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?

IMPORTANT: If your project is taking place in the NHS and is led from England select 'IRAS Form'. If your project is led from Northern Ireland, Scotland or Wales select 'NHS/HSC Research and Development Offices' and/or relevant Research Ethics Committee applications, as appropriate.

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

For NHS/HSC R&D Offices in Northern Ireland, Scotland and Wales the CI must create NHS/HSC Site Specific Information forms, for each site, in addition to the study wide forms, and transfer them to the PIs or local collaborators.

For participating NHS organisations in England different arrangements apply for the provision of site specific information. Refer to IRAS Help for more information.

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 Biomedical Research Unit, NIHR Collaboration for Leadership in Health Research and Care (CLAHRC), NIHR Patient Safety Translational Research Centre or a Diagnostic Evidence Co-operative 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:	2.0
B.4 Sponsor's protocol date:	31/07/2018

(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:	Chris
Contact Family name:	Counsell
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:	chris.counsell@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 applicable[4]:

- 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_07
Version:
Date: 2018/11/05

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:

Patient Information Sheet v3.0 18 October 2018
Patient Consent Form v3.0 18 October 2018
Legal Representative Information Sheet v3.0 18 October 2018
Legal Representative Consent Form v3.0 18 October 2018

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

If yes specify:

Relatives Poster v1.0 29 October 2018

E.2.5 This amendment concerns mainly urgent safety measures already implemented[5]: ○ Yes ◉ No

E.2.6 This amendment is to notify a temporary halt of the trial[6]: ○ Yes ◉ No

E.2.7 This amendment is to request the restart of the trial[7]: ○ 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:
Change to inclusion and exclusion criteria.

Clarification and minor wording changes - see Protocol v3.0, 18 October 2018.

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 AMENDMENT[9]

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)*

Page 4: ~~Nafisa Boota~~ Emma Skilton

Page 9: Adult patients in an intensive care unit (ICU) diagnosed with septic shock as defined by consensus criteria (Sepsis-3) who, having received adequate fluid resuscitation, are receiving noradrenaline treatment at >=0.1mcg/kg/min continuously for longer than 24 hours (but less than 72 ~~48~~ hours) to maintain a predefined mean arterial pressure (usually of 65 mmHg) and continue to have a heart rate (HR) more than 94 bpm (>=95bpm).

~~Once Landiolol has been discontinued for 12 hours it should not be restarted.~~ Landiolol should be weaned and, if necessary, stopped whilst the HR is below 80 bpm. It may be restarted at any point if noradrenaline continues. Once the end of noradrenaline treatment visit has passed and the landiolol has been stopped for 12 hours or more, it should not be restarted.

Pages 10, 24 & 25 :

- Receiving vasopressor support ~~with noradrenaline~~ to maintain a target blood pressure for ≥24 hours
- >~~48~~ 72 hours in the current cause of septic shock after start of vasopressor therapy
- Untreated phaeochromocytoma ~~pheochromocytoma~~
- Advanced liver disease with Child-Pugh Score of ≥B
- ~~Participants who have participated in another research trial involving an investigational medicinal product in the past 30 days~~ Participants who have been administered an investigational medicinal product for another research trial in the past 30 days

Page 18: By targeting patients with spontaneous persisting tachycardia and vasopressor requirement, the study group is a particular at-risk cohort.

Page 19 :Blood will also be drawn at study entry (D0), ~~and at~~ Day 1 and end of noradrenaline treatment (EONT) to be retained by the BioBank; it is our intention to apply for a separate grant to perform genetic (Day 0) and transcriptomic (Day 0, ~~and~~ 1 and EONT) analyses on these samples

All data will be stored securely and held in accordance with the new Data Protection Action 2018 ~~Data Protection Act 1998~~.

Page 20: Participant information sheets have been updated to include a data transparency statement in in line with GDPR guidance from the HRA.

Page 21: The trial will take place in approximately 35 UK adult intensive care units (ICUs).

Page 23: ~~The initial phase of this study will establish the rate of screening, recruitment: number of admissions and patients already on ICU and consenting patients per ICU per unit time. Narrative records of the reason for eligible patients not recruited (to be analysed by emerging themes) or any inability to complete protocol will be collected, as will mortality rate in the control group.~~

Page 26: 3.5 Co-enrolment Co-enrolment of STRESS-L participants onto other interventional studies will be considered where there is no possible conflict with the STRESS-L trial objectives. A list of appropriate and agreed studies will be produced at a national level to guide co-enrolment. Co-enrolment will be discussed and confirmed with sites at the time of site set-up and monitored throughout the recruitment phase. In addition, the CI will review the protocols for other studies at sites and will consider co-enrolment in conjunction with the Trial Management Committee where appropriate.

