NHS indemnity scheme will apply (NHS sponsors only)
- ☒ Other insurance or indemnity arrangements will apply (give details below)

The University has in force a Public and Products Liability policy which provides cover for claims for "negligent harm" and the activities here are included within that coverage subject to the terms, conditions and exceptions of the policy.

Please enclose a copy of relevant documents.

A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? Please tick box(es) as applicable.

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.

- ☒ NHS indemnity scheme will apply (protocol authors with NHS contracts only)
- ☒ Other insurance or indemnity arrangements will apply (give details below)

The University has in force a Public and Products Liability policy which provides cover for claims for "negligent harm" and the activities here are included within that coverage subject to the terms, conditions and exceptions of the policy.

Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.

- ☒ NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)
- ☐ Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

Please enclose a copy of relevant documents.

A77. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?

☐ Yes ☒ No

Please enclose a copy of relevant documents.

A78. Could the research lead to the development of a new product/process or the generation of intellectual property?

☒ Yes ☐ No ☐ Not sure

Part B Section 1: Investigational Medicinal Products**Information on each IMP.**

Information on each 'bulk product' before trial-specific operations (blinding, trial specific packaging and labelling) should be provided in this section for each investigational medicinal product (IMP) being tested including each comparator, if applicable.

If the trial is performed with several products please create a separate set of the following questions for each product. If the product is a combination product please give separate information for each active substance. Click on the first row and enter details of the product in the following screens. When you have completed the details, click on the navigate button or the "See All" link and return to this section to enter details of the next product. When you have completed details of all products please move to question 13 using the navigation screen.

Investigational medicinal productsPR1 Mannitol 20%PR9 Mannitol 10%PR10 Mannitol 15%PR2 Sodium chloride 2.7%PR3 Sodium chloride 5%PR8 Sodium chloride (bespoke concentration)PR4 Sodium chloride 30%**13. Indicate which of the following is described below then repeat as necessary for each:**This refers to the IMP number: **PR1**

Investigational medicinal product category:

Test IMP

14. STATUS OF THE IMP

If the IMP has a marketing authorisation in the Member State concerned by this application but the trade name and marketing authorisation holder are not fixed in the protocol, go to question 14-.2

14-1. Does the IMP to be used in the trial have a marketing authorisation?

☒ Yes ☐ No ☐ Not Answered

Trade name:

Mannitol 20%

EV Product Code

Name of the MA holder:

Fresenius Kabi Limited

MA number (if MA granted by a Member State):

PL 08828/0023

Is the IMP modified in relation to its MA?

☐ Yes ☒ No ☐ Not Answered

Which country granted the MA?

UNITED KINGDOM

Is this the Member State concerned with this application?

☒ Yes ☐ No ☐ Not Answered

14-2. Situations where an IMP to be used in the CT has a MA in the MS concerned, but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start

In the protocol, is treatment defined only by active substance?

☒ Yes ☐ No ☐ Not Answered

If 'Yes', give active substance in D.3.8 or D.3.9

In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?

☒ Yes ☐ No ☐ Not Answered

If 'Yes', give active substance in D.3.8 or D.3.9

The products to be administered as IMPs are defined as belonging to an ATC group

☒ Yes ☐ No ☐ Not Answered

If yes, give the ATC group of the applicable authorised codes in the ATC code field (level 3 or the level that can be defined) in D.3.1

Other :

☐ Yes ☒ No ☐ Not Answered

14-3. IMPD submitted:

Full IMPD

☐ Yes ☒ No ☐ Not Answered

Simplified IMPD

☐ Yes ☒ No ☐ Not Answered

Provide justification for using simplified dossier in the covering letter

Summary of product characteristics (SmPC) only

☒ Yes ☐ No ☐ Not Answered

14-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

☐ Yes ☒ No ☐ Not Answered

14-5. Has the IMP been designated in this indication as an orphan drug in the Community?

☐ Yes ☒ No ☐ Not Answered

14-6. Has the IMP been the subject of scientific advice related to this clinical trial?

☐ Yes ☒ No ☐ Not Answered

Please indicate source of advice and provide a copy in the CTA request:

From the CHMP?

☐ Yes ☒ No ☐ Not Answered

CHMP = Committee for Medicinal Products for Human Use

From a MS competent authority?

☐ Yes ☒ No ☐ Not Answered

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

Description of IMP

15-1. Description of IMP

Product name where applicable	Mannitol 20%
Product code where applicable	
ATC codes, if officially registered	B05BC01
Pharmaceutical form (use standard terms)	Solution For Infusion
Is this a specific paediatric formulation?	<input type="radio"/> Yes <input checked="" type="radio"/> No <input type="radio"/> Not Answered
Maximum duration of treatment of a subject according to the protocol	If intracranial pressure remains >20mmHg boluses can be repeated until serum sodium is >155mmol/L

Dose allowed

First dose for first-in-human clinical trial	
Specify per day or total:	<input type="radio"/> per day <input type="radio"/> total <input checked="" type="radio"/> Not Answered
Specify total dose (number and unit)	
Route of administration (relevant to the first dose):	Intravenous Use
Maximum dose allowed	The dose given will depend on the requirements of the individual patient and the judgement of the clinician
Specify per day or total	<input type="radio"/> per day <input type="radio"/> total <input checked="" type="radio"/> Not Answered
Specify total dose (number and unit)	
Route of administration (relevant to the maximum dose):	Intravenous Use

Routes of administration for this IMP

Intravenous Use

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

15-2. Active substances

Complete all fields that currently apply to this Active Substance in this Product. If you have IMPs with different concentrations of the Active Substance complete a new Sub-section D for each.

Active Substance 1

Name of active substance (INN or proposed INN if available): Mannitol

CAS number: 69-65-8

Current sponsor code:

Other descriptive name:

Full Molecular formula $C_6H_{14}O_6$

Chemical/biological description of the Active Substance: Chemically, mannitol is an alcohol and a sugar, or a polyol; it is similar to xylitol or sorbitol

Strength

Concentration unit: % percent

Concentration type: equal

Concentration number (only use both fields for range): 20

15-3. Type of IMP

Does the IMP contain an active substance:

Of chemical origin?

☒ Yes ☐ No ☐ Not Answered

Of biological / biotechnological origin?(other than Advanced Therapy IMP (ATIMP))

☐ Yes ☒ No ☐ Not Answered

Is this a:

Advanced Therapy IMP (ATIMP) ⁽¹⁾

☐ Yes ☒ No ☐ Not Answered

Combination product that includes a device, but does not involve an Advanced Therapy

☐ Yes ☒ No ☐ Not Answered

Radiopharmaceutical medicinal product?

☐ Yes ☒ No ☐ Not Answered

Immunological medicinal product (e.g. vaccine, allergen, immune serum)?

☐ Yes ☒ No ☐ Not Answered

Plasma derived medicinal product?

☐ Yes ☒ No ☐ Not Answered

Extractive medicinal product?

☐ Yes ☒ No ☐ Not Answered

Recombinant medicinal product?

☐ Yes ☒ No ☐ Not Answered

Medicinal product containing genetically modified organisms?

☐ Yes ☒ No ☐ Not Answered

Herbal medicinal product?

☐ Yes ☒ No ☐ Not Answered

Homeopathic medicinal product?

☐ Yes ☒ No ☐ Not Answered

Another type of medicinal product?

☐ Yes ☒ No ☐ Not Answered

Specify the mode of action for the active substance in this medicinal product

The mode of action should briefly describe the chemical, biochemical, immunological or biological means that the IMP uses to effect its pharmaceutical action. Mannitol is an osmotic diuretic. The mechanism of action of mannitol is as an osmotic activity. The physiologic effect of mannitol is by means of increased diuresis.

Is it an IMP to be used in a first-in-human clinical trial?

☐ Yes ☒ No ☐ Not Answered

(1,2,3,4,5) Complete sections D.4, D.5, D.6. and D.7, as applicable

(2,3) As defined in Annex 1 part IV of Directive 2001/83/EC as amended

(4) As defined in Article 2(1)(b) of Regulation 1394/2007/EC

(6) Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007

DRAFT

13. Indicate which of the following is described below then repeat as necessary for each:This refers to the IMP number: **PR2**

Investigational medicinal product category:

Test IMP

14. STATUS OF THE IMP*If the IMP has a marketing authorisation in the Member State concerned by this application but the trade name and marketing authorisation holder are not fixed in the protocol, go to question 14-2***14-1. Does the IMP to be used in the trial have a marketing authorisation?**☒ Yes ☐ No ☐ Not Answered

Trade name:

Sodium chloride 2.7%

EV Product Code

Name of the MA holder:

Fresenius Kabi Limited

MA number (if MA granted by a Member State):

PL 08828/0052

Is the IMP modified in relation to its MA?

☐ Yes ☒ No ☐ Not Answered

Which country granted the MA?

UNITED KINGDOM

Is this the Member State concerned with this application?

☒ Yes ☐ No ☐ Not Answered**14-2. Situations where an IMP to be used in the CT has a MA in the MS concerned, but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start**

In the protocol, is treatment defined only by active substance?

