STRESS-L Master Documents Version Log

Name	Version number	Document Date	Submission Date	REC Approval Date	Reason for change	Summary of changes made
ISF Section 2: Protocol						
Protocol	1.0	10/08/2017	23/08/2017	09/11/2017		
Protocol	2.0	31/07/2018	01/08/2018	14/08/2018	New drug labelling company and ambient batch of drug.	
Protocol	3.0	18/10/2018	30/11/2018	18/12/2018	Updates to eligibility criteria and further minor clarifications	• See protocol version log.
Protocol	4.0	02/04/2019	08/07/2019	29/07/2019	Updates to eligibility criteria, removal of Day 28 SOFA score and further clarifications	• See protocol version log
Protocol	5.0	17/12/2019	20/02/2020	15/04/2020	Updates to eligibility criteria, safety reporting clarifications and definition of End of Noadrenaline Treatment Visit timepoint.	• See protocol version log
Protocol	**6.0**	**26/06/2020**	N/A	N/A	Updates to processes in response to the ongoing COVID-19 pandemic	• See protocol version log
ISF Section 3: Information for Participants						
Patient Information Sheet	2.0	17/10/2017	20/10/2017	09/11/2017		
Patient Information Sheet	2.1	07/06/2018	13/08/2018	N/A	GDPR	• Additional text to clarify data processes in accordance with GDPR transparency requirements.
Patient Information Sheet	3.0	18/10/2018	30/11/2018	18/12/2018	Addition of biobank sample, and location of sample storage	• Additional text to include the addition of biobank blood sample, and to clarify blood samples to be sent to the University of Birmingham
Patient Information Sheet	4.0	24/01/2020	20/02/2020	15/04/2020	Minor clarification regarding the method used to extract blood from the patient as part of their standard clinical care.	• 'As part of your standard clinical care blood will have been taken from your cannula (a thin tube inserted into an artery or body cavity to administer medication)'.

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Patient Information Sheet	5.0	06/08/2020	N/A	N/A	Updated in response to the ongoing COVID-19 pandemic	• Verbal consent may be sought if there are concerns regarding risk of infection transmission due to the COVID-19 pandemic. • If patient has suspected or confirmed COVID-19, blood samples will not be taken to minimise risk of viral transmission.
Patient Information Sheet	**6.0**	**21/12/2020**	13/01/2021	03/02/2021	Updated in response to the ongoing COVID-19 pandemic	• Add two additional personal data special category variables (ethnicity and postcode) will be collected from trial participants. This information is relevant and key for the data analysis for the trial in this patient population. • A further change has also been added to clarify the research blood samples will be analysed at Higher Education Institutes other than the University of Birmingham.
Short Patient Information Sheet	2.0	17/10/2017	20/10/2017	09/11/2017		
Short Patient Information Sheet	3.0	18/10/2018	30/11/2018	18/12/2018	Addition of biobank sample, and location of sample storage	• Additional text to include the addition of biobank blood sample, and to clarify blood samples to be sent to the University of Birmingham
Short Patient Information Sheet	**4.0**	**20/08/2020**	N/A	N/A	Updated in response to the ongoing COVID-19 pandemic	• If patient has suspected or confirmed COVID-19, blood samples will not be taken to minimise risk of viral transmission.
Legal Representative Information Sheet	2.0	17/10/2017	20/10/2017	09/11/2017		
Legal Representative Information Sheet	2.1	07/06/2018	13/06/2018	N/A	GDPR	• Additional text to clarify data processes in accordance with GDPR transparency requirements.
Legal Representative Information Sheet	3.0	18/10/2018	30/11/2018	18/12/2018	Addition of biobank sample, and location of sample storage	• Additional text to include the addition of biobank blood sample, and to clarify blood samples to be sent to the University of