Patients on ICU that develop sepsis after their arrival will be screened and included if the eligibility criteria is met. Patients may also be included if they recommence noradrenaline treatment for a new bout of sepsis 72 hours after previous noradrenaline treatment. If the patient recommences noradrenaline treatment less than 12 hours prior to first round of noradrenaline treatment this will be classified as the same episode of treatment when assessing

eligibility.

Once eligibility criteria are met there is a ~~24~~ 48 hour window for randomisation

It will be made clear to the patient or their legal representative that if they do not remain on vasopressor therapy at the ~~24~~ 48 hour mark and are no longer tachycardic they will not be eligible for randomisation.

Pages 27:

They will be asked to consider the wishes of the participant and if the agree to provide ongoing participation for their relative, partner or close friend in the trial. Similarly, if a patient regains capacity they will be informed of their participation in the trial and if they agree consent for ongoing participation will be sought. The patient or PerLR will be asked for consent to continue follow-up in the trial or will be supported if they wish to withdraw. It will be confirmed that data already collected will be retained by default unless the participant or their PerLR requests otherwise.

Page 29: The study drug should not be started until the treating physician is confident that adequate fluid resuscitation has been achieved and the patient has reached the target mean arterial pressure ~~pre-defined~~ by the treating clinician overseeing care (suggested target 65-70 mmHg but this may be varied as detailed below) using vasopressors.

Landiolol may be administered peripherally or centrally but MUST be on a dedicated line.

~~Once the landiolol infusion has been stopped for more than 12 hours it should not be recommenced~~; The landiolol should be weaned and, if necessary, stopped whilst the HR is below 80 bpm. It may be restarted according to protocol (Appendix B) at any point before the EONT (see definition). Once EONT has passed, attempts to wean Landiolol should continue to maintain HR between the target rates of 80-94 bpm. Once the EONT has passed and the landiolol has been stopped for 12 hours or more, landiolol should not be restarted. Landiolol treatment should also stop if it is 14 days following randomisation; the use of alternative beta blockade is at the discretion of the treating clinician.

The study drug infusion should continue even when vasopressors have finished and the EONT visit has occurred whilst the patient remains tachycardic ~~without landiolol.~~

Page 30: If the treating clinician deems beta blockade necessary, this will be captured on the Case Report Form and reported as a protocol deviation.

Page 31: ~~In all patients w~~We will compare oxygen delivery between treatment groups using central venous oxygen saturations ($ScvO_2$) and matched to the arterial saturations (SaO_2). Where possible, ~~T~~this should be measured and recorded at baseline, and days 1, 2, 4 and 6 after randomisation if central venous access is available.

After fluid resuscitation, it should be titrated to maintain a target mean arterial pressure (MAP) ~~that is pre-defined~~ by the clinician overseeing care.

Page 32: Final trial packaging and labelling will be carried out by CSM Germany and final QP release of trial drug will be carried out by AOP Orphan Pharmaceuticals. The trial drug will then be ~~CSM Germany and~~ distributed to sites by Mawdsleys. All sites involved have the appropriate licenses in place.

Landiolol may be administered peripherally or centrally but MUST be on a dedicated line.

Page 33: The trial drug will be stored ~~under temperature controlled conditions~~ in the UK by a 3rd party contractor for distribution to participating trial centres.

~~It is envisaged between 2 and 4 vials will be required per participant for a 24 hour infusion.~~

Page 34: ~~As a result, if the clearance of landiolol is affected, lower infusion rates will be used because the patient response will be stronger~~. In the event that the clearance of Landiolol is affected, the targeting of a physiological endpoint will be achieved through lower infusion rates.

Page 35: This study will end when the specified number of patients have been recruited, all patients have completed 3 ~~6~~-month follow-up and the database is locked.

Page 36: Randomisation should not occur until ~~noradrenaline~~ vasopressor therapy has been running for ≥24 hours, are being treated with noradrenaline at rate >0.1 mcg/kg/min and the patient remains tachycardic.

Baseline visit ~~– start of infusion~~ 24 hours prior and up to the time of randomisation (Day 0)

An electro~~electrocho~~cardiogram (ECG) will be recorded.

The rates of noradrenaline infusion and landiolol infusion (if randomised to this group) should be recorded hourly until day 2 to allow comparison of noradrenaline dosing and then 6 hourly thereafter, heartrate data should be collected to allow assessment of landiolol infusion compliance.

Page 37: The plasma ~~serum~~ will be removed and stored as per detailed instructions provided in the trial Laboratory manual.

~~Specifically chosen participating sites, close to suitable analysers, will retain part of the fresh blood samples taken at the above time points to measure changes in neutrophil function and oxidative burst activity. Details will be provided in a site specific laboratory manual should this assay be required by a participating centre.~~

A Biobank blood sample will be collected on Day 0 ~~and Day~~ 1, and EONT visit if the patient (or their legal representative) has consented to provide these.

