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:	V3.0
B.4 Sponsor's protocol date:	18/10/2018

(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:	Deborah
Contact Family name:	Popoola
Address:	1st Floor, Institute of Translational Medicine (ITM), Queen Elizabeth Hospital (old), Mindelsohn Way
Town/city:	Edgbaston, Birmingham
Post code:	B15 2GW
Telephone:	01213718006
Fax:	
E-mail:	deborah.popoola@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_10
Version:
Date: 2019/05/28

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:

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

If yes specify:

E.2.5 This amendment concerns mainly urgent safety measures already implemented[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 v4.0, 02 April 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 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:

~~Keith Young~~ Matthew Robinson

Prof Rupert Pears~~e~~e

Page 14:

The maximum treatment duration is 14 days

Pages 15, 16 & 31:

o Any form of compensatory tachycardia

o Any form of vasodilatory shock that is not caused by sepsis

~~o Have been treated with any beta-blocker drug in the seventy two hours prior to randomisation.~~

o Decision of withdrawal of care is in place or imminently anticipated

Page 16:

o ~~Individual organ failure-days in ICU survivors through measures of oxygenation, renal, hepatic and coagulation function; d~~Dose and duration of vasopressor treatment (total daily administered doses~~) of adrenaline, dobutamine, phosphodiesterase inhibitors~~)

o Myocardial Injury – Troponin-T, Beta Natriuretic Peptide, Creatine Kinase-MB, Arrhythmia, ~~Changes in ECG between Randomisation and End of ICU~~

Pages 26 & 27:

The trial will take place in approximately ~~35~~ 41 UK adult intensive care units (ICUs).

Adult patients in ICU with septic shock as defined by Sepsis-3 criteria who have required continuous vasopressor therapy for at least 24 hours, are being treated with 0.1 mcg/kg/min noradrenaline and a heart rate of 95bpm or greater will be eligible for entry. ~~Patients having received beta-blocker therapy in the previous 72 hours;~~ Patients with any form of compensatory tachycardia, patients with any form of vasodilatory shock that is not caused by sepsis, known sensitivity to beta-blockers; pre-existing severe cardiac dysfunction (NYHA grade 4 or more; treatment with a beta-agonist before the initiation of noradrenaline); or untreated second or third degree heart block will be excluded from the trial. Similarly, patients known to be pregnant; untreated phaeochromocytoma; pre-existing severe pulmonary hypertension (mean PA pressures >55mmHg); acute severe bronchospasm (due to asthma or COPD); known Prinzmetal's angina; a past history of ischaemic stroke or transient ischaemic attack (TIA) or untreated severe carotid stenosis; advanced liver disease with Child Pugh Score of ≥B; terminal illness other than septic shock with a life expectancy of <28 days, will be excluded. Patients who, in the opinion of the clinical staff, are about to finish noradrenaline therapy or have been administered an ~~in an IMP~~ for another IMP trial in the previous 30 days will also be ineligible.

Once eligibility criteria are met there is a ~~24~~48-hour window for recruitment. We aim to assess the efficacy, safety and mechanisms of beta-blockade within this population.

The primary outcome is the mean SOFA score over the first 14 days from entry into the trial and whilst in ICU. Secondary outcomes include mortality at day 28 and 90; length of ICU and hospital stay~~;~~ and reduction in dose and duration of vasopressor treatment ~~and individual organ failure-days in 28-day survivors~~. SOFA score and other data measurements will be collected for 14 days, and follow up data will be obtained at days 28 and 90. The DMC will review the available data at 6 monthly intervals and advise the TSC of any safety concerns.

Page 28:

Daily screening in ~~35~~ 41 ICUs for 36 months (N ~ 27500)

Page 29:

~~o Individual organ failure-days in 28-day survivors through measures of oxygenation, renal, hepatic and coagulation function~~
o Reduction in dose and duration of vasopressor treatment (total daily administered doses) ~~doses of adrenaline, dobutamine, phosphodiesterase inhibitors)~~

Page 30:

o In addition samples will be stored for subsequent analysis (e.g. genetics / proteomics / metabolomics) ~~as appropriate~~in order to investigate early cellular responses during the resolution of sepsis.

