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)
EVIS

1. Is your project research?

(●) Yes ( ) No

2. Select one category from the list below:

(●) Clinical trial of an investigational medicinal product

( ) Combined trial of an investigational medicinal product and an investigational medical device

( ) Clinical investigation or other study of a 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 UKCA/CE UKNI/CE Mark, or a UKCA/CE UKNI/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)

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

◉ Yes ○ No

5c. You have indicated that your study has sites located in England. For the research sites located in England, do you wish for the study to be considered for NIHR Clinical Research Network (CRN) support and inclusion in the NIHR Clinical Research Network (CRN) Portfolio? Please see information button for further details

◉ Yes ○ No

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 familar to lay reviewers of the application.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
EVIS

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

REC Name:
Scotland A

REC Reference Number:
22\SS\0009

Submission date:
21/12/2021

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

Early vasopressors in Sepsis

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

- (●) National coordinating investigator
- ( ) Principal investigator

Given name	Alasdair
Family name	Corfield
Qualification (MD...)	MBCHB, MRCP(UK), FRDEM< MPH
ORCID ID	0000 0003 0878 7867
Institution name	NHS Greater Glasgow & Clyde
Institution department name	Royal Alexandria Hospital
Street address	Corsebar Road
Town/city	Paisley
Post Code	PA2 9PN
Country	United Kingdom

Work E-mail	alasdair.corfield@ggc.scot.nhs.uk
* Personal E-mail	
Work Telephone	01413146601
* Personal Telephone/Mobile	
Fax	

** 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
		Pamela	Sandu
Address	Research & Innovation		
	Dykebar Hospital, Ward 11		
	1st floor, Grahamston Road		
Post Code	PA2 7DE		
E-mail	pamela.sandu@ggc.scot.nhs.uk		
Telephone	01413144012		
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):	GN20AE342
Sponsor's/protocol number:	GN20AE342
Protocol Version:	2.0
Protocol Date:	16/12/2022
Funder's reference number (enter the reference number or state not applicable):	NIHR132594
Project website:	https://www.evis.scot.nhs.uk/

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):	
ClinicalTrials.gov Identifier (NCT number):	NCT05179499
European Clinical Trials Database (EudraCT) number:	2021-006886-39

Additional reference number(s):

Ref.Number Description	Reference Number
N/A	N/A

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.*

Sepsis is a life-threatening reaction to an infection. It happens when the immune system overreacts to an infection and starts to damage the body's tissues and organs.

The aim of this research study is to compare the effectiveness of giving a vasopressor drug (norepinephrine) against a Balanced Crystalloid both of which are given via a drip in the arm. Vasopressors work by increasing the blood pressure which allows a better blood flow to internal organs. We plan to see which is better and to see if they have a role in improving a patient's recovery time, reducing complications, the length of time they stay in hospital and longer term poor health.

Based on research that has already been done, we believe treating patients with vasopressors when they arrive in the Emergency Department, may have potential advantages over the standard fluids used today. However, the evidence is not clear and that is why we are doing this research.

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.

Current practice in the UK is guided by NICE Sepsis Guidance and the International Surviving Sepsis Campaign (SSC) consensus recommendations. Both specify intranvenous fluid administration as a central tenet of early resuscitation od patients with septic shock, with intravenous vasopressor administration recommended after intravenous fluid resuscitation. NICE recommend boluses of 500ml of crystalloid and "refer to critical care for review of management including need for central venous access and initiation of vasopressors." SSC recommend 30ml/kg crystalloid in first hour, followed by vasopressors to maintain MAP>65.

The current NICE fluid resuscitation guideline, November 2020 continues to emphasise 500ml boluses of crystalloid as usual care. A recent international survey of 100 critical care and EM physicians regarding intravenous fluid resucitation ractice, confirmed that an initial bolus of 1000ml of crystalloid followed by 500ml boluses of crystalloid remained the most common management strategy for the initial treatment of septic shock. This persisted despite the lack of benefit demonstrated in three landmark trials of protocolised sepsis management. f benefit demonstrated in three landmark trials of protocolised sepsis.

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 determine whether early PVI (peripheral vasopressor infusion) (within 12 hours of admission) targeted to MAP of > 65 mmHG improves clinical effectiveness (30 day mortality) in hospitalised adult patients with septic shock compared with usual care, in the first 48 hours.

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

Secondary objectives are to assess the effects of PVI, compared with usual care, on clinical, patient centred, health service and economic outcomes in the acute hospital setting and during the six months after participant randomisation. These will include protocol adherence and safety outcomes

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

Globally, 27 million people develop sepsis every year occurring in all ages and social groups. 1 in 5 patients with sepsis die in the UK and if they are critically unwell with low blood pressure "shock" this increases to 1 in every 3 patients dying. Survivors can face lifelong complications including depression, weakness and chronic pain. Like heart attacks and strokes, sepsis needs to be treated quickly after it develops. Current UK and international guidelines focus on the public and professionals recognising sepsis early and delivering early treatment with

antibiotics, fluids via a drip into a vein and other treatments. Medication to improve blood pressure (vasopressors) are also recommended later in treatment guidelines after initial attempts to stabilise the patient. There is evidence based on observations looking back at previous patients that using vasopressors earlier in the patient journey may be beneficial. There has been no prospective clinical study looking at whether these potential benefits remain when vasopressors are given via a small drip in the arm as part of early treatment when the patient arrives in hospital.

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.*

The study will investigate two different approaches to early treatment, in very unwell patients who have sepsis. Patients will either receive standard treatment with early intravenous fluid resuscitation and later use of vasopressors as required, or early use of vasopressors with additional intravenous fluid resuscitation as required.

Patients who meet the study entry criteria will be asked to be involved by trained clincial or research staff. If they consent they will be randomly allocated to either standard treatment or early vasopressor treatment for the first 48 hours after the start of the study. All other care will be decided by the clinician in communication with the patient. Patients will be free to withdraw from the study at any time. This type of clinical study design, known as randomised, is the best study design to allow us to decide if there is any difference between these two approaches.

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?

- [x] Design of the research
- [x] Management of the research
- [x] Undertaking the research
- [x] Analysis of results
- [x] Dissemination of findings
- [ ] None of the above

Give details of involvement, or if none please justify the absence of involvement.
We have PPI during the study design including a PPI co-applicant from the charity Sepsis Research. Our PPI engagement has shaped the choice of outcomes used and the group has reviewed relevant documentation. We will continue to work with our existing sepsis PPI group when the study is running, when the results are available and during the write up of the study. Lastly we anticipate significant PPI in sharing the results with health care professionals, charities and guideline groups.

