

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

SUBSTANTIAL AMENDMENT FORM <sup>1</sup>

## NOTIFICATION OF A SUBSTANTIAL AMENDMENT TO A CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE TO THE COMPETENT AUTHORITIES AND FOR OPINION OF THE ETHICS COMMITTEES IN THE EUROPEAN UNION

*For official use:*

|   |  |
|---|--|
| Date of receiving the request:                        | Grounds for non acceptance/negative opinion: |
|   | Date:  |
| Date of start of procedure:                           | Authorisation/ positive opinion:             |
|   | Date:  |
| Competent authority registration number of the trial: | Withdrawal of amendment application:         |
| Ethics committee registration number of the trial:    | Date:  |

*To be filled in by the applicant:**This form is to be used both for a request to the Competent Authority for authorisation of a **substantial** amendment and to an Ethics Committee for its opinion on a **substantial** amendment. Please indicate the relevant purpose in Section A.*

## A TYPE OF NOTIFICATION

**A.1 Member State in which the substantial amendment is being submitted:**

United Kingdom

**A.2 Notification for authorisation to the competent authority:**☐**A.3 Notification for an opinion to the ethics committee:**☒

<sup>(1)</sup> Cf. Section 3.7.b of the Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (OJ, C82, 30.3.2010, p.1) hereinafter referred to as 'detailed guidance CT-1'.

## B TRIAL IDENTIFICATION (When the amendment concerns more than one trial, repeat this form as necessary.)

**B.1 Does the substantial amendment concern several trials involving the same IMP?** <sup>2</sup> ☐ Yes ☒ No**B.2 EudraCT number:** 2019-001688-66**B.3 Full title of the trial:** Sugar or Salt (SOS) trial: Hyperosmolar therapy in traumatic brain injury**B.4 Sponsor's protocol code number:** SC.14/18.19**B.4 Sponsor's protocol version number:** 2.0**B.4 Sponsor's protocol date:** 15/08/2019

<sup>(2)</sup> Cf. Section 3.7. of the detailed guidance CT-1

**C IDENTIFICATION OF THE SPONSOR RESPONSIBLE FOR THE REQUEST**

**C.1 Sponsor**

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

**C.2 Legal representative <sup>3</sup> of the sponsor in the European Union for the purpose of this trial (if different from the sponsor)**

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

*(3) As stated in Article 19 of Directive 2001/20/EC.*

**D APPLICANT IDENTIFICATION, (please tick the appropriate box)**

**D1. Request for the competent authority**

D.1.1 Sponsor ☐  
D.1.2 Legal representative of the sponsor ☐  
D.1.3 Person or organisation authorised by the sponsor to make the application. ☐  
D.1.4 Complete below:

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

**D2. Request for the Ethics Committee**

- D.2.1 Sponsor ☒
- D.2.2 Legal representative of the sponsor ☐
- D.2.3 Person or organisation authorised by the sponsor to make the application. ☐
- D.2.4 Investigator in charge of the application if applicable<sup>4</sup>:
- Co-ordinating investigator (for multicentre trial): ☐
  - Principal investigator (for single centre trial): ☐
- D.2.5 Complete below:

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

Telephone 02476575732

Fax

E-mail sponsorship@warwick.ac.uk

<sup>(4)</sup> According to national legislation.

**E SUBSTANTIAL AMENDMENT IDENTIFICATION****E.1 Sponsor's substantial amendment information for the clinical trial concerned:**

Code Number: 4.0

Version:

Date: 2020/04/02

**E.2 Type of substantial amendment**

E.2.1 Amendment to information in the CT application form ☒ Yes ☐ No

E.2.2 Amendment to the protocol ☒ Yes ☐ No

E.2.3 Amendment to other documents appended to the initial application form ☒ Yes ☐ No

If yes specify:

Changes to the GP letter\_GOS-E to inform GPs of the payment available.

Changes to the patient information sheets and consent forms.