Page 38: Baseline~~-~~ (Day 0 -24hr – T0)

Day 1 (T0+24)

Central Venous Blood Gas / Arterial Blood Gas

Rate of Vasopressor / inotropes

Page 39: The blood samples will be centrifuged and the plasma ~~serum~~ isolated will be temporarily stored at -20°C or -80°C/-70°C at the respective sites. Freezer temperature excursions will be monitored in accordance with local Trust policy.

Batch ~~Regular~~ frozen shipments of plasma ~~serum~~ will be arranged to the University of Birmingham for storage and ~~University Hospitals of Birmingham NHS Foundation Trust (UHB) for~~ subsequent analysis.

A Biobank blood sample (5ml) will be collected on Day 0 ~~and~~ Day 1 and EONT visit, if the patient (or their legal representative) has consented to provide these.

Whole blood ~~As with the research blood samples these will be centrifuged and the serum isolated~~ will be temporarily stored at -20°C ~~or -70°C~~ and then transferred to -80°C/-70°C at the respective sites. The frozen blood ~~serum~~ will be sent in batches to the Human Biomaterials Resource Centre (HBRC) at the University of Birmingham.

Samples stored at ~~UHB and~~ the University of Birmingham will be stored in accordance with the Human Tissue Act 2004.

Page 41: Hepatic impairment as measured by Transaminases ~~<1000IU/L~~ 10xULN (Upper Limit Normal)

Page 42: SAEs and SUSARs will be reported by sites using the paper SAE form and later transcribed by the trial coordinating centre in the participant's eCRF.

Page 43: Section 4.8 of T~~t~~he Summary of Product Characteristics (SPC) for landiolol will be used to assess expectedness of events (known as the reference safety information).

Page 46-47: Personal data collected during the trial will be handled and stored in accordance with the new Data Protection Act 2018.

Page 48: A~~maximum~~ minimum recruitment rate of 0.36 patients per month per centre will be required, based on a recruitment target of 340 participants over 36 months from 35 sites.

Page 49: The DMC ~~Interim analyses~~ will meet ~~be conducted~~ every 6 months to closely monitor the accumulating data, focusing on safety.

Page 52: Confidential reports containing recruitment, protocol compliance, safety and outcome data ~~and interim assessments of outcomes~~ will be reviewed by the DMC.

Page 64: For participants below 40 kg or over 100 kg ideal body weight will be used (method as per local practice)

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 v3.0, 18 October 2018.

The key amendments are as follows:
- Minor additional and clarification wording changes regarding staff changes, new data protection act, data collection, consent, safety reporting and DMC meetings.

- Extension of current exclusion criteria to allow vasopressors to continue up to 72 hours instead of 48 hours to allow more time to capture the required patient population

- Landiolol can be started again after 12 hours if the patient remains tachycardic and is receiving noradrenaline due to the hypothesis that the noradrenaline is driving the fast heart rate; therefore, restarting Landiolol to reduce the heart rate is permitted

Evidence suggests that the dose and time of exposure to catecholamines (i.e. noradrenaline and adrenaline) can cause harm through immunosuppression and cardiac damage. One of our hypotheses is that Landiolol offers protection to patients. Restarting the landiolol may increase that protection especially as a tachycardia may be induced by endogenous or exogenous (i.e. the patient's own or administered) noradrenaline. Increasing the window for recruitment enables us to study the effect of landiolol exposed longer to catecholamines for similar reasons.

- The vasopressin start dose has been amended to 0.03 u/min and stepping up to 0.06 u/min to allow variability of different practices at each site.

- Addition of end of noradrenaline treatment visit day biobank blood sample. The addition of this blood sample will further the understanding of the mechanistic outcomes involved when noradrenaline has stopped and the patient's deranged physiological status has been resolved.

- Additional wording to clarify co-enrolment can take place with other interventional studies where there is no possible conflict with STRESS-L trial objectives

- Additional wording to clarify Landilol may be administered peripherally or centrally but must be on a dedicated line

- Clarification that blood samples will be stored at -80 or -70 and sent in batches in the University of Birmingham instead of University Hospitals of Birmingham NHS Foundation Trust as stated in previous protocol

(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)

G.1.2 Removal of an existing site

G.1.2.1 Principal investigator (provide details below)

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

G.1.4 Change of principal investigator at an existing site (provide details below of the new 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 document[11] ☑

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:

This section was signed electronically by Miss Emma Skilton on 30/11/2018 15:04.

Job Title/Post: Trial Manager

Organisation: Warwick Clinical Trials Unit

Email: e.skilton@warwick.ac.uk

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:

This section was signed electronically by Miss Emma Skilton on 30/11/2018 15:04.

Job Title/Post: Trial Manager

Organisation: Warwick Clinical Trials Unit

Email: e.skilton@warwick.ac.uk

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