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
- [x] 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: 18	Years
Upper age limit:	Years

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

Age 18 years and over
Clinically suspected or proven infection resulting in principal reason for acute illness
SBP<90mmHg or MAP of < 65mmHg
Measured serum lactate of >2mmol/L at the time of eligibility assessment
Hospital presentation within last 12 hours

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

>1500ml of intravenous fluid prior to screening
Clinically judged to require immediate surgery (within one hour of eligibility assessment)
Immediate (<1 hour) requirement for central venous access
Chronic renal replacement therapy
Known allergy/adverse reaction to norepinepherine
Palliation/end of life care (explicit decision by family/care in conjunction with clinical team that active treatment beyond symptomatic relief is not appropriate)
Previous recruitment in the trial
Patients with permanent incapacity
Pregnancy. All women of childbearing potential (WoCBP) must have a negative urine or serum pregnancy test result completed as part of screening requirements. WoCBP are defined as fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
Other primary causes of shock (e.g. suspected cardiogenic shock, haemorrhagic shock, etc)
History or evidence of any other medical, neurological or psychological condition that would expose the subject to an undue risk of a significant Adverse Effect as determined by the clinical judgement of the investigator
Participation in other clinical trials of investigational medicinal products

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
Informed consent	1	0	30	Member of the research team
Review of inclusion / exclusion criteria	1	0	15	Member of the research team
Study Questionnaire (EQ-5D)	3	0	5	Member of the research team
Adverse event review	5	0	10	member of the research team

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	15	Clinician
Vital signs	6	6	10	as per standard of care - nursing stadd
Routine blood tests	6	6	10	as per standard of care eg phlebotomist
Con med review	12	3	5	member of the study team
IV fluid administration	5	5	10	member of the clinical care team
IV norepinepherine	5	5	15	member of the clinical care team

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?

90 days (3 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.

Extravasation - the inadvertent leakage of any drug or fluid into the surrounding tissue. We will minimise the risk of

this by regular hourly monitoring of the infusion site to enable early recognition and management of extravasation events. An extravasation management plan will be provided to ensure the correct guidance is available and followed.

Fluid administration - potential risk of fluid overload, including acute congestive heart failure, breathing difficulties and increased peripheral oedema.

Vasopressor administration - cardiac ischaemia, cardiac dysrhythmias, bowel ischemia or limb ischemia. Patients receiving vasopressors in either arm will be cared for in an appropriate clinical environment where any complications can be appropriately acted upon

Blood samples - extra volumes will be taken for future ethically approved research. Where possible additional research blood samples will be obtained at the same time as routine blood samples. The risks of drawing blood are uncommon and include bleeding and bruising. Any blood sampling undertaken will be done so by staff with the appropriate training.

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

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

There will not be a direct medical benefit to the participants taking part in the study. The collection of data for the study will mean that participants are closely monitored.

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.*

At the end of the trial, participants will return to usual care as defined by local and national guidelines which may include continuation of the protocol assigned treatment.

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

There are no additional risks for the researchers above that of normal standard of care.

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).*

The patient will receive routine acute clinical care assessment including severity of illness assessment and be treated in accordance with current UK guidelines. This includes measuring serum lactate. All women of childbearing potential, regardless of contraception use must have pregnancy excluded. The results of these will inform trial eligibility and the patient will be approached as soon as these are available.

The research team, where it is locally agreed that they are part of the clinical care team will identify patients using triage information and clinical or electronic records in the Emergency Department, Medical or Surgical Assessment Units or any other area used for acute assessment in the recruiting site. In this case it is anticipated that they would identify patients and make the first approach. Any member of the clinical team who has received general and trial specific training and is on the delegation log may also identify patients this way.

Where researchers are not considered to be part of the research team, the researcher should ask a member of the

direct care team to identify suitable patients and ask permission from the patient (or patients family) to be approached by the researcher to discuss.

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:
All patients will be identified by the clinical team responsible for the patient

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 (or carer) will be approached by appropriately trained members of the research team. Participants will be fully informed of the study and will have the oppourtunity to ask questions. The patient information sheet will be given to the patient (or carer) and they will be encouraged to read it carefully and discuss its contents with family, friends or their GP. Patients will be given at most 30-40 minutes but may only be 10-15 if they feel happy to make a decision. This is to ensure there is no delay in administering treatment.

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.

Potentially eligible participants who are willing to take part in the study, and have capacity to do so, will be asked to provide written informed consent. Consent will be obtained by GCP trained members of the clinical team, or members of the research team who have been delegated this responsibility. A record of eligibility will be made recorded in the participant's clinical notes.
The patient will be given a Patient Information Sheet (PIS), which will explain the aims of the trial and the potential risks and benefits of the study treatments. If necessary, a Summary PIS will be provided first to provide a brief outline of the study and allow potential participants to decide whether or not they wish to proceed and before the full Patient Information Sheet is provided.

The patient will be given enough time to consider the trial and ask questions regarding their participation in the trial. Due to nature of the study the treatment will start ideally within one hour and there may not be long for the participant to consider the trial. Ideally, a period of 30-40 minutes will be given but it may be only 10-15 minutes due to the need for fluid resuscitation to begin. The research teams are experienced at recruiting patients and given the nature of the intervention and the burden of the trial we believe this to be reasonable. Potential participants will receive adequate oral and written information. The oral explanation to the patient will be performed by a member of the research team or a trained and delegated member of the clinical team and must cover all the elements specified in the Participant Information Sheet and Consent Form. The patient must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The patient must be given sufficient time to consider all the information provided. It should be emphasised that the patient may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by representatives of the sponsor(s).

The Investigator or delegated member of the trial team and the participant will sign and date the Consent Form to confirm that consent has been obtained. If the participant is unable to sign the consent form for themselves then the witnessed verbal consent form can be used.

The original consent form will be filed in the Investigator Site File (ISF), the participant will receive a copy of this document and a copy filed in the participant's medical notes.

Due to the emergency nature of the clinical trial and the need for assessment and decisions to be made under pressure and within tight timescales it is an anticipated that this may, on occasion, result in some unintentional issues during the consent process. Should the consent form not be fully completed or completed incorrectly at the time of the consent process then as soon as feasibly possibly and at least prior to the date of the discharge responsible parties should complete or amend the form as appropriate as per the intention on the day of consent. Any additions or changes to the consent form should be initialed and dated by the responsible party. Where this is not possible, for reasons other than incapacity of the patient, the reason for incomplete consent should be fully documented within the patients' medical records.

Capacity will be assessed by the Principal Investigator (PI) or a clinician responsible for the treatment of the participant. This assessment of capacity will be documented in the participant's medical records. If patients lack capacity and it is not categorised as permanent incapacity, then the processes in Part B section 6 will be followed.

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

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

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

Patients (or carer) will be given up to 40 minutes to consider the trial this is to ensure to delay in administering treatment.

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?

Co-enrollment in observational studies will be permitted.

Other CTIMP enrollment is not permitted, however where participants who are in long-term follow up (where only data is being collected) co-enrolment may be permitted if both sponsors agree.