Page 32:

Where potential participants on ICU with septic shock are identified by a member of their usual care team as meeting the criteria of commencement of noradrenaline and having received adequate fluid resuscitation, will contact the research team at their hospital. If 24 hours after the start of noradrenaline, the potential participant remains tachycardic and on noradrenaline at >=0.1 mcg/kg/min, they may be screened against the inclusion and exclusion criteria to be eligible for the study. There is no restriction on the length of hospital or ICU stay prior to screening. Patients on ICU that develop sepsis after their arrival will be screened and included if the eligibility criteria ~~is~~are met. Patients may also be included if they recommence noradrenaline treatment for a new bout of sepsis more than 72 hours after the previous noradrenaline treatment has ended. If the patient recommences noradrenaline treatment less than 72 hours following the previous round of noradrenaline, the coordinating centre should be contacted to advise eligibility.~~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 48 hour window for randomisation. Due to this short window, informed consent may be sought during the first 24 hours of noradrenaline therapy. Randomisation should not occur until noradrenaline therapy has been running for ≥24 hours and the patient must b~~eremains~~ tachycardic. It will be made clear to the patient or their legal representative that if they do not remain on vasopressor therapy at the ~~48~~ 72 hour mark and are no longer tachycardic they will not be eligible for randomisation.

Page 34:

The randomisation will be stratified by recruiting site and noradrenaline dose where the dose reflects the participant's severity. The dose will be dichotomised using a value of 0.3 mcg/kg/min (i.e. ≥0.1 mcg/kg/min -to 0.3 mcg/kg/min and >0.3 mcg/kg/min) taken from the LeoPARDS trial as an indicator of low and high severity to ensure participant severity is balanced across both arms (81).

Once written informed consent has been obtained, a member of the local research team will use an interactive voice response (IVR) application to randomise. Due to the nature of this population an out of hour's randomisation service is required. Eligibility will be confirmed by an investigator prior to randomisation. Sites will only be given access to the application once they have been given the 'green light' to begin recruitment and all required approvals are in place. The IVR application will capture all the essential data required to randomise a participant and then provide the researcher with the unique participant trial number and allocation. ~~Additionally~~Additionally, an email confirmation of the allocation and participant ID/randomisation number will be sent to the site research team. Clinical notes will be labelled with a sticker, flagging the participant's ID and inclusion in the trial. In centres with electronic patient records, virtual flags will be placed where possible.

Page 35:

3.9.1.1 Starting Landiolol Infusion

3.9.1.2 Administering Landiolol Infusion
An intravenous infusion of landiolol starting at 1.0 mcg/kg/min and progressively increasing every 15 minutes at increments of 1.0 mcg/kg/min, to reach the target heart rate of 80-94 bpm usually within 6 hours. Landiolol may be administered peripherally or centrally but MUST be on a dedicated line. Landiolol has an elimination half-life of 2.3 to 4 minutes (48) and so a loading dose is unnecessary. The landiolol infusion should be continued until the pulse rate is persistently below 95.

While a patient is receiving vasopressor agents (noradrenaline, vasopressin), the landiolol infusion should be adjusted accordingly to maintain the target heart rate of 80-94bpm as per the landiolol infusion protocol (APPENDIX B: STRESS-L Study Drug Infusion Protocol) and APPENDIX E: Timing and Weaning of the Study Drug). Once the patient is consistently within the target heart rate of 80-94bpm, the Landiolol Infusion should continue and not be adjusted. If all vasopressor agents have been discontinued for less than 12 hours, the Landiolol Infusion will continue as per Appendix E.

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 End of Noradrenaline Treatment Visit (EONT) (see

section 3.9.5 Definition of End of Noradrenaline Treatment). This trial allows for up to 14 days of landiolol treatment per participant.

~~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. Landiolol infusion should not be stopped during procedures including trips to theatre, percutaneous tracheostomy, central line insertions etc.~~

3.9.1.3 Stopping the Landiolol Infusion
Once all vasopressor agents (noradrenaline, vasopressin) have been stopped for 12 hours, and the patient is consistently within target heart rate range, the landiolol infusion should begin to be reduced. However, the study drug infusion should continue even when vasopressors have finished and the EONT visit has occurred whilst the patient remains tachycardic.