☒ Yes ☐ No ☐ Not Answered*If 'Yes', give active substance in D.3.8 or D.3.9*

In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?

☒ Yes ☐ No ☐ Not Answered*If 'Yes', give active substance in D.3.8 or D.3.9*

The products to be administered as IMPs are defined as belonging to an ATC group

☒ Yes ☐ No ☐ Not Answered*If yes, give the ATC group of the applicable authorised codes in the ATC code field (level 3 or the level that can be defined) in D.3.1*

Other :

☐ Yes ☒ No ☐ Not Answered**14-3. IMPD submitted:**

Full IMPD

☐ Yes ☒ No ☐ Not Answered

Simplified IMPD

☐ Yes ☒ No ☐ Not Answered

Provide justification for using simplified dossier in the covering letter

Summary of product characteristics (SmPC) only

☒ Yes ☐ No ☐ Not Answered

14-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

☐ Yes ☒ No ☐ Not Answered

14-5. Has the IMP been designated in this indication as an orphan drug in the Community?

☐ Yes ☒ No ☐ Not Answered

14-6. Has the IMP been the subject of scientific advice related to this clinical trial?

☐ Yes ☒ No ☐ Not Answered

Please indicate source of advice and provide a copy in the CTA request:

From the CHMP?

☐ Yes ☒ No ☐ Not Answered

CHMP = Committee for Medicinal Products for Human Use

From a MS competent authority?

☐ Yes ☒ No ☐ Not Answered

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

Description of IMP**15-1. Description of IMP**

Product name where applicable Sodium chloride 2.7%

Product code where applicable

ATC codes, if officially registered A12CA01

Pharmaceutical form (use standard terms) Solution For Infusion

Is this a specific paediatric formulation? ☐ Yes ☒ No ☐ Not Answered

Maximum duration of treatment of a subject according to the protocol If intracranial pressure remains >20mmHg boluses can be repeated until serum sodium is >155mmol/L

Dose allowed

First dose for first-in-human clinical trial

Specify per day or total:

☐ per day ☐ total ☒ Not Answered

Specify total dose (number and unit)

Route of administration (relevant to the first dose):

Intravenous Use

Maximum dose allowed

The dose given will depend on the requirements of the individual patient and the judgement of the clinician

Specify per day or total

☐ per day ☐ total ☒ Not Answered

Specify total dose (number and unit)

Route of administration (relevant to the maximum dose):

Intravenous Use

Routes of administration for this IMP

Intravenous Use

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

15-2. Active substances

Complete all fields that currently apply to this Active Substance in this Product. If you have IMPs with different concentrations of the Active Substance complete a new Sub-section D for each.

Active Substance 1

Name of active substance (INN or proposed INN if available): Sodium Chloride

CAS number: 7647-14-5

Current sponsor code:

Other descriptive name:

Full Molecular formula NaCl

Chemical/biological description of the Active Substance sodium chloride

Strength

Concentration unit: % percent

Concentration type: equal

Concentration number (only use both fields for range): 2.7

15-3. Type of IMP

Does the IMP contain an active substance:

Of chemical origin?

☒ Yes ☐ No ☐ Not Answered

Of biological / biotechnological origin?(other than Advanced Therapy IMP (ATIMP))

☐ Yes ☒ No ☐ Not Answered

Is this a:

Advanced Therapy IMP (ATIMP) ⁽¹⁾

☐ Yes ☒ No ☐ Not Answered

Combination product that includes a device, but does not involve an Advanced Therapy

☐ Yes ☒ No ☐ Not Answered

Radiopharmaceutical medicinal product?

☐ Yes ☒ No ☐ Not Answered

Immunological medicinal product (e.g. vaccine, allergen, immune serum)?

☐ Yes ☒ No ☐ Not Answered

Plasma derived medicinal product?

☐ Yes ☒ No ☐ Not Answered

Extractive medicinal product?

☐ Yes ☒ No ☐ Not Answered

Recombinant medicinal product?

☐ Yes ☒ No ☐ Not Answered

Medicinal product containing genetically modified organisms?

☐ Yes ☒ No ☐ Not Answered

Herbal medicinal product?

☐ Yes ☒ No ☐ Not Answered

Homeopathic medicinal product?

☐ Yes ☒ No ☐ Not Answered

Another type of medicinal product?

☐ Yes ☒ No ☐ Not Answered

Specify the mode of action for the active substance in this medicinal product

The mode of action should briefly describe the chemical, biochemical, immunological or biological means that the IMP uses to effect its pharmaceutical action. Hypertonic saline has a core mechanisms of action through increasing the osmotic pressure of plasma. This draws water into the circulation from tissue extracellular spaces and so increases circulating volume, cardiac output and possibly blood pressure, whilst decreasing blood viscosity. These effects all increase cerebral blood flow and oxygen delivery. The osmotic effect also draws fluid from extracellular spaces in brain tissue, decreasing brain tissue volume and hence ICP.

Is it an IMP to be used in a first-in-human clinical trial?

☐ Yes ☒ No ☐ Not Answered

^(1,2,3,4,5) Complete sections D.4, D.5, D.6. and D.7, as applicable

^(2,3) As defined in Annex 1 part IV of Directive 2001/83/EC as amended

⁽⁴⁾ As defined in Article 2(1)(b) of Regulation 1394/2007/EC

⁽⁶⁾ Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007

13. Indicate which of the following is described below then repeat as necessary for each:This refers to the IMP number: **PR3**

Investigational medicinal product category:

Test IMP

14. STATUS OF THE IMP*If the IMP has a marketing authorisation in the Member State concerned by this application but the trade name and marketing authorisation holder are not fixed in the protocol, go to question 14-2***14-1. Does the IMP to be used in the trial have a marketing authorisation?**☒ Yes ☐ No ☐ Not Answered

Trade name:

Sodium chloride 5%

EV Product Code

Name of the MA holder:

Fresenius Kabi Limited

MA number (if MA granted by a Member State):

PL 08828/0051

Is the IMP modified in relation to its MA?

☐ Yes ☒ No ☐ Not Answered

Which country granted the MA?

UNITED KINGDOM

Is this the Member State concerned with this application?

☒ Yes ☐ No ☐ Not Answered**14-2. Situations where an IMP to be used in the CT has a MA in the MS concerned, but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start**

In the protocol, is treatment defined only by active substance?

☒ Yes ☐ No ☐ Not Answered*If 'Yes', give active substance in D.3.8 or D.3.9*

In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?

☒ Yes ☐ No ☐ Not Answered*If 'Yes', give active substance in D.3.8 or D.3.9*

The products to be administered as IMPs are defined as belonging to an ATC group

☒ Yes ☐ No ☐ Not Answered*If yes, give the ATC group of the applicable authorised codes in the ATC code field (level 3 or the level that can be defined) in D.3.1*

Other :

☐ Yes ☒ No ☐ Not Answered**14-3. IMPD submitted:**

Full IMPD

☐ Yes ☒ No ☐ Not Answered

Simplified IMPD

☐ Yes ☒ No ☐ Not Answered

Provide justification for using simplified dossier in the covering letter

Summary of product characteristics (SmPC) only

☒ Yes ☐ No ☐ Not Answered

14-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

☐ Yes ☒ No ☐ Not Answered

14-5. Has the IMP been designated in this indication as an orphan drug in the Community?

☐ Yes ☒ No ☐ Not Answered

14-6. Has the IMP been the subject of scientific advice related to this clinical trial?

☐ Yes ☒ No ☐ Not Answered

Please indicate source of advice and provide a copy in the CTA request:

From the CHMP?

☐ Yes ☒ No ☐ Not Answered

CHMP = Committee for Medicinal Products for Human Use

From a MS competent authority?

☐ Yes ☒ No ☐ Not Answered

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

Description of IMP**15-1. Description of IMP**

Product name where applicable Sodium chloride 5%

Product code where applicable

ATC codes, if officially registered A12CA01

Pharmaceutical form (use standard terms) Solution For Infusion

Is this a specific paediatric formulation? ☐ Yes ☒ No ☐ Not Answered

Maximum duration of treatment of a subject according to the protocol If intracranial pressure remains >20mmHg boluses can be repeated until serum sodium is >155mmol/L

Dose allowed

First dose for first-in-human clinical trial

Specify per day or total:

☐ per day ☐ total ☒ Not Answered

Specify total dose (number and unit)

Route of administration (relevant to the first dose):

Intravenous Use

Maximum dose allowed

The dose given will depend on the requirements of the individual patient and the judgement of the clinician

Specify per day or total

☐ per day ☐ total ☒ Not Answered

Specify total dose (number and unit)

Route of administration (relevant to the maximum dose):

Intravenous Use

Routes of administration for this IMP

Intravenous Use

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

15-2. Active substances

Complete all fields that currently apply to this Active Substance in this Product. If you have IMPs with different concentrations of the Active Substance complete a new Sub-section D for each.