E.2.4 Amendment to other documents or information: ☐ Yes ☒ No

If yes specify:

E.2.5 This amendment concerns mainly urgent safety measures already implemented<sup>5</sup>: ☐ Yes ☒ No

E.2.6 This amendment is to notify a temporary halt of the trial<sup>6</sup>: ☐ Yes ☒ No

E.2.7 This amendment is to request the restart of the trial<sup>7</sup>: ☐ Yes ☒ No

<sup>(5)</sup> Cf. Section 3.9. of the detailed guidance CT-1.

<sup>(6)</sup> Cf. Section 3.10. of the detailed guidance CT-1

<sup>(7)</sup> Cf. Section 3.10. of the detailed guidance CT-1

**E.3 Reasons for the substantial amendment:**

E.3.1 Changes in safety or integrity of trial subjects

☐ Yes ☒ No

E.3.2 Changes in interpretation of scientific documents/value of the trial

☐ Yes ☒ No

E.3.3 Changes in quality of IMP(s)

☐ Yes ☒ No

E.3.4 Changes in conduct or management of the trial

☒ Yes ☐ No

E.3.5 Change or addition of principal investigator(s), co-ordinating investigator

☐ Yes ☒ No

E.3.6 Change/addition of site(s)

☐ Yes ☒ No

E.3.7 Other change

☒ Yes ☐ No

E.3.7.1 If yes specify:

To bring to your attention the addition of a trial website and a trial Twitter account.

E.3.8 Other case

☐ Yes ☒ No

E.3.8.1 If yes specify:

**E.4 Information on temporary halt of trial:<sup>8</sup>**

E.4.1 Date of temporary halt

E.4.2 Recruitment has been stopped

☐ Yes ☐ No

E.4.3 Treatment has been stopped

☐ Yes ☐ No

E.4.4 Number of patients still receiving treatment at time of the temporary halt in the MS concerned by the amendment

E.4.5 Briefly describe:

Justification for a temporary halt of the trial (*free text*):

The proposed management of patients receiving treatment at time of the halt (*free text*):

The consequences of the temporary halt for the evaluation of the results and for overall risk benefit assessment of the investigational medicinal product (*free text*):

<sup>(8)</sup> Cf. Section 3.10. of the detailed guidance CT-1

**F DESCRIPTION OF EACH SUBSTANTIAL AMENDMENT<sup>9</sup>**

Please use this section to detail each substantial amendment which is being notified. If you are notifying more than one substantial amendment, please use the "Add Amendment" button as required

Substantial amendment 1

**Previous and new wording:(tracked)**

Changes to approved documents - please see tracked change versions attached:

SOS Protocol V2.0 15/08/2019, replaced by SOS Protocol V3.0 11/03/2020

GP letter\_GOS-E V1.0 17/04/2019, replaced by V2.0 26/02/2020

SOS Patient Information Sheet V3.0 22/10/2019, replaced by V4.0 26/02/2020

SOS PerLR Pre Enrolment Information Sheet V3.0 22/10/2019, replaced by V4.0 26/02/2020

SOS PerLR Post Enrolment Information Sheet V3.0 22/10/2019 replaced by V4.0 26/02/2020

SOS ProfLR Pre Enrolment Information Sheet V2.0 22/10/2019, replaced by V3.0 26/02/2020

SOS ProfLF Post Enrolment Information Sheet V2.0 22/10/2019, replaced by V3.0 26/02/2020

SOS Consent Form - Patient post-enrolment V1.0 31/05/2019, replaced by V2.0 26/02/2020

SOS Consent Form - PerLR pre-enrolment V1.0 31/05/2019, replaced by V2.0 26/02/2020

SOS Consent Form - PerLR post-enrolment V1.0 31/05/2019, replaced by V2.0 26/02/2020

SOS Consent Form - ProfLR post-enrolment V1.0 31/05/2019, replaced by V2.0 26/02/2020

**New wording:**

New documents:

SOS Consent form - ProfLR pre-enrolment V1.0 26/02/2020

SOS - Follow up reminders V1.0 03/03/2020

SOS Twitter Account Guidance V1.0 06/02/2020

**Comments/ explanation/ reasons for substantial amendment:**

Main changes to trial protocol:

- Contact details updated to reflect change in Trial Manager.
- Following correspondence with CAG throughout the initial approvals process, it was agreed that screening by the patient's direct clinical care team was permitted under the Medicines for Human Use (Clinical Trials) Regulations and CAG approval was not required. As SOS falls outside of CAG's remit, mention of applying for section 251 support has been removed from the protocol.
- Addition of text message/email reminder sent to patients or their legal representatives to inform them when the follow up questionnaires have been posted to them. This is to help encourage completion and return of follow up information.
- Addition of the use of a paper-based emergency randomisation system at WCTU as a back up to the online database.
- Reference to hypertonic saline 3% has been changed to the correct concentration of 2.7% to ensure the protocol is in line with the SmPC and CTA application.
- Clarification that only the PI's CV and GCP certificate will be collected by WCTU, in line with WCTU procedures. CVs and evidence of GCP training for other site staff should be made available on request for monitoring purposes.
- Minor changes to list of abbreviations.
- Minor clarifications and corrections of typographical errors.

Changes to GP letter\_GOS-E:

Addition of payment details to inform GPs of the £20 reimbursement available for completing and returning the patient's GOS-E score.

Changes to Patient Information Sheets:

Removal of the words 'send a text message to' from page 8 of the PIS to allow the trial team at WCTU to contact the patient/legal representative by other means if needed to alert them that a questionnaire is on its way or has not been completed e.g. if the patient/legal representative changes their phone number, an email could be sent instead of a text message.



**Changes to consent forms:**

Addition of clause to obtain explicit consent from the patient/legal representative for WCTU to use the contact details they have provided to contact them about the study. This could be via phone, text message, email or letters sent in the post.

**Professional legal representative consent form:**

An additional consent form has been produced to document written informed consent obtained from a professional legal representative before the patient is enrolled into the study. A professional legal representative pre-enrolment information sheet (V2.0 22/10/2019) was submitted and approved with the initial application.

**Example follow up reminders:**

Examples of text messages and emails for reminding patients or their legal representatives to complete their follow up questionnaires have been produced. A text or email will be sent from WCTU to let them know once the questionnaire is on its way to them. A text or email may also be sent to act as a reminder in cases where a completed questionnaire is not returned to WCTU. The content of the example text message and email reminders have been reviewed by PPI representatives.

**Addition of website and Twitter account:**

As mentioned in the initial application, SOS has a University of Warwick owned website, which is expected to provide information and trial updates for site staff and the research community. To provide more detail, the website will provide information on the trial, sites, traumatic brain injury and the evidence and support for the trial. This may include the use of video clips and statements from PPI representatives. The website will have information for health professionals and will include training materials and frequently asked questions. Any publicity and publications/trial results will also be made available on the website. The website will not be signposted to patients or the general public, however as it is in the public domain, they may come across it if they were to search for it. We will therefore also include an information for the public page, which will use wording from the current approved patient information sheets.

The SOS Twitter account will be used to generate interest and advertise progress of the trial to the medical community. From experience with other trials, the use of Twitter has significant benefit in motivating sites and sharing trial news. The Twitter account will be updated regularly with content around general recruitment and site updates, any trial learning, news about upcoming weeks, noteworthy achievements and publications. Tweets will be directed at clinicians and site staff, and will not be directed at patients. The Twitter account will be managed by the SOS co-investigators and the trial team at WCTU, where we will have oversight of content and followers. A guidance document on the use of the Twitter account has been put together (attached) to inform sites of the role of the Twitter account, and to reiterate appropriate use of the account e.g. should they 're-tweet' or 'tag' the SOS account in any of their posts. Patients will not be signposted to the Twitter account.