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 Landiolol infusion should begin to be weaned at the ~~s~~end ~~tart~~ of Day 14 and eventually stopped. The use of alternative beta blockade is at the discretion of the treating clinician.

Landiolol infusion should not be stopped during procedures including trips to theatre, percutaneous tracheostomy, central line insertions etc.

There is no End of Therapy (EOT) visit defined in the Protocol as it is impossible to define for the group who receive Usual Treatment alone.

It is recommended that Landiolol infusion is stopped for at least 12 hours before the patient is discharged from the ICU. ~~However~~However, ICU stay should not be prolonged just for heart rate control. Landiolol should not be administered outside ICU. Oral beta blocker use after ICU discharge should be at discretion of the clinicians.

Page 36 & 37:

~~3.10.3 Stopping the study drug infusion~~
~~The landiolol infusion should be continued until pulse rate is persistently below 95. The study drug infusion should continue even when vasopressors have finished and the EONT visit has occurred whilst the patient remains tachycardic. The Study Drug infusion should run according to the protocol (APPENDIX B: STRESS-L Study Drug Infusion Protocol). This trial allows for up to 14 days of landiolol treatment per participant.~~
~~There is no End of Therapy (EOT) visit defined in the Protocol as it is impossible to define for the group who receive Usual Treatment alone.~~

~~It is recommended that Landiolol infusion is stopped for at least 12 hours before the patient is discharged from the ICU. However ICU stay should not be prolonged just for heart rate control. Landiolol should not be administered outside ICU. Oral beta blocker use after ICU discharge should be at discretion of the clinicians.~~

Page 39:

Treatment is up to 14 days. ~~Participants will be started on a dose of 1.0 mcg/kg/min landiolol intravenous infusion, progressively increasing every 15 minutes at increments of 1.0 mcg/kg/min, to reach the target heart rate of 80-94 bpm usually occurring over a period of 6 hours. Landiolol may be administered peripherally or centrally but MUST be on a dedicated line. Landiolol has an elimination half-life of 2.3 to 4 minutes and so a loading dose is unnecessary. The intervention treatment will be reduced if the patient's heart rate falls below 80 bpm. The landiolol infusion will continue until the patient's heart rate is persistently below 95 bpm, and will be reduced when all vasopressor agents have stopped for 12 hours. Once the landiolol infusion has been stopped for more than 12 hours, it should not be recommenced.~~ The maximum recommended daily dosage of landiolol for this patient population is 57.6mg/kg per day (based on 40 mcg/kg/min ~~in a 24 hour infusion~~).

Page 43:

The rates of noradrenaline infusion ~~and landiolol infusion (if randomised to this group)~~ will be recorded hourly.

Day 1 (time of randomisation to post 24 hours) up to day 14

Page 44:

Research blood samples will be collected on Days 0, 1, 2, 4 and 6 and the EONT visit (if this does not fall on a blood sampling day). Day 0 blood samples must be taken prior to start of Landiolol Infusion. Days 1, 2, 4, 6 and EONT blood samples can be taken when is convenient within the 24 hour time period. The plasma will be removed and stored as per detailed instructions provided in the trial Laboratory manual. These research blood samples are mandatory as the results are required to answer the secondary outcomes of the trial.

Page 45:

Central Venous Blood Gas / Arterial ~~Blood Gas~~ BG

Page 48:

They will encourage the clinical staff to use the guidance for infusion management in the Appendices of this protocol (see APPENDIX B: STRESS-L Study Drug Infusion Protocol and APPENDIX E: Timing and Weaning of the Study Drug) and support the clinical team in the decision to change the rate of the landiolol infusion but have no input into the management of blood pressure.

Page 49:

5.1.4 Clinical outcomes exempt from reporting
Clinical outcomes from sepsis are exempt from adverse event reporting, unless the investigator deems the event to be related to the administration of the study drug. The following events will be considered clinical outcomes and not liable for reporting as Adverse Events, Adverse Reactions, Serious Adverse Events and Suspected Unexpected Serious Adverse Events:

All SAEs / SUSARs occurring from the time of randomisation to the final follow up visit at day 90 must be recorded on the STRESS-L SAE Report Form and ~~faxed~~ emailed to the coordinating centre within 24 hours of the research staff becoming aware of the event.