Active Substance 1

Name of active substance (INN or proposed INN if available): Sodium Chloride

CAS number: 7647-14-5

Current sponsor code:

Other descriptive name:

Full Molecular formula NaCl

Chemical/biological description of the Active Substance sodium chloride

Strength

Concentration unit: % percent

Concentration type: equal

Concentration number (only use both fields for range): 5

15-3. Type of IMP

Does the IMP contain an active substance:

Of chemical origin?

☒ Yes ☐ No ☐ Not Answered

Of biological / biotechnological origin?(other than Advanced Therapy IMP (ATIMP))

☐ Yes ☒ No ☐ Not Answered

Is this a:

Advanced Therapy IMP (ATIMP) ⁽¹⁾

☐ Yes ☒ No ☐ Not Answered

Combination product that includes a device, but does not involve an Advanced Therapy

☐ Yes ☒ No ☐ Not Answered

Radiopharmaceutical medicinal product?

☐ Yes ☒ No ☐ Not Answered

Immunological medicinal product (e.g. vaccine, allergen, immune serum)?

☐ Yes ☒ No ☐ Not Answered

Plasma derived medicinal product?

☐ Yes ☒ No ☐ Not Answered

Extractive medicinal product?

☐ Yes ☒ No ☐ Not Answered

Recombinant medicinal product?

☐ Yes ☒ No ☐ Not Answered

Medicinal product containing genetically modified organisms?

☐ Yes ☒ No ☐ Not Answered

Herbal medicinal product?

☐ Yes ☒ No ☐ Not Answered

Homeopathic medicinal product?

☐ Yes ☒ No ☐ Not Answered

Another type of medicinal product?

☐ Yes ☒ No ☐ Not Answered

Specify the mode of action for the active substance in this medicinal product

The mode of action should briefly describe the chemical, biochemical, immunological or biological means that the IMP uses to effect its pharmaceutical action. Hypertonic saline has a core mechanisms of action through increasing the osmotic pressure of plasma. This draws water into the circulation from tissue extracellular spaces and so increases circulating volume, cardiac output and possibly blood pressure, whilst decreasing blood viscosity. These effects all increase cerebral blood flow and oxygen delivery. The osmotic effect also draws fluid from extracellular spaces in brain tissue, decreasing brain tissue volume and hence ICP

Is it an IMP to be used in a first-in-human clinical trial?

☐ Yes ☒ No ☐ Not Answered

^(1,2,3,4,5) Complete sections D.4, D.5, D.6. and D.7, as applicable

^(2,3) As defined in Annex 1 part IV of Directive 2001/83/EC as amended

⁽⁴⁾ As defined in Article 2(1)(b) of Regulation 1394/2007/EC

⁽⁶⁾ Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007

13. Indicate which of the following is described below then repeat as necessary for each:This refers to the IMP number: **PR4**

Investigational medicinal product category:

Test IMP

14. STATUS OF THE IMP*If the IMP has a marketing authorisation in the Member State concerned by this application but the trade name and marketing authorisation holder are not fixed in the protocol, go to question 14-2***14-1. Does the IMP to be used in the trial have a marketing authorisation?**☒ Yes ☐ No ☐ Not Answered

Trade name:

Sodium chloride 30%

EV Product Code

Name of the MA holder:

Torbay Pharmaceuticals

MA number (if MA granted by a Member State):

PL 13079/0007

Is the IMP modified in relation to its MA?

☐ Yes ☒ No ☐ Not Answered

Which country granted the MA?

UNITED KINGDOM

Is this the Member State concerned with this application?

☒ Yes ☐ No ☐ Not Answered**14-2. Situations where an IMP to be used in the CT has a MA in the MS concerned, but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start**

In the protocol, is treatment defined only by active substance?

☒ Yes ☐ No ☐ Not Answered*If 'Yes', give active substance in D.3.8 or D.3.9*

In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?

☒ Yes ☐ No ☐ Not Answered*If 'Yes', give active substance in D.3.8 or D.3.9*

The products to be administered as IMPs are defined as belonging to an ATC group

☒ Yes ☐ No ☐ Not Answered*If yes, give the ATC group of the applicable authorised codes in the ATC code field (level 3 or the level that can be defined) in D.3.1*

Other :

☐ Yes ☒ No ☐ Not Answered**14-3. IMPD submitted:**

Full IMPD

☐ Yes ☒ No ☐ Not Answered

Simplified IMPD

☐ Yes ☒ No ☐ Not Answered

Provide justification for using simplified dossier in the covering letter

Summary of product characteristics (SmPC) only

☒ Yes ☐ No ☐ Not Answered

14-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

☐ Yes ☒ No ☐ Not Answered

14-5. Has the IMP been designated in this indication as an orphan drug in the Community?

☐ Yes ☒ No ☐ Not Answered

14-6. Has the IMP been the subject of scientific advice related to this clinical trial?

☐ Yes ☒ No ☐ Not Answered

Please indicate source of advice and provide a copy in the CTA request:

From the CHMP?

☐ Yes ☒ No ☐ Not Answered

CHMP = Committee for Medicinal Products for Human Use

From a MS competent authority?

☐ Yes ☒ No ☐ Not Answered

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

Description of IMP**15-1. Description of IMP**

Product name where applicable Sodium chloride 30%

Product code where applicable

ATC codes, if officially registered A12CA01

Pharmaceutical form (use standard terms) Solution For Infusion

Is this a specific paediatric formulation? ☐ Yes ☒ No ☐ Not Answered

Maximum duration of treatment of a subject according to the protocol If intracranial pressure remains >20mmHg boluses can be repeated until serum sodium is >155mmol/L

Dose allowed

First dose for first-in-human clinical trial

Specify per day or total:

☐ per day ☐ total ☒ Not Answered

Specify total dose (number and unit)

Route of administration (relevant to the first dose):

Intravenous Use

Maximum dose allowed

The dose given will depend on the requirements of the individual patient and the judgement of the clinician

Specify per day or total

☐ per day ☐ total ☒ Not Answered

Specify total dose (number and unit)

Route of administration (relevant to the maximum dose):

Intravenous Use

Routes of administration for this IMP

Intravenous Use

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

15-2. Active substances

Complete all fields that currently apply to this Active Substance in this Product. If you have IMPs with different concentrations of the Active Substance complete a new Sub-section D for each.

Active Substance 1

Name of active substance (INN or proposed INN if available): Sodium Chloride

CAS number: 7647-14-5

Current sponsor code:

Other descriptive name:

Full Molecular formula NaCl

Chemical/biological description of the Active Substance sodium chloride

Strength

Concentration unit: % percent

Concentration type: equal

Concentration number (only use both fields for range): 30

15-3. Type of IMP

Does the IMP contain an active substance:

Of chemical origin?

☒ Yes ☐ No ☐ Not Answered

Of biological / biotechnological origin?(other than Advanced Therapy IMP (ATIMP))

☐ Yes ☒ No ☐ Not Answered

Is this a:

Advanced Therapy IMP (ATIMP) ⁽¹⁾

☐ Yes ☒ No ☐ Not Answered

Combination product that includes a device, but does not involve an Advanced Therapy

☐ Yes ☒ No ☐ Not Answered

Radiopharmaceutical medicinal product?

☐ Yes ☒ No ☐ Not Answered

Immunological medicinal product (e.g. vaccine, allergen, immune serum)?

☐ Yes ☒ No ☐ Not Answered

Plasma derived medicinal product?

☐ Yes ☒ No ☐ Not Answered

Extractive medicinal product?

☐ Yes ☒ No ☐ Not Answered

Recombinant medicinal product?

☐ Yes ☒ No ☐ Not Answered

Medicinal product containing genetically modified organisms?

☐ Yes ☒ No ☐ Not Answered

Herbal medicinal product?

☐ Yes ☒ No ☐ Not Answered

Homeopathic medicinal product?

☐ Yes ☒ No ☐ Not Answered

Another type of medicinal product?

☐ Yes ☒ No ☐ Not Answered

Specify the mode of action for the active substance in this medicinal product

The mode of action should briefly describe the chemical, biochemical, immunological or biological means that the IMP uses to effect its pharmaceutical action. Hypertonic saline has a core mechanisms of action through increasing the osmotic pressure of plasma. This draws water into the circulation from tissue extracellular spaces and so increases circulating volume, cardiac output and possibly blood pressure, whilst decreasing blood viscosity. These effects all increase cerebral blood flow and oxygen delivery. The osmotic effect also draws fluid from extracellular spaces in brain tissue, decreasing brain tissue volume and hence ICP.

Is it an IMP to be used in a first-in-human clinical trial?