*(9) Cf. Section 3.7.c. of the detailed guidance CT-1. The sponsor may submit this documentation on a separate sheet.*

## G CHANGE OF CLINICAL TRIAL SITE(S)/INVESTIGATOR(S) IN THE MEMBER STATE CONCERNED BY THIS AMENDMENT

**Type of change:****G.1.1 Addition of a new site****G.1.1.1 Principal investigator** (provide details below)

Given name  
Middle name(if applicable)  
Family name  
Qualification (MD...)  
Professional address

**G.1.2 Removal of an existing site****G.1.2.1 Principal investigator** (provide details below)

Given name  
Middle name(if  
applicable)  
Family name  
Qualification  
(MD...)  
Professional  
address

**G.1.3 Change of co-ordinating investigator** (provide details below of the new coordinating investigator)

Given name  
Middle name(if  
applicable)  
Family name  
Qualification  
(MD...)  
Professional  
address

G.1.3.6 Indicate the name of the previous co-ordinating investigator:

**G.1.4 Change of principal investigator at an existing site** (provide details below of the new principal investigator)

Given name  
Middle name(if  
applicable)  
Family name  
Qualification  
(MD...)  
Professional  
address

G.1.4.6 Indicate the name of the previous principal investigator:

**H CHANGE OF INSTRUCTIONS TO CA FOR FEEDBACK TO SPONSOR**

**H.1 Change of e-mail contact for feedback on application\***

**H.2 Change to request to receive an .xml copy of CTA data**

☐ Yes ☒ No

H.2.1 Do you want a .xml file copy of the CTA form data saved on EudraCT?

☐ Yes ☒ No

H.2.1.1 If yes provide the e-mail address(es) to which it should be sent (up to 5 addresses):

**H.2.2 Do you want to receive this via password protected link(s)<sup>10</sup>?**

☐ Yes ☒ No

If you answer no to question H.2.2 the .xml file will be transmitted by less secure e-mail link(s)

**H.2.3 Do you want to stop messages to an email for which they were previously requested?** ☐ Yes ☒ No

H.2.3.1 If yes provide the e-mail address(es) to which feedback should no longer be sent:

(\*This will only come into effect from the time at which the request is processed in EudraCT).

(10) This requires a EudraLink account. (See [eudract.emea.europa.eu](http://eudract.emea.europa.eu) for details)

#### I LIST OF THE DOCUMENTS APPENDED TO THE NOTIFICATION FORM (cf. Section 3.7 of detailed guidance CT-1)

*Please submit only relevant documents and/or when applicable make clear references to the ones already submitted. Make clear references to any changes of separate pages and submit old and new texts. Tick the appropriate box(es).*

**I.1 Cover letter**



**I.2 Extract from the amended document in accordance with Section 3.7.c. of detailed guidance CT-1 (if not contained in Part F of this form)**



**I.3 Entire new version of the document<sup>11</sup>**



**I.4 Supporting information**



**I.5 Revised .xml file and copy of initial application form with amended data highlighted**



**I.6 Comments on any novel aspect of the amendment if any :**

(11) Cf. Section 3.7.c. of the detailed guidance CT-1

#### J SIGNATURE OF THE APPLICANT IN THE MEMBER STATE

*Please submit only relevant documents and/or when applicable make clear references to the ones already submitted. Make clear references to any changes of separate pages and submit old and new texts. Tick the appropriate box(es).*

**J.1 I hereby confirm that/ confirm on behalf of the sponsor that** (delete which is not applicable)

- The above information given on this request is correct;
- The trial will be conducted according to the protocol, national regulation and the principles of good clinical practice; and
- It is reasonable for the proposed amendment to be undertaken.

**J.2 APPLICANT OF THE REQUEST FOR THE COMPETENT AUTHORITY**(as stated in section D.1): ☐

J.2.1 Signature <sup>12</sup>: .....

J.2.2 Print name:

J.2.3 Date:

**J.3 APPLICANT OF THE REQUEST FOR THE ETHICS COMMITTEE** (as stated in section D.2): ☐

J.3.1 Signature <sup>13</sup>: .....

J.3.2 Print name:

J.3.3 Date:

This section was signed electronically by Mrs Jane Prewett on 02/04/2020 16:05.

Job Title/Post: Head of Research Governance

Organisation: University of Warwick

Email: jane.prewett@warwick.ac.uk

*(12) On an application to the Competent Authority only, the applicant to the Competent Authority needs to sign.*

*(13) On an application to the Ethics Committee only, the applicant to the Ethics Committee needs to sign.*