Participants who are active in the interventional phase of a non-CTIMP may be co-enrolled to the EVIS study – this must be agreed in advance and a co-enrolment checklist must be completed before co-enrolment can commence.

In addition, when considering permitting co-enrolment, investigators should be mindful of the potential burden upon participants, their families and research staff.

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 prepare patient facing documentation in other common languages, and use NHS translation services for verbal communication

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?

The research team acknowledges that National Institute for Social Care and Health Research (NISCHR) Permissions coordinating Unit (PCU) commits to provide bilinguial or Welsh translations of patient facing information to be provided to study participants on request. Should bilinguial or welsh translations of patient facing documents be requested at study sites, the research team will contact NISCHR PCU to arrange translation of these documents through the NISCHR PCU translation service.

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?

If updated information becomes available whilst a patient is still participating in the study, the patient information sheet will be updated and patients will be issues with a copy of the new information and reconsented to the study as appropriate.

The responsible clinician and/or local PI will inform the participant of clinically relevant information. If required the GP will be contacted also.

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)*

- [x] Access to medical records by those outside the direct healthcare team
- [ ] Access to social care records by those outside the direct social care team
- [x] 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
- [x] Storage of personal data on any of the following:
  - [x] Manual files (includes paper or film)
  - [x] NHS computers
  - [ ] Social Care Service computers
  - [ ] Home or other personal computers
  - [x] University computers
  - [ ] Private company computers
  - [ ] Laptop computers

Further details:

A37. Please describe the physical security arrangements for storage of personal data during the study?

In this study the location of the majority of the source data will be the hospital medical records including subject case notes and laboratory records. The source data transcribed into the eCRF from the medical records must be accurate and verifiable. For questionnaires completed by trial participants the completed questionnaires will be regarded as

the source data location. In cases where data is transcribed directly into the eCRF and no other paper or electronic source exists then the eCRF will be considered as the source record. In these cases, this data should be prospectively documented in the medical records to ensure a full record of the trial is available at site.

Personal information will be collected via the eCRF to enable record linkage to be carried out and to provide a copy of the informed consent form to the study monitors. These data items will be encrypted and only authorised individuals will have access i.e. the person performing the record linkage, participating site staff and the trial monitors. All electronic data will be held in accordance with ISO 27001:2013 at the Edinburgh 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 Edinburgh Clinical Trials Unit staff are required to sign confidentiality agreements and to follow standard operating procedures in accordance with Good Clinical Practice and ISO certification.

The trial data manager, statistician and any other members of staff who will perform data related tasks will only be able to access depersonalised data where the participants identifying information is replaced by a unique study identifier.

An eCRF, developed by the Edinburgh Clinical Trials Unit, will capture all data required to meet the protocol requirements. Access to the eCRF will be restricted, via a study-specific web portal and only authorised site-specific personnel will be able to make enteries to their patients' data via the web portal. The investigator or his/her designee will be responsible for all enteries into the eCRF and will confirm that the data are accurate, complete and verifiable.

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.*

Statisticians will have access to de-identified data which will include the CHI number to enable record linkage.

At a local site level only those that have been trained and approved will be able to enter or view any data via the web portal. Each site can only see their own patients' data. Patient consent forms will be stored at the study site in a secure location accessible only to the study teams.

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?

Data management will be provided by Edinburgh Clinical Trials Unit

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

	Title	Forename/Initials	Surname
	Dr	Alasdair	Corfield
Post	Emergency Consultant (NOT DATA CONTROLLER)		
Qualifications	MBCHB, MRCP(UK), FRCEM, MPH		
Work Address	Royal Alexandria Hospital		
	Corsebar Road		
	Paisley		
Post Code	PA2 9PN		
Work Email	alasdair.corfield@ggc.scot.nhs.uk		
Work Telephone	01413146601		
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:
Based on written, informed consent, electronic record linkage will be undertaken to assess for patient health and wellbeing including NHS resource use.

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

Years: 25
Months:

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.*

All electronic data will be held securely in accordance with ISO 27001:2013 on the servers at Edinburgh Clinical Trials Unit. These data items will be encrypted and only those individuals who require to see these data i.e. the person performing the record linkage and site research team staff or the study monitor as appropriate will be able to view them.

Long term storage arrangements for the study data will follow SOPS and data will be archived/destroyed accordingly. Any additional research utilising this data will be subject to grants/funding and appropriate regulatory approvals.

Personal data will be collected and stored in compliance with the Data Protection Act 2018 and GDPR.

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

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.

A49-2. Will you seek permission from the research participants to inform their GP or other health/ care professional?

◉ Yes ○ No

It should be made clear in the participant's information sheet if the GP/health professional will be informed.

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.
This trial will be registered with clinicaltrials.gov

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?

No identifiable personal data will be published

A53. How and when will you inform participants of the study results?

If there will be no arrangements in place to inform participants please justify this.
Patients will be offered contact details to find out final results if they wish. We can send trial results on request where appropriate.

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:
We have collaborated with a multi-disciplinary team of UK experts in sepsis, emergency care and critical care, alongside methodologists and clinicians with strong track records in delivering large-scale NHS trials for emergency, acute and critical care medicine.

Our patient and public collaborators have been involved through every stage of this project, and will continue to do so as the project progresses. The primary research question was identified in partnership with the James Lind Alliance as part of a priority setting exercise. We have partnered with two large organisations - Sepsis Research (FEAT) and UK Sepsis Trust, in addition to working with our previous Sepsis PPI group. These groups, which include patients and relatives who have experienced sepsis and acute hospital care, provide crucial insights for our proposed study and its acceptability for NHS patients.

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
	Dr	Jacqueline	Stephen
Department	Edinburgh Clinical Trials Unit		
Institution	Edinburgh Clinical Trials Unit		
Work Address	Usher Institute		
	Level 2, Nine Edinburgh Quarter		
	9 Little France Road		
Post Code	EH1 4UX		
Telephone	+44 (0)131 651 9952		

Fax
Mobile
E-mail Jacqueline.Stephen@ed.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?

To determine whether early peripheral vasopressor infusion (PVI) targeted to MAP of > 65 mmHG improves clinical effectiveness (30 day mortality) in hospitalised adult patients with septic shock compared with usual care in the first 48 hours.

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

Secondary objectice are to assess the effects of PVI, compared with usual care, on clinial, patient centred, health service and economic outcomes in the acute hospital setting and during three months follow-up post randomisation. These will include protocol adherence and safety outcomes.