☐ Yes ☒ No ☐ Not Answered

^(1,2,3,4,5) Complete sections D.4, D.5, D.6. and D.7, as applicable

^(2,3) As defined in Annex 1 part IV of Directive 2001/83/EC as amended

⁽⁴⁾ As defined in Article 2(1)(b) of Regulation 1394/2007/EC

⁽⁶⁾ Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007

13. Indicate which of the following is described below then repeat as necessary for each:This refers to the IMP number: **PR8**

Investigational medicinal product category:

Test IMP

14. STATUS OF THE IMP*If the IMP has a marketing authorisation in the Member State concerned by this application but the trade name and marketing authorisation holder are not fixed in the protocol, go to question 14-2***14-1. Does the IMP to be used in the trial have a marketing authorisation?**☒ Yes ☐ No ☐ Not Answered

Trade name:

Sodium chloride (bespoke concentration)

EV Product Code

Name of the MA holder:

Torbay Pharmaceuticals

MA number (if MA granted by a Member State):

PL13079/0007

Is the IMP modified in relation to its MA?

☐ Yes ☒ No ☐ Not Answered

Which country granted the MA?

UNITED KINGDOM

Is this the Member State concerned with this application?

☒ Yes ☐ No ☐ Not Answered**14-2. Situations where an IMP to be used in the CT has a MA in the MS concerned, but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start**

In the protocol, is treatment defined only by active substance?

☒ Yes ☐ No ☐ Not Answered*If 'Yes', give active substance in D.3.8 or D.3.9*

In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?

☒ Yes ☐ No ☐ Not Answered*If 'Yes', give active substance in D.3.8 or D.3.9*

The products to be administered as IMPs are defined as belonging to an ATC group

☒ Yes ☐ No ☐ Not Answered*If yes, give the ATC group of the applicable authorised codes in the ATC code field (level 3 or the level that can be defined) in D.3.1*

Other :

☒ Yes ☐ No ☐ Not Answered

Please specify :

Participating hospitals may prepare bespoke concentrations of sodium chloride for use according to their local protocol for treating raised intracranial pressure. This is established practice and is permitted within the trial protocol (please see section 2.11.1). To achieve bespoke concentrations Sodium Chloride 30% is diluted with water for injection or saline prior to use.

14-3. IMPD submitted:

Full IMPD

☐ Yes ☒ No ☐ Not Answered

Simplified IMPD

☐ Yes ☒ No ☐ Not Answered*Provide justification for using simplified dossier in the covering letter*

Summary of product characteristics (SmPC) only

☒ Yes ☐ No ☐ Not Answered**14-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?**☐ Yes ☒ No ☐ Not Answered**14-5. Has the IMP been designated in this indication as an orphan drug in the Community?**☐ Yes ☒ No ☐ Not Answered**14-6. Has the IMP been the subject of scientific advice related to this clinical trial?**☐ Yes ☒ No ☐ Not Answered

Please indicate source of advice and provide a copy in the CTA request:

From the CHMP?

☐ Yes ☒ No ☐ Not Answered*CHMP = Committee for Medicinal Products for Human Use*

From a MS competent authority?

☐ Yes ☒ No ☐ Not Answered

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

Description of IMP**15-1. Description of IMP**

Product name where applicable Sodium chloride (bespoke concentration)

Product code where applicable

ATC codes, if officially registered A12CA01

Pharmaceutical form (use standard terms) Solution For Infusion

Is this a specific paediatric formulation? ☐ Yes ☒ No ☐ Not Answered

Maximum duration of treatment of a subject according to the protocol

If intracranial pressure remains >20mmHg boluses can be repeated until serum sodium is >155mmol/L

Dose allowed

First dose for first-in-human clinical trial

Specify per day or total:

☐ per day ☐ total ☒ Not Answered

Specify total dose (number and unit)

Route of administration (relevant to the first dose):

Maximum dose allowed

The dose given will depend on the requirements of the individual patient and the judgement of the clinician

Specify per day or total

☐ per day ☐ total ☒ Not Answered

Specify total dose (number and unit)

Route of administration (relevant to the maximum dose):

Routes of administration for this IMP

Intravenous Use

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

15-2. Active substances

Complete all fields that currently apply to this Active Substance in this Product. If you have IMPs with different concentrations of the Active Substance complete a new Sub-section D for each.

Active Substance 1

Name of active substance (INN or proposed INN if available): Sodium Chloride

CAS number: 7647-14-5

Current sponsor code:

Other descriptive name:

Full Molecular formula NaCl

Chemical/biological description of the Active Substance sodium chloride

Strength

Concentration unit: % percent

Concentration type: range

Concentration number (only use both fields for range): >0 30

15-3. Type of IMP

Does the IMP contain an active substance:

Of chemical origin? ☒ Yes ☐ No ☐ Not Answered

Of biological / biotechnological origin?(other than Advanced Therapy IMP (ATIMP)) ☐ Yes ☒ No ☐ Not Answered

Is this a:

Advanced Therapy IMP (ATIMP) ⁽¹⁾ ☐ Yes ☒ No ☐ Not Answered

Combination product that includes a device, but does not involve an Advanced Therapy ☐ Yes ☒ No ☐ Not Answered

Radiopharmaceutical medicinal product? ☐ Yes ☒ No ☐ Not Answered

Immunological medicinal product (e.g. vaccine, allergen, immune serum)? ☐ Yes ☒ No ☐ Not Answered

Plasma derived medicinal product? ☐ Yes ☒ No ☐ Not Answered

Extractive medicinal product? ☐ Yes ☒ No ☐ Not Answered

Recombinant medicinal product? ☐ Yes ☒ No ☐ Not Answered

Medicinal product containing genetically modified organisms? ☐ Yes ☒ No ☐ Not Answered

Herbal medicinal product? ☐ Yes ☒ No ☐ Not Answered

Homeopathic medicinal product? ☐ Yes ☒ No ☐ Not Answered

Another type of medicinal product? ☐ Yes ☒ No ☐ Not Answered

Specify the mode of action for the active substance in this medicinal product

The mode of action should briefly describe the chemical, biochemical, immunological or biological means that the IMP uses to effect its pharmaceutical action. Hypertonic saline has a core mechanisms of action through increasing the osmotic pressure of plasma. This draws water into the circulation from tissue extracellular spaces and so increases circulating volume, cardiac output and possibly blood pressure, whilst decreasing blood viscosity. These effects all increase cerebral blood flow and oxygen delivery. The osmotic effect also draws fluid from extracellular spaces in brain tissue, decreasing brain tissue volume and hence ICP.

Is it an IMP to be used in a first-in-human clinical trial? ☐ Yes ☒ No ☐ Not Answered

^(1,2,3,4,5) Complete sections D.4, D.5, D.6. and D.7, as applicable

^(2,3) As defined in Annex 1 part IV of Directive 2001/83/EC as amended

⁽⁴⁾ As defined in Article 2(1)(b) of Regulation 1394/2007/EC

⁽⁶⁾ Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007

13. Indicate which of the following is described below then repeat as necessary for each:This refers to the IMP number: **PR9**

Investigational medicinal product category:

Test IMP

14. STATUS OF THE IMP*If the IMP has a marketing authorisation in the Member State concerned by this application but the trade name and marketing authorisation holder are not fixed in the protocol, go to question 14-2***14-1. Does the IMP to be used in the trial have a marketing authorisation?**☒ Yes ☐ No ☐ Not Answered

Trade name:

Mannitol 10%

EV Product Code

Name of the MA holder:

Baxter Healthcare Limited

MA number (if MA granted by a Member State):

PL 00116/0367

Is the IMP modified in relation to its MA?

☐ Yes ☒ No ☐ Not Answered

Which country granted the MA?

UNITED KINGDOM

Is this the Member State concerned with this application?

☒ Yes ☐ No ☐ Not Answered**14-2. Situations where an IMP to be used in the CT has a MA in the MS concerned, but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start**

In the protocol, is treatment defined only by active substance?

☒ Yes ☐ No ☐ Not Answered*If 'Yes', give active substance in D.3.8 or D.3.9*

In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?

☒ Yes ☐ No ☐ Not Answered*If 'Yes', give active substance in D.3.8 or D.3.9*

The products to be administered as IMPs are defined as belonging to an ATC group

☒ Yes ☐ No ☐ Not Answered*If yes, give the ATC group of the applicable authorised codes in the ATC code field (level 3 or the level that can be defined) in D.3.1*

Other :

☐ Yes ☒ No ☐ Not Answered**14-3. IMPD submitted:**

Full IMPD

☐ Yes ☒ No ☐ Not Answered

Simplified IMPD

☐ Yes ☒ No ☐ Not Answered

Provide justification for using simplified dossier in the covering letter

Summary of product characteristics (SmPC) only

☒ Yes ☐ No ☐ Not Answered

14-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

☐ Yes ☒ No ☐ Not Answered

14-5. Has the IMP been designated in this indication as an orphan drug in the Community?

☐ Yes ☒ No ☐ Not Answered

14-6. Has the IMP been the subject of scientific advice related to this clinical trial?

☐ Yes ☒ No ☐ Not Answered

Please indicate source of advice and provide a copy in the CTA request:

From the CHMP?

☐ Yes ☒ No ☐ Not Answered

CHMP = Committee for Medicinal Products for Human Use

From a MS competent authority?

