

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)
Study into the Reversal of Septic Shock with Landiolol (Beta Blockade)

1. Is your project research?

Yes No

2. Select one category from the list below:

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

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

Other study

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

Yes No

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

Yes No

2c. Please answer the following question:

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

Yes No

2d. Please answer the following question:

Is this a trial of a gene therapy medicinal product?

Yes No

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

a) Does the study involve the use of any ionising radiation?

Yes No

b) Will you be taking new human tissue samples (or other human biological samples)?

Yes No

c) Will you be using existing human tissue samples (or other human biological samples)?

Yes No

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

- England
- Scotland
- Wales
- Northern Ireland

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

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

4. Which applications do you require?

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

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

Yes No

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

Please see information button for further details.

Yes No

Please see information button for further details.

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

Please see information button for further details.

Yes No

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

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

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

Yes No

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

Yes No

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

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

Yes No

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

Yes No

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

Yes No

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

Yes No

SUBSTANTIAL AMENDMENT FORM ¹

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

For official use:

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

To be filled in by the applicant:

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

A TYPE OF NOTIFICATION

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

UK

A.2 Notification for authorisation to the competent authority:

A.3 Notification for an opinion to the ethics committee:

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

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

B.1 Does the substantial amendment concern several trials involving the same IMP? ² Yes No

B.2 EudraCT number: 2017-001785-14

B.3 Full title of the trial: STRESS-L: STudy into the REversal of Septic Shock with Landiolol (Beta Blockade)

B.4 Sponsor's protocol code number: RRK5911

B.4 Sponsor's protocol version number: v4.0

B.4 Sponsor's protocol date: 02/04/2019

⁽²⁾ Cf. Section 3.7. of the detailed guidance CT-1

C IDENTIFICATION OF THE SPONSOR RESPONSIBLE FOR THE REQUEST

C.1 Sponsor

Organisation: University Hospitals Birmingham NHS Foundation Trust
Contact Given name: Clark
Contact Family name: Crawford
Address: 1st Floor, Institute of Translational Medicine (ITM), Queen Elizabeth Hospital (old), Mindelsohn Way
Town/city: Edgbaston, Birmingham
Post code: B15 2GW
Telephone: 01213714185
Fax:
E-mail: r&d@uhb.nhs.uk

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

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

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

D APPLICANT IDENTIFICATION, (please tick the appropriate box)

D1. Request for the competent authority

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

Name of organisation University of Warwick
Contact Given name Emma
Contact Family name Skilton
Address Warwick Clinical Trials Unit, University of Warwick, Gibbet Hill Campus
Town/city Coventry

Post code	CV4 7AL
Telephone	02476572905
Fax	
E-mail	stress-l@warwick.ac.uk

D2. Request for the Ethics Committee

- D.2.1 Sponsor
- D.2.2 Legal representative of the sponsor
- D.2.3 Person or organisation authorised by the sponsor to make the application.
- D.2.4 Investigator in charge of the application if applicable⁴:
- Co-ordinating investigator (for multicentre trial):
 - Principal investigator (for single centre trial):

D.2.5 Complete below:

Name of organisation University of Warwick

Given name Emma

Family name Skilton

Address Warwick Clinical Trials Unit, University of Warwick, Gibbet Hill
Campus

Town/city Coventry

Post code CV4 7AL

Telephone 02476572905

Fax

E-mail stress-l@warwick.ac.uk

⁽⁴⁾ According to national legislation.

E SUBSTANTIAL AMENDMENT IDENTIFICATION

E.1 Sponsor's substantial amendment information for the clinical trial concerned:

Code Number: SA_14

Version:

Date: 2020/02/04

E.2 Type of substantial amendment

- E.2.1 Amendment to information in the CT application form Yes No
- E.2.2 Amendment to the protocol Yes No
- E.2.3 Amendment to other documents appended to the initial application form Yes No

If yes specify:

STRESS-L Patient Information Sheet
STRESS-L Legal Representative Information Sheet

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

If yes specify:

E.2.5 This amendment concerns mainly urgent safety measures already implemented⁵: Yes No

- E.2.6 This amendment is to notify a temporary halt of the trial⁶: Yes No
- E.2.7 This amendment is to request the restart of the trial⁷: Yes No

⁽⁵⁾ Cf. Section 3.9. of the detailed guidance CT-1.

⁽⁶⁾ Cf. Section 3.10. of the detailed guidance CT-1

⁽⁷⁾ Cf. Section 3.10. of the detailed guidance CT-1

E.3 Reasons for the substantial amendment:

- E.3.1 Changes in safety or integrity of trial subjects Yes No
- E.3.2 Changes in interpretation of scientific documents/value of the trial Yes No
- E.3.3 Changes in quality of IMP(s) Yes No
- E.3.4 Changes in conduct or management of the trial Yes No
- E.3.5 Change or addition of principal investigator(s), co-ordinating investigator Yes No
- E.3.6 Change/addition of site(s) Yes No
- E.3.7 Other change Yes No
- E.3.7.1 If yes specify:
Changes to inclusion and exclusion criteria
- Clarification and minor wording changes - see Protocol v5.0 17 December 2019
- E.3.8 Other case Yes No
- E.3.8.1 If yes specify:

E.4 Information on temporary halt of trial:⁸

- E.4.1 Date of temporary halt
- E.4.2 Recruitment has been stopped Yes No
- E.4.3 Treatment has been stopped Yes No
- E.4.4 Number of patients still receiving treatment at time of the temporary halt in the MS concerned by the amendment
- E.4.5 Briefly describe:
- Justification for a temporary halt of the trial (*free text*):
- The proposed management of patients receiving treatment at time of the halt (*free text*):
- The consequences of the temporary halt for the evaluation of the results and for overall risk benefit assessment of the investigational medicinal product (*free text*):

⁽⁸⁾Cf. Section 3.10. of the detailed guidance CT-1

F DESCRIPTION OF EACH SUBSTANTIAL AMENDMENT⁹

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

Substantial amendment 1

Previous and new wording:*(tracked)*

Patient Information Sheet

As part of your standard clinical care blood will have been taken from your cannula (a thin tube inserted into an ~~vein~~ **artery** or body cavity to administer medication).

Legal Representative Information Sheet

As part of their standard clinical care blood will be taken from his/her cannula (a thin tube inserted into an ~~vein~~ **artery** or body cavity to administer medication).

Protocol

Please see attached Protocol v5.0 version log with a summary of all tracked changes.

New wording:

Comments/ explanation/ reasons for substantial amendment:

Please see the table of protocol changes which includes the old and new/additional wording for Protocol v5.0, 17 December 2019.

- Minor updates and clarifications to lead name for Sponsor, definition of End of Noradrenaline Treatment Visit timepoint and landiolol dosing chart.
- Updated inclusion criteria 'Aged 18 years or above'. Reference to gender 'Male of female' has been removed as gender can be considered as non-binary.
- Updated inclusion criteria 'Heart rate \geq 95bpm (at the time of randomisation)' to clarify a patient does not have to be tachycardia for the entire 24 hour vasopressor therapy time window.
- Updated exclusion criteria 'Tachycardia as a result of pain, discomfort from medical devices (including endotracheal tubes), during interventions or other patient distress' to clarify a patient with tachycardia not driven by sepsis will not be eligible for the trial.
- Updated exclusion criteria '>72 hours after start of vasopressor therapy' to clarify patients will not be eligible for the trial if they have exceeded 72 hours of vasopressor therapy even if they initially received vasopressor therapy to treat another medical condition.
- Addition of exclusion criteria '<12 hours since noradrenaline to treat a medical condition other than septic shock stopped'. This is to clarify the patient must be receiving established noradrenaline treatment for the purpose of septic shock and patients who have initially received noradrenaline to treat another medical condition continuously will be excluded. This will minimise prolonged use of noradrenaline treatment to treat another medical condition after they have recovered from septic shock otherwise this could skew the primary outcome data (mean SOFA score over the first 14 days from entry to the trial and whilst in ICU)
- Addition of exclusion criteria 'Receiving extracorporeal membrane oxygenation (ECMO) treatment' to clarify patients receiving this type of treatment will not be eligible for the trial as this could skew the primary outcome data (mean SOFA score over the first 14 days from entry to the trial and whilst in ICU).
- Clarification patients will potentially not have capacity to consent to inclusion in the trial due to an underlying condition which may not be limited to septic shock.
- Clarification patients with fast atrial fibrillation will be eligible for the trial as this may be an indicator of septic shock.
- Amendment to secondary objectives to clarify the trial aims to improve mortality and length of hospital stay compared with current best clinical practice in patients who have septic shock.
- Amendment to safety section to clarify specified cardiovascular safety outcomes must be reported as a Serious Adverse Event if the event fulfils the serious criteria or is deemed related to the drug. Events must be reported for patients in the control and interventional arm. Further clarification that all events will be followed up until the final visit at Day 90 and will not extend beyond this timepoint.

The Patient Information sheet & Legal Representative Information sheet have been updated as per the REC's request following submission of the previous trial amendment. The Committee noted it is misleading to inform patients and legal representatives that blood will be taken through a venous cannula as it is common practice for bloods to be taken through an artery for patients on ITU with septic shock.

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

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

Type of change:

G.1.1 Addition of a new site

G.1.1.1 Principal investigator (provide details below)

Given name	Atul
Middle name(if applicable)	
Family name	Garg
Qualification (MD...)	MD
Professional address	Walsall Healthcare NHS Trust, Moat Road, Walsall, WS2 9PS

G.1.2 Removal of an existing site

G.1.2.1 Principal investigator (provide details below)

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

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

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

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

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

Given name	
Middle name(if applicable)	
Family name	
Qualification	

(MD...)
Professional
address

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

H CHANGE OF INSTRUCTIONS TO CA FOR FEEDBACK TO SPONSOR

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

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

Yes No

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

Yes No

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

H.2.2 Do you want to receive this via password protected link(s)¹⁰?

Yes No

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

H.2.3 Do you want to stop messages to an email for which they were previously requested?

Yes No

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

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

⁽¹⁰⁾ This requires a EudraLink account. (See eudract.emea.europa.eu for details)

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

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

I.1 Cover letter

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

I.3 Entire new version of the document¹¹

I.4 Supporting information

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

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

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

J SIGNATURE OF THE APPLICANT IN THE MEMBER STATE

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

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

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

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

J.2.1 Signature ¹²:

J.2.2 Print name:

J.2.3 Date:

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

J.3.1 Signature ¹³:

J.3.2 Print name:

J.3.3 Date:

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

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