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: 3286
Total international sample size (including UK): 3286
Total in European Economic Area:

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 sample size is based on clinical consensus of a minimal clinically important difference, likely economic benefit and the findings of previous studies (See section 4), we have chosen a difference in 30-day all-cause mortality of 5% for the primary outcome. The study would require 2928 randomised participants to detect this 5% difference (control 25% vs. intervention 20%) at 90% power and 5% level of significance (Stata 15.1 'power twoproportions'). This is increased to a maximum 3187 participants to allow for up to four interim analyses under a non-binding Hwang-Shih-DeCani spending function group sequential design (R 3.4.1 gsDesign module), which allows for early stopping for either overwhelming evidence of benefit, or for futility; and then further adjusted upwards to 3286 to allow 3% randomised missing data for 30-day mortality.
The Data Monitoring Committee (DMC) will consider advising the Trial Steering Committee (TSC) on re-estimation of the sample size based on aggregated, blinded data on the first 200 participants with complete 30-day mortality data available at around 1 month from the end of the 6-month internal pilot. Any other new relevant trial data will also be considered to inform discussions. The final decision on re-estimation of the sample size will be taken by the Chief Investigator and Trial Management Group.

A61. Will participants be allocated to groups at random?

(●) Yes ( ) No

If yes, please give details of the intended method of randomisation:
Randomisation will happen at baseline and will be done via IVRS. The investigator will allocate the participant a study specific identifier and the system will check the participants eligibility from information already entered in the eCRF and the randomisation group will be allocated.

Eligible and consenting patients will be randomised with equal probability to either standard care group or intervention group.

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.

All of the analyses will be carried out according to a detailed Statistical Analysis Plan (to be written and approved prior to database lock)

Primary outcome analysis
The main analysis will be according to the intention to treat principle and use a logistic regression model for the primary outcome of 30-day mortality, adjusting for centre as a random effect (or e.g. centres combined at a regional level if there are many small centres) and any pre-specified baseline covariates strongly predictive of outcome. We will run sensitivity type analyses that investigate the robustness of the findings to any patterns of missing data (expected to be negligible for the primary mortality outcome).
Secondary outcome analysis
We will investigate the influence of compliance (cumulative dose received) on the primary outcome using causal models (for example, using an instrumental variables approach).
The secondary outcomes will be analysed in a similar way to the primary analysis, using statistical models appropriate to the distribution of the outcome (mainly linear or logistic mixed effects models).
Likewise, safety outcomes will be analysed in similar ways appropriate to their distribution, and the findings presented descriptively.

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
	Professor	Alasdair	Gray
Post			
Qualifications	MD		
Employer	NHS Lothian		
Work Address	Edinburgh Royal Infirmary 51 Little France Crescent Edinburgh		
Post Code	EH16 4SA		
Telephone			
Fax			
Mobile			
Work Email	alasdair.gray@ed.ac.uk		

	Title	Forename/Initials	Surname
	Professor	Paul	Dark
Post	Chair of Critical Care Medicine		
Qualifications	MD		
Employer	Salford Royal NHS Foundation Trust		
Work Address	Stott Lane Salford		
Post Code	M6 8HD		
Telephone			
Fax			
Mobile			
Work Email	paul.m.dark@manchester.ac.uk		

	Title	Forename/Initials	Surname
	Professor	Derek	Bell
Post	Faculty of Medicine, School of Public Health		
Qualifications	MD		
Employer	Chelsea & Westminster Hospital		
Work Address	369 Fulham Road Chelsea		
Post Code	SW10 9NH		
Telephone			
Fax			
Mobile			
Work Email	d.bell@imperial.ac.uk		

	Title	Forename/Initials	Surname
	Professor	Manu	Shankar - Hari
Post	Professor of Critical Care Medicine		
Qualifications	MD		
Employer	University of Edinburgh		
Work Address			
Post Code	SE1 9RT		
Telephone			
Fax			
Mobile			
Work Email	manu.shankar-hari@ed.ac.uk		

	Title	Forename/Initials	Surname
	Dr	Dan	Horner
Post	Consultant in Emergency Medicine & Intensive Care		
Qualifications	MD		
Employer	Salford Royal NHS Foundation Trust		
Work Address	Stott Lane		
Post Code	M6 8HD		
Telephone			
Fax			
Mobile			
Work Email	danielhorner@nhs.net		

	Title	Forename/Initials	Surname
	Dr	Nazir	Lone
Post	Anaesthesia, Criticial Care & Pain Medicine		
Qualifications	MD		
Employer	NHS Lothian		
Work Address	Edinburgh Royal Infirmary 51 Little France Crescent Edinburgh		

Post Code	EH16 4SA
Telephone	
Fax	
Mobile	
Work Email	nazir.lone@ed.ac.uk

Title	Forename/Initials	Surname
Professor	Kevin	Rooney

Post Qualifications	Consultant in Anasthesia & Intensice Care Medicine
Employer	NHS Greater Glasgow & Clyde
Work Address	Royal Alexandria Hospital Corsebar Road
Post Code	PA2 9PN
Telephone	
Fax	
Mobile	
Work Email	kevin.rooney2@ggc.scot.nhs.uk

Title	Forename/Initials	Surname
Professor	Olivia	Wu

Post Qualifications	Director of Health Economics & Health Technology Assessment
Employer	University of Glasgow
Work Address	1 Lilybank Gardens
Post Code	G12 8PZ
Telephone	
Fax	
Mobile	
Work Email	olivia.wu@glasgow.ac.uk

Title	Forename/Initials	Surname
Ms	Rachel	O'Brien

Post Qualifications	EMERGE Research Team BSc
Employer	NHS Lothian
Work Address	Royal Infirmary of Edinburgh 51 Little France Crescent
Post Code	EH16 4SA
Telephone	
Fax	
Mobile	
Work Email	rachel.o'brien@nhslothian.scot.nhs.uk

	Title	Forename/Initials	Surname
	Prof	Heather	Jarman
Post	Consultant Nurse		
Qualifications			
Employer	University of London - St Georges		
Work Address	University of London		
	St Georges Hospital		
	Cranmer Terrace		
Post Code	SW17 0RE		
Telephone	02082666922		
Fax			
Mobile			
Work Email	heather.jarman@stgeorges.nhs.uk		

	Title	Forename/Initials	Surname
	Ms	Evi	Germeni
Post	Health Economics and Health Technology Assessment		
Qualifications			
Employer	University of Glasgow		
Work Address	1 Lilybank Gardens		
Post Code	G12 8PZ		
Telephone			
Fax			
Mobile			
Work Email			

	Title	Forename/Initials	Surname
	Professor	John	Norrie
Post	Statistician		
Qualifications			
Employer	Edinburgh University		
Work Address	Edinburgh Clinical Trials Unit		
	level 2 Nine Edinburgh Bio Quarter		
	9 Little France Crescent		
Post Code			
Telephone			
Fax			
Mobile			
Work Email	john.norrie@ed.ac.uk		

A64. Details of research sponsor(s)

A64-1. Sponsor

SP1

Status: (•) NHS or HSC care organisation ( ) Academic

Commercial status: Non-Commercial

- ◯ 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	NHS Greater Glasgow & Clyde
Given name	Pamela
Family name	Sandu
Address	Research & Development
Town/city	Dykebar Hospital, Ward 11
Post code	PA2 7DE
Country	
Telephone	01413144012
Fax	
E-mail	pamela.sandu@ggc.scot.nhs.uk

Legal Representative for the purpose of this CTIMP.
A legal representative must be appointed for a clinical trial of an investigational medicinal product (CTIMP) if the sponsor is not established in the UK or on the MHRA approved country list (please refer to question specific guidance).