☐ Yes ☒ No ☐ Not Answered

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

Description of IMP**15-1. Description of IMP**

Product name where applicable Mannitol 10%

Product code where applicable

ATC codes, if officially registered B05BC01

Pharmaceutical form (use standard terms) Solution For Infusion

Is this a specific paediatric formulation? ☐ Yes ☒ No ☐ Not Answered

Maximum duration of treatment of a subject according to the protocol If intracranial pressure remains >20mmHg boluses can be repeated until serum sodium is >155mmol/L

Dose allowed

First dose for first-in-human clinical trial

Specify per day or total:

☐ per day ☐ total ☒ Not Answered

Specify total dose (number and unit)

Route of administration (relevant to the first dose):

Intravenous Use

Maximum dose allowed

The dose given will depend on the requirements of the individual patient and the judgement of the clinician

Specify per day or total

☐ per day ☐ total ☒ Not Answered

Specify total dose (number and unit)

Route of administration (relevant to the maximum dose):

Intravenous Use

Routes of administration for this IMP

Intravenous Use

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

15-2. Active substances

Complete all fields that currently apply to this Active Substance in this Product. If you have IMPs with different concentrations of the Active Substance complete a new Sub-section D for each.

Active Substance 1

Name of active substance (INN or proposed INN if available): Mannitol

CAS number: 69-65-8

Current sponsor code:

Other descriptive name:

Full Molecular formula $C_6H_{14}O_6$

Chemical/biological description of the Active Substance: Chemically, mannitol is an alcohol and a sugar, or a polyol; it is similar to xylitol or sorbitol

Strength

Concentration unit: % percent

Concentration type: equal

Concentration number (only use both fields for range): 10

15-3. Type of IMP

Does the IMP contain an active substance:

Of chemical origin?

☒ Yes ☐ No ☐ Not Answered

Of biological / biotechnological origin?(other than Advanced Therapy IMP (ATIMP))

☐ Yes ☒ No ☐ Not Answered

Is this a:

Advanced Therapy IMP (ATIMP) ⁽¹⁾

☐ Yes ☒ No ☐ Not Answered

Combination product that includes a device, but does not involve an Advanced Therapy

☐ Yes ☒ No ☐ Not Answered

Radiopharmaceutical medicinal product?

☐ Yes ☒ No ☐ Not Answered

Immunological medicinal product (e.g. vaccine, allergen, immune serum)?

☐ Yes ☒ No ☐ Not Answered

Plasma derived medicinal product?

☐ Yes ☒ No ☐ Not Answered

Extractive medicinal product?

☐ Yes ☒ No ☐ Not Answered

Recombinant medicinal product?

☐ Yes ☒ No ☐ Not Answered

Medicinal product containing genetically modified organisms?

☐ Yes ☒ No ☐ Not Answered

Herbal medicinal product?

☐ Yes ☒ No ☐ Not Answered

Homeopathic medicinal product?

☐ Yes ☒ No ☐ Not Answered

Another type of medicinal product?

☐ Yes ☒ No ☐ Not Answered

Specify the mode of action for the active substance in this medicinal product

The mode of action should briefly describe the chemical, biochemical, immunological or biological means that the IMP uses to effect its pharmaceutical action. Mannitol is an osmotic diuretic. The mechanism of action of mannitol is as an osmotic activity. The physiologic effect of mannitol is by means of increased diuresis.

Is it an IMP to be used in a first-in-human clinical trial?

☐ Yes ☒ No ☐ Not Answered

^(1,2,3,4,5) Complete sections D.4, D.5, D.6. and D.7, as applicable

^(2,3) As defined in Annex 1 part IV of Directive 2001/83/EC as amended

⁽⁴⁾ As defined in Article 2(1)(b) of Regulation 1394/2007/EC

⁽⁶⁾ Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007

13. Indicate which of the following is described below then repeat as necessary for each:This refers to the IMP number: **PR10**

Investigational medicinal product category:

Test IMP

14. STATUS OF THE IMP*If the IMP has a marketing authorisation in the Member State concerned by this application but the trade name and marketing authorisation holder are not fixed in the protocol, go to question 14-2***14-1. Does the IMP to be used in the trial have a marketing authorisation?**☒ Yes ☐ No ☐ Not Answered

Trade name:

Mannitol 15%

EV Product Code

Name of the MA holder:

Baxter Healthcare

MA number (if MA granted by a Member State):

PL 00116/0650

Is the IMP modified in relation to its MA?

☐ Yes ☒ No ☐ Not Answered

Which country granted the MA?

UNITED KINGDOM

Is this the Member State concerned with this application?

☒ Yes ☐ No ☐ Not Answered**14-2. Situations where an IMP to be used in the CT has a MA in the MS concerned, but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start**

In the protocol, is treatment defined only by active substance?

☒ Yes ☐ No ☐ Not Answered*If 'Yes', give active substance in D.3.8 or D.3.9*

In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?

☒ Yes ☐ No ☐ Not Answered*If 'Yes', give active substance in D.3.8 or D.3.9*

The products to be administered as IMPs are defined as belonging to an ATC group

☒ Yes ☐ No ☐ Not Answered*If yes, give the ATC group of the applicable authorised codes in the ATC code field (level 3 or the level that can be defined) in D.3.1*

Other :

☐ Yes ☒ No ☐ Not Answered**14-3. IMPD submitted:**

Full IMPD

☐ Yes ☒ No ☐ Not Answered

Simplified IMPD

☐ Yes ☒ No ☐ Not Answered

Provide justification for using simplified dossier in the covering letter

Summary of product characteristics (SmPC) only

☒ Yes ☐ No ☐ Not Answered

14-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

☐ Yes ☒ No ☐ Not Answered

14-5. Has the IMP been designated in this indication as an orphan drug in the Community?

☐ Yes ☒ No ☐ Not Answered

14-6. Has the IMP been the subject of scientific advice related to this clinical trial?

☐ Yes ☒ No ☐ Not Answered

Please indicate source of advice and provide a copy in the CTA request:

From the CHMP?

☐ Yes ☒ No ☐ Not Answered

CHMP = Committee for Medicinal Products for Human Use

From a MS competent authority?

☐ Yes ☒ No ☐ Not Answered

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

Description of IMP**15-1. Description of IMP**

Product name where applicable Mannitol 15%

Product code where applicable

ATC codes, if officially registered B05BC01

Pharmaceutical form (use standard terms) Solution For Infusion

Is this a specific paediatric formulation? ☐ Yes ☒ No ☐ Not Answered

Maximum duration of treatment of a subject according to the protocol If intracranial pressure remains >20mmHg boluses can be repeated until serum sodium is >155mmol/L

Dose allowed

First dose for first-in-human clinical trial

Specify per day or total:

☐ per day ☐ total ☒ Not Answered

Specify total dose (number and unit)

Route of administration (relevant to the first dose):

Intravenous Use

Maximum dose allowed

The dose given will depend on the requirements of the individual patient and the judgement of the clinician

Specify per day or total

☐ per day ☐ total ☒ Not Answered

Specify total dose (number and unit)

Route of administration (relevant to the maximum dose):

Intravenous Use

Routes of administration for this IMP

Intravenous Use

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

15-2. Active substances

Complete all fields that currently apply to this Active Substance in this Product. If you have IMPs with different concentrations of the Active Substance complete a new Sub-section D for each.

Active Substance 1

Name of active substance (INN or proposed INN if available): Mannitol

CAS number: 69-65-8

Current sponsor code:

Other descriptive name:

Full Molecular formula $C_6H_{14}O_6$

Chemical/biological description of the Active Substance Chemically, mannitol is an alcohol and a sugar, or a polyol; it is similar to xylitol or sorbitol

Strength

Concentration unit: % percent

Concentration type: equal

Concentration number (only use both fields for range): 15

15-3. Type of IMP

Does the IMP contain an active substance:

Of chemical origin?

☒ Yes ☐ No ☐ Not Answered

Of biological / biotechnological origin?(other than Advanced Therapy IMP (ATIMP))

☐ Yes ☒ No ☐ Not Answered

Is this a:

Advanced Therapy IMP (ATIMP) ⁽¹⁾

☐ Yes ☒ No ☐ Not Answered

Combination product that includes a device, but does not involve an Advanced Therapy

☐ Yes ☒ No ☐ Not Answered

Radiopharmaceutical medicinal product?

☐ Yes ☒ No ☐ Not Answered

Immunological medicinal product (e.g. vaccine, allergen, immune serum)?

☐ Yes ☒ No ☐ Not Answered

Plasma derived medicinal product?

☐ Yes ☒ No ☐ Not Answered

Extractive medicinal product?

☐ Yes ☒ No ☐ Not Answered

Recombinant medicinal product?

☐ Yes ☒ No ☐ Not Answered

Medicinal product containing genetically modified organisms?

☐ Yes ☒ No ☐ Not Answered

Herbal medicinal product?

☐ Yes ☒ No ☐ Not Answered

Homeopathic medicinal product?

☐ Yes ☒ No ☐ Not Answered

Another type of medicinal product?