Page 50:

Any change of condition or other follow-up information should be ~~faxed~~ emailed to the Sponsor/coordinating centre as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

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. ~~The Principal Investigator in each centre must report any SAEs and SUSARs to the trial coordinating centre within 24 hours of them becoming aware of the event. The SAE form should be completed and faxed to the dedicated fax at Warwick CTU: 02476 150549.~~ The trial ~~coordinator~~ manager will liaise with the investigator to compile all the necessary information. The trial coordinating centre is responsible for reporting SUSARs to the sponsor, REC and MHRA within required timelines.

Page 55:

All data will be handled in accordance with the new Data Protection Act~~ion~~ 2018.

Page 73:

APPENDIX E: TIMING AND WEANING OF THE STUDY DRUG

New wording:

Comments/ explanation/ reasons for substantial amendment:

Comments/ explanation/ reasons for substantial amendment:
Please see the table of protocol changes which includes the old and new/additional wording for Protocol v4.0, 2nd April 2019.

The key amendments are as follows:
• Minor additional and clarification wording changes regarding updated TSC membership, Landiolol Infusion processes, eligibility time frame window, blood sample timings and SAE reporting process.
• Addition of 'Any form of compensatory tachycardia' inclusion criteria to clarify patients with tachycardia for any reason other than sepsis will not be eligible for the trial. Patients on ICU will commonly experience tachycardia and when assessing eligibility sites must ensure the patient has a persistent sepsis-driven tachycardia to be eligible for the trial.
• Addition of 'Any form of Vasodilatory Shock that is not caused by sepsis' inclusion criteria to clarify patients with vasodilatory shock for any reason other than sepsis will not be eligible for the trial. Patients on ICU will commonly experience vasodilatory shock and when assessing eligibility sites must ensure the patient has a persistent sepsis-driven vasodilatory shock to be eligible for the trial.
• Removal of exclusion criteria 'Have been treated with any beta blocker drug in the seventy two hours prior to randomisation'. Screening Log data has revealed a significant number of patients who fulfil all other inclusion criteria are excluded due to previous beta blocker use 72 hours prior to randomisation. If a patient has received a

previous beta blocker and remain tachycardic this suggests the beta blocker has not worked and the patient could potentially benefit from enrolment into STRESS-L. Initially it was thought previous beta blocker use should be excluded to avoid confounding the analysis when isolating the effects of Landiolol as a sole beta blocker. However, the CRF will be updated post amendment to capture previous beta blocker use to ensure this is factored into the analysis. Furthermore, there are no safety concerns regarding removing this exclusion criteria.
• Addition of 'Decision of withdrawal of care is in place or imminently anticipated' exclusion criteria. This has been included to clarify patients who are actively withdrawing care should not be randomised to the trial.
• Removal of 'Individual organ failure days in 28 day survivors through measures of oxygenation, renal, hepatic and coagulation function'. To investigate this outcome, it was initially intended on using SOFA score data collected at Day 28 to act as a baseline measure to assess whether patients with chronic illness have a better long term outcome if randomised to the Landiolol treatment arm. The Trial Management Group have reviewed the current dataset which has revealed a high proportion of this data is unobtainable as it has proven difficult to retrieve this data from patients who are discharged from ICU and getting better. As the current dataset is not usable and there are no current analysis plans for this data, this secondary outcome will be removed.
• Addition of Appendix E: Timing and Weaning of Study Drug. Following feedback from sites, a flowchart has been devised to clarify how Landiolol should be titrated whilst the patient is either receiving noradrenaline or off noradrenaline.

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

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

Type of change:

G.1.1 Addition of a new site

G.1.1.1 Principal investigator (provide details below)

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

G.1.2 Removal of an existing site

G.1.2.1 Principal investigator (provide details below)

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

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

Given name
Middle name(if applicable)

Family name
Qualification (MD...)
Professional address

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

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

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

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

H CHANGE OF INSTRUCTIONS TO CA FOR FEEDBACK TO SPONSOR

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

H.2 Change to request to receive an .xml copy of CTA data ○ Yes ◉ No

H.2.1 Do you want a .xml file copy of the CTA form data saved on EudraCT? ○ Yes ○ No

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

H.2.2 Do you want to receive this via password protected link(s)[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 03/07/2019 15:27.

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 03/07/2019 15:28.

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.