Legal representative

Contact person

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

Legal representative for clinical investigation of medical device (studies involving Northern Ireland only)
Clinical Investigations of Medical Devices that take place in Northern Ireland must have a legal representative of the sponsor that is based in Northern Ireland or the EU

Contact person

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

A65. Has external funding for the research been secured?

Please tick at least one check box.

- [x] 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	University of Southampton Alpha House, Enterprise Road Southampton
Post Code	SO16 7NS
Telephone	
Fax	
Mobile	
Email	netspostawardsetup@nihr.ac.uk

Funding Application Status: (•) Secured ( ) In progress

Amount: 3065541.90

Duration
Years: 3

Months: 9

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

Name: Edinburgh Clinical Trials Unit

Type of organisation:

( ) NHS (●) Academic ( ) Commercial ( ) Other

Please give further details of sub-contractor and main areas of delegated responsibility: Data Management and eCRF build

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
		Hannah	Greenwood
Organisation	NHS Greater Glasgow & Clyde		
Address	Research & Development		
	Dykebar Hospital, Ward 11		
Post Code	PA2 7DE		
Work Email	hannah.greenwood@ggc.scot.nhs.uk		
Telephone	01413144012		
Fax			
Mobile			

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

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

Planned start date: 01/11/2021

Planned end date: 30/07/2025

Total duration:

Years: 3 Months: 8 Days: 30

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

Planned start date: 01/03/2022
Planned end date: 30/05/2025
Total duration:
Years: 3 Months: 2 Days: 30

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)

12 months after last patient last visit in order to allow for data cleaning and resolution of queries and final study report

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 60

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:*

☑ NHS organisations in England	40
☑ NHS organisations in Wales	3
☑ NHS organisations in Scotland	15
☑ HSC organisations in Northern Ireland	2
☐ GP practices in England	0
☐ GP practices in Wales	0
☐ GP practices in Scotland	0
☐ GP practices in Northern Ireland	0
☐ Joint health and social care agencies (eg community mental health teams)	0
☐ Local authorities	0
☐ Phase 1 trial units	0
☐ Prison establishments	0
☐ Probation areas	0

☐ Independent (private or voluntary sector) organisations	0
☐ Educational establishments	0
☐ Independent research units	0
☐ Other (give details)	0
Total UK sites in study:	60

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?

Monitoring will be conducted by NHS Greater Glasgow & Clyde (GGC) monitor(s) in accordance with local Standard Operating Procedures. The level, frequency and priorities of monitoring will be based on the outcome of the completed risk assessment and will be clearly documented in the Monitoring Plan which will be approved by the NHS GG&C Research Governance Manager.

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 IDMC will be established to include a minimum of two independent experts and an independent statistician. The Edinburgh Clinical Trials Unit will liaise with the committee and ensure that the committee is provided with adequate information about study progress and results.

The IDMC will meet approximately every 6 months. No formal interim analyses are planned. The IDMC will take into account all results and the consistency and plausibility of the findings.

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?

Decision about continuation or termination of the trial or substantial amendments to the protocol will be the responsibility of the Trial Steering Committee who will advise the Sponsor. The TSC will meet at the start of the study and annually thereafter. The TSC will have its own charter outlining the role and responsibilities of its members. The TSC may invite other attendees from the trial team to present or participant in discussions on particular topics.

The IDMC may recommend to the TSC and Sponsor that the study should stop prematurely because of concerns about patient safety or conclusive evidence of overwhelming benefit. The trial may also end if the TSC agrees that the planned sample size has been achieved, there is insufficient funding to continue to support further recruitment or if recruitment is so poor that the completion of the trial cannot be reasonably anticipated. Furthermore the trial may be ended prematurely if new information makes it inappropriate to continue to randomise patients to the study.

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)

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)

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 products

PR1 No Marketing Authorisation - needed to answer D2-2

PR2 Plasma-Lyte® 148

PR3 No Marketing Authorisation - needed to answer D2-2

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:
No Marketing Authorisation - needed to answer D2-2
EV Product Code
Does not apply
Name of the MA holder:
MA number (if MA granted by a Member State):
Is the IMP modified in relation to its MA?
○ Yes ◉ No ○ Not Answered
Which country granted the MA?

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	No Marketing Authorisation - needed to answer D2-2
Product code where applicable	Noradrenaline (Norepinephrine)
ATC codes, if officially registered	C01CA03
Pharmaceutical form (use standard terms)	Concentrate for solution for infusion
Is this a specific paediatric formulation?	○ Yes ◉ No ○ Not Answered
Maximum duration of treatment of a subject according to the protocol	48 hours

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	0.15 micrograms/kg/minute titrated as appropriate to target MAP 65 mmHg. Max total 0.43mg/kg based on maximum rate for 47h after 1h of titration from start rates
Specify per day or total	○ per day ○ total ◉ Not Answered
Specify total dose (number and unit)	0.43 mg/kg milligram(s)/kilogram
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):	Noradrenaline
CAS number:	51-41-2
Current sponsor code:	Noradrenaline
Other descriptive name:	Norepinepherine
Full Molecular formula	C8H11NO3
Chemical/biological description of the Active Substance	(R)-2-Amino-1-(3,4-dihydroxyphenyl)ethanol

Strength

Concentration unit:	mg/ml milligram(s)/millilitre
Concentration type:	equal
Concentration number (only use both fields for range):	1.0

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.
Noradrenaline has a very potent action on alpha receptors and a more moderate effect on beta-1 receptors. NORADRENALINE (NOREPINEPHRINE) 1 MG / ML causes generalised vasoconstriction, except for the coronary vessels which it dilates indirectly by increasing the oxygen consumption. This results in an increase in the force (and in the absence of vagal inhibition) in the rate of myocardial contraction. Peripheral resistance increases, and diastolic and systolic pressures are raised.

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: **PR2**
Investigational medicinal product category:
Comparator

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:
Plasma-Lyte® 148
EV Product Code
Name of the MA holder:
Baxter Healthcare Ltd
MA number (if MA granted by a Member State):
PL 00116/0332
Is the IMP modified in relation to its MA?
○ Yes ◉ No ○ Not Answered

Which country granted the MA?
UK - MHRA
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	Plasma-Lyte® 148
Product code where applicable	Balanced Crystalloid IV fluids
ATC codes, if officially registered	B05BB01
Pharmaceutical form (use standard terms)	Infusion
Is this a specific paediatric formulation?	◯ Yes ◉ No ◯ Not Answered
Maximum duration of treatment of a subject according to the protocol	48 hours

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	none specified
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:	Plasma-lyte 148
Other descriptive name:	
Full Molecular formula	NaCl
Chemical/biological description of the Active Substance	Sodium chloride is the principal sodium salt used as a source of sodium ions.