☐ Yes ☒ No ☐ Not Answered

Specify the mode of action for the active substance in this medicinal product

The mode of action should briefly describe the chemical, biochemical, immunological or biological means that the IMP uses to effect its pharmaceutical action. Mannitol is an osmotic diuretic. The mechanism of action of mannitol is as an osmotic activity. The physiologic effect of mannitol is by means of increased diuresis.

Is it an IMP to be used in a first-in-human clinical trial?

☐ Yes ☒ No ☐ Not Answered

^(1,2,3,4,5) Complete sections D.4, D.5, D.6. and D.7, as applicable

^(2,3) As defined in Annex 1 part IV of Directive 2001/83/EC as amended

⁽⁴⁾ As defined in Article 2(1)(b) of Regulation 1394/2007/EC

⁽⁶⁾ Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007

Information on Placebo

13. Is there a placebo:☐ Yes ☒ No

DRAFT

Index of Sites where the qualified person certifies batch release

14. IMPs and placebos for which no responsible site needs to be identified:

This section is used to identify IMPs and placebos which:

- Have an MA in the EU and
- Are sourced from the EU market and
- Are used in the trial without modification (eg not overencapsulated) and
- The packaging and labeling is carried out for local use only as per article 9.2 of the Directive 2005/28/EC (GCP Directive).

If all the conditions above are met, then select below the IMPs and placebos to which this applies.

Finished IMP
PR1

Finished IMP
PR2

Finished IMP
PR3

Finished IMP
PR4

Finished IMP
PR8

Finished IMP
PR9

Finished IMP
PR10

This section is dedicated to finished IMPs, i.e. medicinal products randomised, packaged, labelled and certified for use in the clinical trial. In the case of multiple sites indicate the product certified by each site.

15. Identify who is responsible in the Community for the certification of the finished IMPs.

Where the product does not have a MA in the EU, but is supplied in bulk and final packaging and labelling for local use is carried out in accordance with article 9.2. of Directive 2005/28/EC (GCP Directive) then enter the site where the product was finally certified for release by the Qualified Person for use in the clinical trial.

RS1

Organisation

Address

Town/city

Post code

Country

Give the manufacturing authorisation number

If no authorisation, give the reasons:

Select the relevant IMP(s) and Placebo(s) from the drop down lists.

DRAFT

Part B: Section 6 - Adults unable to consent for themselves**A. Clinical trials of investigational medicinal products**

In this sub-section, an adult means a person aged 16 or over.

A1. What clinical condition(s) will the participants have? The trial must relate directly to this condition.

Traumatic brain injury

A2. Could the trial be carried out equally effectively if confined to adults capable of giving consent?

☐ Yes ☒ No

A3. Who in the research team will decide whether or not the participants have the capacity to give consent? What training/experience will they have to enable them to reach this decision?

Investigators will have clinical experience in consent taking and in the use of tools for assessment of patient mental capacity. The assessment is done as part of standard medical care on an ongoing basis.

A4. What benefit is the administration of the investigational medicinal product expected to produce for these participants? You may refer back to your answer to Question A24.

The clinical benefit to participants is uncertain as we do not currently know which treatment is better. However participating in the study will provide important information on which is the most effective treatment for patients with traumatic brain injury in the future.

A5. Will the trial involve any foreseeable risk or burden for these participants, or interfere in any way with their freedom of action or privacy?

☐ Yes ☒ No

A6. What arrangements will be made to identify and seek informed consent from a legal representative?

The incapacitating nature of traumatic brain injury precludes obtaining informed consent directly from the patient prior to enrolment. If there is a personal legal representative available, there is sufficient time to obtain informed consent, and it is appropriate to do so, then informed consent will be obtained from the personal legal representative prior to the patient being enrolled. If no personal legal representative is available, a doctor who is not connected with the conduct of the trial may act as a professional legal representative and provide consent.

A7. Is it possible that a participant requiring urgent treatment might need to be recruited into the trial before it is possible to identify and seek consent from a legal representative?

☒ Yes ☐ No

If Yes, outline how decisions will be made on the inclusion of participants and what arrangements will be made to seek consent from the participant (if capacity has been recovered) or a legal representative as soon as practicable thereafter.

If treatment is required urgently to reduce the swelling in the brain, and there is not sufficient time to obtain informed consent from a legal representative, the patient will be enrolled into the trial under deferred consent once they meet all eligibility criteria.

If no consent has been obtained from a legal representative prior to the patient being enrolled, then written informed consent from a legal representative will be obtained as soon as practically possible once the initial emergency has passed. If no suitable personal legal representative is available then consent will be sought from a professional legal representative.

If the patient recovers capacity to consent for themselves while still in hospital they will be informed about their participation in the trial and asked for written informed consent for their ongoing participation in the trial.

A8. What arrangements will be made to continue to consult legal representatives during the course of the research where necessary?

During the course of the trial, the study team will have regular contact with legal representatives, so there will be opportunities for continued consultation.

A9. Will steps be taken to provide information about the trial to participants, according to their capacity of understanding, and to consider the wishes of participants capable of forming an opinion?

☒ Yes ☐ No

If Yes, give details.

We have created separate information sheets which can be given to patients or legal representatives where the wording is tailored depending on the point at which they are approached for consent:

- Version of legal representative approached prior to enrolment
- Version for legal representative approached post-enrolment
- Version for patient approached post-enrolment once capacity is recovered

A10-1. What will be the criteria for withdrawal of participants?

Participants may be withdrawn from the trial intervention at the discretion of the investigator and/or Trial Steering Committee due to safety concerns.

Participants, or their legal representatives on their behalf, may request to be withdrawn from the trial at any time without prejudice.

Patients or legal representatives who decline consent will be logged on the database from the point that they communicate their intention to the trial team and no further contact will be made. Data already collected will be retained and included in the analysis. The information sheet explains the trial and the data that will be collected. Patients and legal representatives will be informed that the research team will continue to collect data remotely as per the protocol until the end of the trial, unless they explicitly withdraw their consent for this.

A10-2. Where a participant is recruited prior to consent being obtained, and consent is later withheld or the participant dies before consent can be given, what provisions will apply to the study data collected up to this point?

Data collected up to the point of death or withdrawal will be anonymised and retained in the trial database. The rationale for this approach is that withdrawal of data would introduce bias and undermine the scientific integrity of the trial.

PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. For further information please refer to guidance.

Investigator identifier	Research site	Investigator Name
IN1	<input checked="" type="radio"/> NHS/HSC Site <input type="radio"/> Non-NHS/HSC Site Organisation name OXFORD UNIVERSITY HOSPITALS NHS FOUNDATION TRUST Address JOHN RADCLIFFE HOSPITAL HEADLEY WAY HEADINGTON OXFORD OXFORDSHIRE Post Code OX3 9DU Country ENGLAND	Forename Matthew Middle name Family name Rowland Email matthew.rowland@ndcn.ox.ac.uk Qualification (MD...) D Phil, MBBS Country UNITED KINGDOM
IN3	<input checked="" type="radio"/> NHS/HSC Site <input type="radio"/> Non-NHS/HSC Site Organisation name NORTH BRISTOL NHS TRUST Address SOUTHMEAD HOSPITAL SOUTHMEAD ROAD WESTBURY-ON-TRYM BRISTOL AVON Post Code BS10 5NB Country ENGLAND	Forename Julian Middle name Family name Thompson Email julian.thompson@nbt.nhs.uk Qualification (MD...) FRCA MD(Res) FRCA FFIC Country UNITED KINGDOM
IN9	<input checked="" type="radio"/> NHS/HSC Site <input type="radio"/> Non-NHS/HSC Site Organisation name THE NEWCASTLE UPON TYNE HOSPITALS NHS FOUNDATION TRUST Address FREEMAN HOSPITAL FREEMAN ROAD	Forename Jonathan Middle name Family name Shelton Email Jonathan.Shelton@nuth.nhs.uk Qualification (MD...) MBBS, FRCA, DICM, FCICM, FFICM Country UNITED KINGDOM

IN12

HIGH HEATON NEWCASTLE-
UPON-TYNE TYNE AND WEAR

Post Code NE7 7DN

Country ENGLAND

☒ NHS/HSC Site☐ Non-NHS/HSC Site

Organisation name SHEFFIELD TEACHING HOSPITALS
NHS FOUNDATION TRUST

Address NORTHERN GENERAL HOSPITAL
HERRIES ROAD
SHEFFIELD SOUTH YORKSHIRE

Post Code S5 7AU

Country ENGLAND

Forename Matthew

Middle name

Family name Wiles

Email matthew.wiles@sth.nhs.uk

Qualification (MD...) BMedSci, BM BS, MRCP,
FRCA, FFICM,
MMedSci(ClinEd)