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						Birmingham
Legal Representative Information Sheet	4.0	24/01/2020	20/02/2020	15/04/2020	Minor clarification regarding the method used to extract blood from the patient as part of their standard clinical care.	• 'As part of their standard clinical care blood will be taken from his/her cannula (a thin tube inserted into an artery or body cavity to administer medication)'.
Legal Representative Information Sheet	5.0	06/08/2020	N/A	N/A	Updated in response to the ongoing COVID-19 pandemic	• Verbal consent can be sought from a relative if there are concerns regarding risk of infection transmission due to the COVID-19 pandemic. • If patient has suspected or confirmed COVID-19, blood samples will not be taken to minimise risk of viral transmission.
Legal Representative Information Sheet	**6.0**	**21/12/2020**	13/01/2021	03/02/2021	Updated in response to the ongoing COVID-19 pandemic	• Add two additional personal data special category variables (ethnicity and postcode) will be collected from trial participants. This information is relevant and key for the data analysis for the trial in this patient population. • A further change has also been added to clarify the research blood samples will be analysed at Higher Education Institutes other than the University of Birmingham.
Consent Form	2.0	17/10/2017	20/10/2017	09/11/2017		
Consent Form	2.1	28/09/2018	28/09/2018	N/A	Correct version number and date	• Version number and date corrected in reference to the information sheet.
Consent Form	3.0	18/10/2018	30/11/2018	18/12/2018	Addition of biobank sample, and location of sample storage	• Additional text to include the addition of biobank blood sample, and to clarify blood samples to be sent to the University of Birmingham
Consent Form	4.0	07/04/2020	08/04/2020	13/05/2020	Version number and date of information sheet changed	• Change to version number an date of information sheet reference following SA_14
Consent Form	**5.0**	**06/07/2020**	N/A	N/A	Updated in response to the	• Addition of witness signature for verbal

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					ongoing COVID-19 pandemic	consent if there are concerns regarding risk of infection transmission due to the COVID-19 pandemic.
Legal Representative Consent Form	2.0	17/10/2017	20/10/2017	09/11/2017		
Legal Representative Consent Form	2.1	28/09/2018	28/09/2018	N/A	Correct version number and date	• Version number and date corrected in reference to the information sheet.
Legal Representative Consent Form	3.0	18/10/2018	30/11/2018	18/12/2018	Addition of biobank sample, and location of sample storage	• Additional text to include the addition of biobank blood sample, and to clarify blood samples to be sent to the University of Birmingham
Legal Representative Consent Form	4.0	07/04/2020	08/04/2020	13/05/2020	Version number and date of information sheet changed	• Change to version number an date of information sheet reference
Legal Representative Consent Form	**5.0**	**26/06/2020**	N/A	N/A	Updated in response to the ongoing COVID-19 pandemic	• Addition of witness signature for verbal consent if there are concerns regarding risk of infection transmission due to the COVID-19 pandemic.
GP Letter	**1.0**	**10/08/2017**	23/08/2017	09/11/2017		
ISF Section 6: Individual Site Information & Approvals						
Investigator Training Log	1.0	07/12/2017	N/A	N/A		
Investigator Training Log	**2.0**	**27/07/2018**	N/A	N/A	Addition of missing field	• Addition of trainer name and role. • Addition of date of training at line level, rather than form level.
Delegation Log	1.0	07/12/2017	N/A	N/A		
Delegation Log	**2.0**	**22/02/2018**	N/A	N/A	Addition of missing field	Addition of delegate signature.
Relatives Poster	**1.0**	**29/10/2018**	30/11/2018	18/12/2018		
Poster for Clinical Areas	1.0	15/10/2018	N/A	N/A		
Poster for Clinical Areas	**1.1**	**25/01/2019**	N/A	N/A	Protocol Amendment	• Reflect change in eligibility for receiving continuous vasopressor infusion for less than 72 hours
Poster for Landiolol infusion	**1.0**	**31/10/2019**	N/A	N/A		
Landiolol Infusion protocol	**1.0**	**12/11/2019**	N/A	N/A		