Strength

Concentration unit:	g/l gram(s)/litre
Concentration type:	equal
Concentration number (only use both fields for range):	5.26

Active Substance 2

Name of active substance (INN or proposed INN if available):	Potassium Chloride
CAS number:	7447-40-7
Current sponsor code:	Plasma-lyte 148
Other descriptive name:	
Full Molecular formula	KCl
Chemical/biological description	Potassium chloride is the principal sodium salt used as a source of sodium

of the Active Substance	ions.

Strength

Concentration unit:	g/l gram(s)/litre
Concentration type:	equal
Concentration number (only use both fields for range):	0.37

Active Substance 3

Name of active substance (INN or proposed INN if available):	Magnesium Chloride hexahydrate
CAS number:	7791-18-6
Current sponsor code:	Plasma-lyte 148
Other descriptive name:	
Full Molecular formula	MgCl2,xH2O
Chemical/biological description of the Active Substance	magnesium chloride is the principal sodium salt used as a source of sodium ions.

Strength

Concentration unit:	g/l gram(s)/litre
Concentration type:	equal
Concentration number (only use both fields for range):	0.30

Active Substance 4

Name of active substance (INN or proposed INN if available):	Sodium Acetate trihydrate
CAS number:	6131-90-4
Current sponsor code:	Plasma-lyte 148
Other descriptive name:	
Full Molecular formula	CH3.CO2Na,3H2O
Chemical/biological description of the Active Substance	Sodium Acetate trihydrate produces bicarbonate and is an alkalinising agent

Strength

Concentration unit:	g/l gram(s)/litre
Concentration type:	equal
Concentration number (only use both fields for range):	3.68

Active Substance 5

Name of active substance (INN or proposed INN if available):	Sodium Gluconate
CAS number:	527-07-1
Current sponsor code:	Plasma-lyte 148
Other descriptive name:	
Full Molecular formula	C6H11NaO7
Chemical/biological description of the Active Substance	Sodium Gluconate produces bicarbonate and is an alkalinising agent

Strength

Concentration unit:	g/l gram(s)/litre
Concentration type:	equal
Concentration number (only use both fields for range):	5.02

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. Plasma-Lyte 148 is an isotonic solution of electrolytes. The electrolytes constituents of their concentrations are designed to match those of plasma. The pharmacological properties of Plasma-Lyte 148 are those of its components (water, sodium, potassium, magnesium, chloride, acetate and gluconate). The main effect is the expansion of the extracellular compartment including both the interstitial fluid and the intravascular fluid. Sodium acetate and gluconate are bicarbonate-producing salts.

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:
Comparator

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:
No Marketing Authorisation - needed to answer D2-2
EV Product Code
Does not apply
Name of the MA holder:
MA number (if MA granted by a Member State):
Is the IMP modified in relation to its MA?
○ Yes ◉ No ○ Not Answered
Which country granted the MA?

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	No Marketing Authorisation - needed to answer D2-2
Product code where applicable	Compound Sodium Lactate Solution for Infusion
ATC codes, if officially registered	B05BB01
Pharmaceutical form (use standard terms)	Infusion
Is this a specific paediatric formulation?	◯ Yes ◉ No ◯ Not Answered
Maximum duration of treatment of a subject according to the protocol	48 hours

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	no maximum
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:	Compound Sodium Lactate Solution for Infusion BP
Other descriptive name:	
Full Molecular formula	NaCl
Chemical/biological description of the Active Substance	Sodium chloride is the principal sodium salt used as a source of sodium ions.

Strength

Concentration unit:	g/l gram(s)/litre
Concentration type:	equal
Concentration number (only use both fields for range):	6.0

Active Substance 2

Name of active substance (INN or proposed INN if available):	Potassium Chloride
CAS number:	7447-40-7
Current sponsor code:	Compound Sodium Lactate Solution for Infusion BP
Other descriptive name:	
Full Molecular formula	KCl
Chemical/biological description	Potassium chloride is the principal sodium salt used as a source of sodium

of the Active Substance	ions.

Strength

Concentration unit:	g/l gram(s)/litre
Concentration type:	equal
Concentration number (only use both fields for range):	0.40

Active Substance 3

Name of active substance (INN or proposed INN if available):	Calcium Chloride dihydrate
CAS number:	10035-04-8
Current sponsor code:	Compound Sodium Lactate Solution for Infusion BP
Other descriptive name:	
Full Molecular formula	CaCl2,2H2O
Chemical/biological description of the Active Substance	Calcium chloride dihydrate is the principal sodium salt used as a source of sodium ions.

Strength

Concentration unit:	g/l gram(s)/litre
Concentration type:	equal
Concentration number (only use both fields for range):	0.27

Active Substance 4

Name of active substance (INN or proposed INN if available):	Sodium Lactate
CAS number:	72-17-3
Current sponsor code:	Compound Sodium Lactate Solution for Infusion BP
Other descriptive name:	
Full Molecular formula	C3H5NaO3
Chemical/biological description of the Active Substance	sodium lactate is an alkalinising agent

Strength

Concentration unit:	g/l gram(s)/litre
Concentration type:	equal
Concentration number (only use both fields for range):	3.20

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. Compound Sodium Lactate solution is an isotonic solution of electrolytes. The constituents their concentrations are designed to match those of plasma. The pharmacological properties of the Compound Sodium Lactate solution are those of its components (sodium, potassium, calcium, chloride and lactate). The main effect is the expansion of the extracellular compartment including both the interstitial fluid and the intravascular fluid.

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

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

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.

Part B: Section 5 – Use of newly obtained human tissue(or other human biological materials) for research purposes

1. What types of human tissue or other biological material will be included in the study?

2. Who will collect the samples?

3. Who will the samples be removed from?

- ☐ Living donors
- ☐ The deceased

6. Will any tissues or cells be used for human application or to carry out testing for human application in this research?

○ Yes ◉ No

8. Will the samples be stored: *[Tick as appropriate]*

In fully anonymised form? *(link to donor broken)*
○ Yes ◉ No

In linked anonymised form? *(linked to stored tissue but donor not identifiable to researchers)*
○ Yes ◉ No

In a form in which the donor could be identifiable to researchers?
○ Yes ◉ No

9. What types of test or analysis will be carried out on the samples?

10. Will the research involve the analysis or use of human DNA in the samples?

○ Yes ◉ No

11. Is it possible that the research could produce findings of clinical significance for donors or their relatives?

○ Yes ◉ No

12. If so, will arrangements be made to notify the individuals concerned?

○ Yes ○ No ◉ Not applicable

13. Give details of where the samples will be stored, who will have access and the custodial arrangements.

14. What will happen to the samples at the end of the research? *Please tick all that apply and give further details.*

☐ Transfer to research tissue bank

(If the bank is in England, Wales or Northern Ireland the institution will require a licence from the Human Tissue Authority to store relevant material for possible further research.)