Country

IN14

☒ NHS/HSC Site☐ Non-NHS/HSC Site

Organisation name NHS Lothian

Address Waverley Gate
2-4 Waterloo Place
Edinburgh Scotland

Post Code EH1 3EG

Country SCOTLAND

Forename Jonathan

Middle name

Family name Rhodes

Email jrhodes1@exseed.ed.ac.uk

Qualification (MD...) PhD, FRCA, MB ChB

Country UNITED KINGDOM

IN17

☒ NHS/HSC Site☐ Non-NHS/HSC Site

Organisation name LEEDS TEACHING HOSPITALS
NHS TRUST

Address ST. JAMES'S UNIVERSITY
HOSPITAL
BECKETT STREET
LEEDS WEST YORKSHIRE

Post Code LS9 7TF

Forename Ian

Middle name

Family name Anderson

Email ian.anderson4@nhs.net

Qualification (MD...) BSc, MB ChB, MRCS(Ed),
PG Cert, FRCS

Country UNITED KINGDOM

Country ENGLAND

IN19

☒ NHS/HSC Site☐ Non-NHS/HSC Site

Forename Mark

Middle name

Family name Wilson

Email acutebrain@gmail.com

Organisation name IMPERIAL COLLEGE HEALTHCARE
NHS TRUSTQualification PhD MB BChir FRCS (SN)
FIMC FRGS MRCAAddress ST. MARYS HOSPITAL
PRAED STREET
LONDON GREATER LONDON

Country UNITED KINGDOM

Post Code W2 1NY

Country ENGLAND

IN22

☒ NHS/HSC Site☐ Non-NHS/HSC Site

Forename Tom

Middle name

Family name Hurst

Email tom.hurst@nhs.net

Organisation name KING'S COLLEGE HOSPITAL NHS
FOUNDATION TRUST

Qualification MB ChB

Address DENMARK HILL

Country UNITED KINGDOM

LONDON GREATER LONDON

Post Code SE5 9RS

Country ENGLAND

IN24

☒ NHS/HSC Site☐ Non-NHS/HSC Site

Forename Jay

Middle name

Family name Naisbitt

Email jay.naisbitt@srft.nhs.uk

Organisation name SALFORD ROYAL NHS
FOUNDATION TRUST

Qualification (MD...)

Address SALFORD ROYAL
STOTT LANE
SALFORD GREATER
MANCHESTER

Country UNITED KINGDOM

Post Code M6 8HD

Country ENGLAND

IN27

- ☒ NHS/HSC Site
☐ Non-NHS/HSC Site

Organisation name HULL AND EAST YORKSHIRE
HOSPITALS NHS TRUST
Address HULL ROYAL INFIRMARY
ANLABY ROAD
HULL NORTH HUMBERSIDE
Post Code HU3 2JZ
Country ENGLAND

Forename Ian
Middle name
Family name Smith
Email ian.smith@hey.nhs.uk
Qualification MBChB FRCA FFICM
(MD...)
Country UNITED KINGDOM

IN28

- ☒ NHS/HSC Site
☐ Non-NHS/HSC Site

Organisation name UNIVERSITY HOSPITALS
BIRMINGHAM NHS FOUNDATION
TRUST
Address TRUST HQ, PO BOX 9551
QUEEN ELIZABETH MEDICAL
CENTRE
EDGBASTON BIRMINGHAM WEST
MIDLANDS
Post Code B15 2TH
Country ENGLAND

Forename Tonny
Middle name
Family name Veenith
Email tonny.veenith@uhb.nhs.uk
Qualification MBBS, MRCP(UK), FRCA,
(MD...) EDIC, FFICM
Country UNITED KINGDOM

IN30

- ☒ NHS/HSC Site
☐ Non-NHS/HSC Site

Organisation name NIHR CRN: North East and North
Cumbria
Address
Post Code NE3 3HD
Country ENGLAND

Forename
Middle name
Family name
Email
Qualification
(MD...)
Country

IN31

- ☒ NHS/HSC Site
☐ Non-NHS/HSC Site

Forename
Middle name
Family name
Email
Qualification
(MD...)
Country

Organisation name
NIHR CRN: North West Coast
Address

Post Code
L7 8XP
Country
ENGLAND

IN32

- ☒ NHS/HSC Site
☐ Non-NHS/HSC Site

Forename
Middle name
Family name
Email
Qualification
(MD...)
Country

Organisation name
NIHR CRN: Yorkshire and Humber
Address

Post Code
S10 2SB
Country
ENGLAND

IN33

- ☒ NHS/HSC Site
☐ Non-NHS/HSC Site

Forename
Middle name
Family name
Email
Qualification
(MD...)
Country

Organisation name
NIHR CRN: Greater Manchester
Address

Post Code
M13 9WL
Country
ENGLAND

IN34

- ☒ NHS/HSC Site
☐ Non-NHS/HSC Site

Forename
Middle name

IN35

Organisation name NIHR CRN: East Midlands
Address

Family name
Email
Qualification
(MD...)
Country

Post Code LE1 5WW
Country ENGLAND

☒ NHS/HSC Site
☐ Non-NHS/HSC Site

Forename
Middle name
Family name
Email
Qualification
(MD...)
Country

Organisation name NIHR CRN: West Midlands
Address

Post Code CV3 2TX
Country ENGLAND

IN36

☒ NHS/HSC Site
☐ Non-NHS/HSC Site

Forename
Middle name
Family name
Email
Qualification
(MD...)
Country

Organisation name NIHR CRN: West of England
Address

Post Code BS1 2NT
Country ENGLAND

IN37

☒ NHS/HSC Site
☐ Non-NHS/HSC Site

Forename
Middle name
Family name
Email
Qualification
(MD...)

Organisation name NIHR CRN: Thames Valley and
South Midlands

	Address	Country
	Post Code OX3 9DU Country ENGLAND	
IN38	<input checked="" type="radio"/> NHS/HSC Site <input type="radio"/> Non-NHS/HSC Site	Forename Middle name Family name Email Qualification (MD...) Country
	Organisation name NIHR CRN: Eastern Address	
	Post Code NR1 1QQ Country ENGLAND	
IN39	<input checked="" type="radio"/> NHS/HSC Site <input type="radio"/> Non-NHS/HSC Site	Forename Middle name Family name Email Qualification (MD...) Country
	Organisation name NIHR CRN: Kent, Surrey and Sussex Address	
	Post Code ME8 0NZ Country ENGLAND	
IN40	<input checked="" type="radio"/> NHS/HSC Site <input type="radio"/> Non-NHS/HSC Site	Forename Middle name Family name Email Qualification (MD...) Country
	Organisation name NIHR CRN: Wessex Address	
	Post Code SO30 2UN	

Country ENGLAND

IN41

☒ NHS/HSC Site
☐ Non-NHS/HSC Site

Organisation name NIHR CRN: South West Peninsula
Address

Post Code PL6 8BX
Country ENGLAND

Forename
Middle name
Family name
Email
Qualification
(MD...)
Country

IN42

☒ NHS/HSC Site
☐ Non-NHS/HSC Site

Organisation name NIHR CRN: North Thames
Address

Post Code W1T 7HA
Country ENGLAND

Forename
Middle name
Family name
Email
Qualification
(MD...)
Country

IN43

☒ NHS/HSC Site
☐ Non-NHS/HSC Site

Organisation name NIHR CRN: South London
Address

Post Code SE1 9RT
Country ENGLAND

Forename
Middle name
Family name
Email
Qualification
(MD...)
Country

IN44

- ☒ NHS/HSC Site
☐ Non-NHS/HSC Site

Forename
Middle name
Family name
Email
Qualification
(MD...)
Country

Organisation name
NIHR CRN: North West London
Address

Post Code
W12 0HT
Country
ENGLAND

IN45

- ☒ NHS/HSC Site
☐ Non-NHS/HSC Site

Forename
Middle name
Family name
Email
Qualification
(MD...)
Country

Organisation name
BETSI CADWALADR UNIVERSITY
LHB
Address
EXECUTIVE OFFICES, YSBYTY
GWYNEDD
PENRHOSGARNEDD
BANGOR GWYNEDD
Post Code
LL57 2PW
Country
WALES

IN46

- ☒ NHS/HSC Site
☐ Non-NHS/HSC Site

Forename
Middle name
Family name
Email
Qualification
(MD...)
Country

Organisation name
HYWEL DDA UNIVERSITY LHB
Address
CORPORATE OFFICES, YSTWYTH
BUILDING
HAFAN DERWEN
ST DAVIDS PARK, JOBSWELL
ROAD CARMARTHEN DYFED
Post Code
SA31 3BB
Country
WALES

IN47

☒ NHS/HSC Site☐ Non-NHS/HSC Site

Forename

Middle name

Family name

Email

Organisation name ABERTAWE BRO MORGANNWG
UNIVERSITY LHBQualification
(MD...)Address ONE TALBOT GATEWAY, SEAWAY
DRIVE

Country

SEAWAY PARADE INDUSTRIAL
ESTATEBAGLAN PORT TALBOT WEST
GLAMORGAN

Post Code SA12 7BR

Country WALES

IN48

☒ NHS/HSC Site☐ Non-NHS/HSC Site

Forename

Middle name

Family name

Email

Organisation name CARDIFF & VALE UNIVERSITY LHB

Qualification
(MD...)

Address CORPORATE HEAD QUARTERS

Country

HEATH PARK

CARDIFF SOUTH GLAMORGAN

Post Code CF14 4XW

Country WALES

IN49

☒ NHS/HSC Site☐ Non-NHS/HSC Site

Forename

Middle name

Family name

Email

Organisation name CWM TAF UNIVERSITY LHB

Qualification
(MD...)

Address DEWI SANT HOSPITAL

Country

ALBERT ROAD

PONTYPRIDD MID GLAMORGAN

Post Code CF37 1LB

Country WALES

IN50

- ☒ NHS/HSC Site
☐ Non-NHS/HSC Site

Organisation name ANEURIN BEVAN UNIVERSITY LHB
Address HEADQUARTERS - ST CADOC'S HOSPITAL
LODGE ROAD
CAERLEON NEWPORT GWENT
Post Code NP18 3XQ
Country WALES

Forename
Middle name
Family name
Email
Qualification (MD...)
Country

IN51

- ☒ NHS/HSC Site
☐ Non-NHS/HSC Site

Organisation name POWYS TEACHING LHB
Address GLASBURY HOUSE
BRONLLYS HOSPITAL
BRECON POWYS
Post Code LD3 0LS
Country WALES

Forename
Middle name
Family name
Email
Qualification (MD...)
Country

IN52

- ☒ NHS/HSC Site
☐ Non-NHS/HSC Site

Organisation name NHS Ayrshire and Arran
Address PO Box 13, Boswell House
10 Arthur Street
AYR Scotland
Post Code KA7 1QJ
Country SCOTLAND

Forename
Middle name
Family name
Email
Qualification (MD...)
Country

IN53

- ☒ NHS/HSC Site
☐ Non-NHS/HSC Site

Forename
Middle name

IN54

Organisation name NHS Borders
Address Newstead

Post Code MELROSE Scotland
TD6 9DB
Country SCOTLAND

Family name
Email
Qualification
(MD...)
Country

- ☒ NHS/HSC Site
☐ Non-NHS/HSC Site

Organisation name NHS Fife
Address Springfield House

Post Code CUPAR Scotland
KY15 5UP
Country SCOTLAND

Forename
Middle name
Family name
Email
Qualification
(MD...)
Country

IN55

- ☒ NHS/HSC Site
☐ Non-NHS/HSC Site

Organisation name NHS Greater Glasgow and Clyde
Address J B Russell House

Gartnavel Royal Hospital
1055 Great Western Road
Glasgow Glasgow Scotland
Post Code G12 0XH
Country SCOTLAND

Forename
Middle name
Family name
Email
Qualification
(MD...)
Country

IN56

- ☒ NHS/HSC Site
☐ Non-NHS/HSC Site

Forename
Middle name
Family name
Email

IN57

Organisation name NHS Highland
Address Reay House
17 Old Edinburgh Road
INVERNESS Scotland
Post Code IV2 3HG
Country SCOTLAND

Qualification
(MD...)
Country

- ☒ NHS/HSC Site
☐ Non-NHS/HSC Site

Forename
Middle name
Family name
Email

Organisation name NHS Lanarkshire
Address 14 Beckford Street

HAMILTON Scotland
Post Code ML3 0TA
Country SCOTLAND

Qualification
(MD...)
Country

IN58

- ☒ NHS/HSC Site
☐ Non-NHS/HSC Site

Forename
Middle name
Family name
Email

Organisation name NHS Grampian
Address Summerfield House
2 Eday Road
ABERDEEN Scotland
Post Code AB15 6RE
Country SCOTLAND

Qualification
(MD...)
Country

IN59

- ☒ NHS/HSC Site
☐ Non-NHS/HSC Site

Forename
Middle name
Family name
Email

Organisation name NHS Orkney
Address Garden House
New Scapa Road

Qualification
(MD...)
Country

IN60

KIRKWALL
Orkney Scotland
Post Code KW15 1BQ
Country SCOTLAND

☒ NHS/HSC Site
☐ Non-NHS/HSC Site

Organisation name NHS Lothian
Address Waverley Gate
2-4 Waterloo Place
Edinburgh Scotland
Post Code EH1 3EG
Country SCOTLAND

Forename
Middle name
Family name
Email
Qualification
(MD...)
Country

IN61

☒ NHS/HSC Site
☐ Non-NHS/HSC Site

Organisation name NHS Tayside
Address Ninewells Hospital and Medical
School
James Arrott Drive
Dundee Scotland
Post Code DD1 9SY
Country SCOTLAND

Forename
Middle name
Family name
Email
Qualification
(MD...)
Country

IN62

☒ NHS/HSC Site
☐ Non-NHS/HSC Site

Organisation name NHS Forth Valley
Address 33 Spittal Street

STIRLING Scotland
Post Code FK8 1DX

Forename
Middle name
Family name
Email
Qualification
(MD...)
Country

Country SCOTLAND

IN63

- ☒ NHS/HSC Site
☐ Non-NHS/HSC Site

Forename
Middle name
Family name
Email
Qualification
(MD...)
Country

Organisation name NHS Western Isles
Address 37 South Beach Street
Isle of Lewis STORNOWAY Scotland
Post Code HS1 2BN
Country SCOTLAND

IN64

- ☒ NHS/HSC Site
☐ Non-NHS/HSC Site

Forename
Middle name
Family name
Email
Qualification
(MD...)
Country

Organisation name NHS Dumfries and Galloway
Address Grierson House
The Crichton
Bankend Road DUMFRIES Scotland
Post Code DG1 4ZG
Country SCOTLAND

IN65

- ☒ NHS/HSC Site
☐ Non-NHS/HSC Site

Forename
Middle name
Family name
Email
Qualification
(MD...)
Country

Organisation name NHS Shetland
Address Brevik House
South Road
LERWICK Scotland
Post Code ZE1 0RB
Country SCOTLAND

IN66

☒ NHS/HSC Site☐ Non-NHS/HSC Site

Forename

Middle name

Family name

Email

Qualification
(MD...)

Country

Organisation
name

NICRNP

Address

4th Floor, Dunluce Health Centre
1, Dunluce Avenue
BELFAST

Post Code

BT9 7HR

Country

NORTHERN IRELAND

DRAFT

PART D: Declarations**D1. Declaration by Chief Investigator**

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.
2. I undertake to fulfil the responsibilities of the chief investigator for this study as set out in the UK Policy Framework for Health and Social Care Research.
3. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.
4. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.
5. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.
6. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.
7. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.
8. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.
9. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 2018.
10. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:
 - ◊ Will be held by the REC (where applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
 - ◊ May be disclosed to the operational managers of review bodies, or the appointing authority for the REC (where applicable), in order to check that the application has been processed correctly or to investigate any complaint.
 - ◊ May be seen by auditors appointed to undertake accreditation of RECs (where applicable).
 - ◊ Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.
 - ◊ May be sent by email to REC members.
11. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 2018.
12. I understand that the main REC or its operational managers may share information in this application or supporting documentation with the Medicines and Healthcare products Regulatory Agency (MHRA) where it is relevant to the Agency's statutory responsibilities.
13. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the Health Research Authority (HRA) together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after the issue of the ethics committee's final opinion or the withdrawal of the application.

Contact point for publication *(Not applicable for R&D Forms)*

HRA would like to include a contact point with the published summary of the study for those wishing to seek further information. We would be grateful if you would indicate one of the contact points below.

- ☐ Chief Investigator
- ☐ Sponsor
- ☒ Study co-ordinator
- ☐ Student
- ☐ Other – please give details
- ☐ None

Access to application for training purposes *(Not applicable for R&D Forms)*

Optional – please tick as appropriate:

☐ I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

This section was signed electronically by Prof Gavin Perkins on 22/10/2019 15:11.

Job Title/Post: Professor

Organisation: Warwick

Email: g.d.perkins@warwick.ac.uk

D2. Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co-sponsors by a representative of the lead sponsor named at A64-1.

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.
2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.
3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.
4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.
5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.
6. The responsibilities of sponsors set out in the UK Policy Framework for Health and Social Care Research will be fulfilled in relation to this research.
7. The statutory responsibilities of sponsors set out in the Medicines for Human Use (Clinical Trials) Regulations 2004 will be undertaken in relation to this trial.

Please note: The declarations below do not form part of the application for approval above. They will not be considered by the Research Ethics Committee.

8. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.
9. Specifically, for submissions to the Research Ethics Committees (RECs) I declare that any and all clinical trials approved by the HRA since 30th September 2013 (as defined on IRAS categories as clinical trials of medicines, devices, combination of medicines and devices or other clinical trials) have been registered on a publically accessible register in compliance with the HRA registration requirements for the UK, or that any deferral granted by the HRA still applies.

This section was signed electronically by Mrs Jane Prewett on 24/10/2019 10:59.

Job Title/Post: Head of Research Governance
Organisation: University of Warwick
Email: jane.prewett@warwick.ac.uk