☐ Storage by research team pending ethical approval for use in another project

(Unless the researcher's institution holds a storage licence from the Human Tissue Authority, or the tissue is stored in Scotland, or it is not relevant material, a further application for ethical review should be submitted before the end of this project.)

☐ Storage by research team as part of a new research tissue bank

(The institution will require a licence from the Human Tissue Authority if the bank will be storing relevant material in England, Wales or Northern Ireland. A separate application for ethical review of the tissue bank may also be submitted.)

☐ Storage by research team of biological material which is not "relevant material" for the purposes of the Human Tissue Act

☐ Disposal in accordance with the Human Tissue Authority's Code of Practice

☐ Other

☐ Not yet known

Please give further details of the proposed arrangements:

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.*

The patient will receive routine acute clinical assessment including severity of illness assessment and be treated in accordance with current UK guidelines (Sepsis 6). The results of these will inform trial eligibility and the patient will be approached as soon as these are available.

Inclusion criteria
• Age >18 years
• Clinically suspected or proven infection resulting in principal reason for acute illness
• SBP <90 mmHg or MAP < 65 mmHg
Measured serum lactate of > 2 mmol/L at the time of eligibility assessment
• Hospital presentation within last 12 hours

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?

Capacity will be assessed by the Principal Investigator (PI) or a clinician responsible for the treatment of the participant.

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.*

As per section A24

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?

Laws governing consent procedures, and in particular those governing incapacitated adults and their involvement in research, must be followed. Written informed consent from the patient should always be sought where possible. If this is not possible because the patient cannot read or write, the randomising investigator or nurse can gain witnessed verbal consent.

If a Personal Representative is present, they will be given information about the trial in the Personal Representative Information Sheet. The Personal Representative will be given enough time to consider the trial and ask questions regarding their relative's participation in the trial. Ideally, a period of 30-40 minutes will be given but this may be only 10-15 minutes due to the need for fluid resuscitation to begin within one hour.

The Personal Representative will be told they are being asked to give consent on behalf of the incapacitated adult, that they are free to decide whether they wish to make this decision or not and that they are being asked to consider what the adult would want, and to set aside their own personal views when making this decision. They will be informed that their relative will be asked whether or not they wish to continue in the study once they have regained capacity to do so.

If they indicate they have had time to consider the trial, the impact on their relative and provided with the opportunity to

have any trial related questions they will be asked to provide written consent. The Investigator or delegated member of the trial team and the Personal Representative will sign and date the Consent Form to confirm that consent has been obtained. The original consent form will be filed in the Investigator Site File (ISF), the participant will receive a copy of this document and a copy filed in the participant's medical notes.

Consent via Telephone

Every effort will be made to approach and consent the Personal Representative in person. If the Personal Representative is only contactable by telephone then the informed consent process is permitted via telephone or an appropriate video conferencing technology such as NHS near me, provided the following:
The Representative who is being contacted has previously had the opportunity to discuss the clinical aspects of the patient's care with the clinical team, before any contact is made by the research team; in some circumstances the research team will be part of the clinical care team. However, the approach to discuss consent is clearly separate to any discussions made between the representative and the clinical team.
A member of the research team will contact the Personal Representative by telephone/videoconferencing technology to explain what the study entails and answer any questions they may have. The Personal Representative will be given time to read and consider the information sheet. In situations where the Personal Representative does not have a copy of the PIS this will be read to them, or can be sent via email. Ideally, a period of 30-40 minutes will be given but this may be only 10-15 minutes due to the need for fluid resuscitation to begin within one hour. If the Personal Representative chooses to enrol the patient onto the study, verbal consent will be obtained by a member of the research team who conducted the interview and will sign the consent form. This will be witnessed by another member of clinical or research staff.
A copy of the signed Personal Rep Witness consent form will be sent to the Personal Representative electronically or by post along with a Personal Representative PIS and Consent form.
If a Personal Representative objects to the inclusion of the patient in the trial, their views will be respected.
The participant must also receive information, according to their capacity of understanding, about the trial and its risks and benefits.
If there is not a Personal Representative immediately available (within 20 minutes), a Professional Representative will be approached to determine if it is appropriate for the patient to be entered into the trial so that treatment could be commenced within one hour. A Personal Representative should be approached for consent to continue as soon as they are available, and it is feasible to do so. If the Personal Representative is unable to visit the hospital in person the consent form will be sent to them by email.
All methods of patient consent must be documented in the patient's notes.
If there is not a Personal Representative immediately available (within 20 minutes), a Professional Representative will be approached to determine if it is appropriate for the patient to be entered into the trial so that treatment could be commenced within one hour. A Professional legal representative is a doctor responsible for the medical treatment of the adult if they are independent of the study, or a person nominated by the healthcare provider. A Personal Representative should be approached for consent to continue as soon as they are available, and it is feasible to do so.

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.

Patients who have "life threatening features" and who lack temporary capacity due to their current illness can be recruited to the trial using deferred consent if there is no Personal/Professional Representative to give consent on their behalf within 30 minutes so that treatment can be commenced within one hour. The decision to defer consent should be made by a doctor at training level ST4 or above or an associate PI or consultant who has appropriate trial training and this should be clearly documented in the medical notes.

The patient would be enrolled into the trial and receive their allocated treatment. Consent would be sought as soon as possible from a Personal Representative (or a Professional Representative if they are available sooner). If a Personal/Professional Representative declines to give consent for continuation at this stage, their wishes will be respected and the withdrawal process will be followed.

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

Where granted, Professional legal representation for patients in the study will be available for the 48 hour study

intervention window.

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.

The patient will be given enough time to consider the trial and ask questions regarding their participation in the trial. Due to the need to ideally start treatment within one hour, there may not be long for the participant to consider the trial. Ideally, a period of 30-40 minutes will be given but it may be only 10-15 minutes due to the need for fluid resuscitation to begin. The research teams are experienced at recruiting patients and given the nature of the intervention and the burden of the trial we believe this to be reasonable. Potential participants will receive adequate oral and written information. The oral explanation to the patient will be performed by a member of the research team or a trained and delegated member of the clinical team and must cover all the elements specified in the Participant Information Sheet and Consent Form. The patient must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information.

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

The participant can decide to withdraw from the trial at any time for no reason. The CI or principal investigator also has the right to withdraw patients from the trial if deemed in the best interests of the patient or in the event of protocol deviations, administrative or other reasons. If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's eCRF, if possible. The participant/their Representative will have the option of withdrawal from:
• Study treatment with continuation of the collection of clinical and safety data
OR
• All aspects of the trial but continued use of data collected up to that point. To safeguard rights, the minimum personal information possible will be collected.

Randomised patients who wish to be withdrawn from the study before they have undertaken any study related procedures will be withdrawn from the study and another participant will be recruited to replace them. Data on the original participant will be kept on the eCRF/database.

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?

Where no consent is given by any legal representative, i.e. deferred consent is used and no subsequent consent obtained, or a participant dies before any consent obtained the patient data collected up to that point. To safeguard rights, the minimum personal information possible will be collected.

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	
IN2	◉ NHS/HSC Site ○ Non-NHS/HSC Site		Forename Middle name Family name Email	Kevin Ross Rooney Kevin.Rooney2@ggc.scot.nhs.uk
	Organisation name	NHS Greater Glasgow and Clyde	Qualification (MD...)	MBChB, MPH, MRCP(UK),FRCEM, DipIMC (RCSEd), Dip RTM
	Address	J B Russell House Gartnavel Royal Hospital 1055 Great Western Road Glasgow GLASGOW LANARKSHIRE	Country	United Kingdom
	Post Code	G12 0XH		
	Country	SCOTLAND		
IN3	◉ NHS/HSC Site ○ Non-NHS/HSC Site		Forename Middle name Family name Email	Alasdair Gray alasdair.gray@ed.ac.uk
	Organisation name	NHS Lothian	Qualification (MD...)	MD
	Address	Waverley Gate 2-4 Waterloo Place EDINBURGH MIDLOTHIAN	Country	United Kingdom
	Post Code	EH1 3EG		
	Country	SCOTLAND		
IN4	◉ NHS/HSC Site ○ Non-NHS/HSC Site		Forename Middle name Family name Email	Benjamin Michael Bloom ben.bloom@nhs.net
	Organisation name	BARTS HEALTH NHS TRUST	Qualification (MD...)	MB ChB BSc PhD FRCEM MRCS DRCOG
	Address	THE ROYAL LONDON HOSPITAL 80 NEWARK STREET	Country	United Kingdom

	LONDON
Post Code	E1 2ES
Country	ENGLAND

IN5

- (●) NHS/HSC Site
- ( ) Non-NHS/HSC Site

Forename	Nicolas
Middle name	
Family name	Truman
Email	Nicholas.Truman@elht.nhs.uk
Qualification (MD...)	MB ChB, BSc (HONS), FRCA, FFICM
Country	United Kingdom

Organisation name	EAST LANCASHIRE HOSPITALS NHS TRUST
Address	ROYAL BLACKBURN HOSPITAL
	HASLINGDEN ROAD
	BLACKBURN
Post Code	BB2 3HH
Country	ENGLAND

IN6

- (●) NHS/HSC Site
- ( ) Non-NHS/HSC Site

Forename	Matthew
Middle name	
Family name	Frise
Email	Matthew.Frise@royalberkshire.nhs.uk
Qualification (MD...)	
Country	

Organisation name	ROYAL BERKSHIRE NHS FOUNDATION TRUST
Address	ROYAL BERKSHIRE HOSPITAL
	LONDON ROAD
	READING
Post Code	RG1 5AN
Country	ENGLAND

IN7

- (●) NHS/HSC Site
- ( ) Non-NHS/HSC Site

Forename	Andrew
Middle name	
Family name	Tabner
Email	andrew.tabner@nhs.net
Qualification (MD...)	BMBS, MMedSci, FRCEM
Country	United Kingdom

Organisation name	UNIVERSITY HOSPITALS OF DERBY AND BURTON NHS FOUNDATION TRUST
Address	ROYAL DERBY HOSPITAL
	UTTOXETER ROAD
	DERBY

Post Code	DE22 3NE
Country	ENGLAND

IN8

- (●) NHS/HSC Site
- ( ) Non-NHS/HSC Site

Organisation name	NHS Fife
Address	Hayfield House Hayfield Road KIRKCALDY FIFE
Post Code	KY2 5AH
Country	SCOTLAND

Forename	Rajendra
Middle name	
Family name	Raman
Email	rajendra.raman@nhs.scot
Qualification (MD...)	MD
Country	United Kingdom

IN9

- (●) 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 LANARKSHIRE
Post Code	G12 0XH
Country	SCOTLAND

Forename	David
Middle name	
Family name	Lowe
Email	David.Lowe@glasgow.ac.uk
Qualification (MD...)	MD
Country	United Kingdom

IN10

- (●) NHS/HSC Site
- ( ) Non-NHS/HSC Site

Organisation name	St George's University Hospitals NHS Foundation Trust
Address	DERBY ROAD NOTTINGHAM

Forename	Sarah
Middle name	
Family name	Jolly
Email	Sarah.Jolly@stgeorges.nhs.uk
Qualification (MD...)	
Country	United Kingdom

Post Code	
Country	ENGLAND

IN11

- (●) NHS/HSC Site
- ( ) Non-NHS/HSC Site

Organisation name	NHS Lanarkshire
Address	14 Beckford Street
	HAMILTON LANARKSHIRE
Post Code	ML3 0TA
Country	SCOTLAND

Forename	Nicola
Middle name	
Family name	Moultrie
Email	nicola.moultrie@lanarkshire.scot.nhs.uk
Qualification (MD...)	MD
Country	United Kingdom

IN12

- (●) NHS/HSC Site
- ( ) Non-NHS/HSC Site

Organisation name	KETTERING GENERAL HOSPITAL NHS FOUNDATION TRUST
Address	ROTHWELL ROAD
	KETTERING
Post Code	NN16 8UZ
Country	ENGLAND

Forename	Maria
Middle name	
Family name	Iliescu
Email	maria.iliescu@nhs.net
Qualification (MD...)	
Country	United Kingdom

IN13

- (●) NHS/HSC Site
- ( ) Non-NHS/HSC Site

Organisation name	NORTHERN CARE ALLIANCE NHS FOUNDATION TRUST
Address	SALFORD ROYAL
	STOTT LANE
	SALFORD GREATER MANCHESTER
Post Code	M6 8HD

Forename	Dan
Middle name	
Family name	Horner
Email	danielhorner@nhs.net
Qualification (MD...)	MD
Country	United Kingdom

Country	ENGLAND

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 Alasdair Corfield on 20/12/2022 18:33.

Job Title/Post:	Chief Investigator
Organisation:	NHS GG&C
Email:	alasdair.corfield@ggc.scot.nhs.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 Dr. Pamela Sandu on 20/12/2022 18:21.

Job Title/Post:	Research co-ordinator
Organisation:	NHSGGC
Email:	pamela.sandu@ggc.scot.nhs.uk