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compliance						
STRESS-L Trial Certificate	**1.0**	**13/11/2019**	N/A	N/A		
STRESS-L Current Evidence Update	**1.0**	**12/11/2019**	N/A	N/A		
STRESS-L eligibility clarification	**1.0**	**23/10/2020**	N/A	N/A		
STRESS-L trial flexibility	**1.0**	**23/10/2020**	N/A	N/A		
STRESS-L quick consent guide	**1.0**	**23/10/2020**	N/A	N/A		
Eligibility pocket cards	**6.0**	**26/06/2020**	N/A	N/A		
STRESS-L training for ICU clinical staff	**3.0**	**16/08/2021**	N/A	N/A		
STRESS-L training for non-GCP delegated clinical staff	**3.0**	**29/06/2021**	N/A	N/A		
Take the stress out of STRESS-L!	**2.0**	**30/07/2021**	N/A	N/A		
Trial participant completion checklist	**5.0**	**28/06/2021**	N/A	N/A		
ISF Section 7: Study Drugs						
SPC	N/A	**29/06/2016 (Date of revision)**	23/08/2017	09/11/2017		
IMP Management Manual	1.0	20/12/2017	N/A	N/A		
IMP Management Manual	2.0	29/05/2018	N/A	N/A		The following has been clarified/added: • As a minimum, maximum and minimum temperature recordings of IMP should be carried out. • Site number and hospital name should be included in email to AOP when reporting temperature excursions. • AOP take 1-3 working days to respond to temperature excursions or within 24 hours for urgent cases. • Temperature logger data and relevant paperwork should be sent to Mawdsleys

Name	Version number	Document Date	Submission Date	REC Approval Date	Reason for change	Summary of changes made
						upon receipt of a new batch. • Turnaround times of ordering and receiving IMP from Mawdsleys. • Landiolol must be administered intravenously via a separate central line or peripheral line. • A label will be added to reconstituted syringes as per standard local medicines policies. • Expansion of Landiolol dosing chart guide. • Addition of ICU IMP destruction log.
IMP Management Manual – for ambient stock only	3.0	07/08/2018			To accommodate transition to ambient IMP stock.	• Amended to include CSM Germany instead of Reig Jofre will perform final trial labelling and packaging of ambient trial drug • Updated storage conditions of IMP due to new ambient batch. • Removal of temperature excursion reporting process as no longer required. • Confirmation that ideal body weight should be used for patients under 40kg and 100kg when administering Landiolol.
IMP Management Manual – for ambient stock only	3.1	03/10/2018			To clarify small error	• Section 4.3 updated as previously incorrectly stated 'Pharmacy will release 1 box at a time for storage in the ICU refrigerator'. Refrigerator has been removed as no special storage conditions required for ambient IMP.
IMP Management Manual – for ambient stock only	3.2	21/12/2018	N/A	N/A	To clarify processes and inform sites QP release is no longer issued from Mawdsleys.	• For practicality, non-delegated trials pharmacists/technicians can completed IMP Inventory and Destruction log if appropriately trained. • 2 boxes of IMP can be kept within ICU instead of pharmacy if preferred. • QP release from Mawdsleys no longer

Name	Version number	Document Date	Submission Date	REC Approval Date	Reason for change	Summary of changes made
						issued for ambient stock.
IMP Management Manual – for ambient stock only	**3.3**	12/02/2019	N/A	N/A	Addition of version numbers	• Addition of version numbers to the attached Pharmacy IMP Inventory Log, ICU IMP Inventory Log, Pharmacy Training Log, IMP Destruction Log and ICU IMP Destruction Log.
IMP Management Manual	4.0	09/05/2019	N/A	N/A	To accommodate transition to refrigerated IMP stock	• Storage conditions changed to 2-8 degrees and temperature monitoring required.
IMP Management Manual	4.1	07/11/2019	N/A	N/A	To clarify processes regarding temperature excursion reporting and back-up supply	• Addition of out of hours temperature excursions guidance supported by signed AOP Orphan QP statement • Clarification regarding rounding temperature excursions supported by signed AOP Orphan QP statement • Alteration to number of back-up supply boxes as sites should have a minimum of 80 vials on site • Extended Landiolol Dosing chart table
IMP Management Manual	5.0	17/08/2020	N/A	N/A	Additional stability data to support temperature excursions up to 25 degrees for a maximum of 1 week	• Updated information regarding identifying and reporting temperature excursions with new flow chart.
IMP Management Manual	**5.1**	**07/10/2020**	N/A	N/A	To clarify processes regarding 1 week temperature excursion reporting	• Clarified guidance regarding 1-week temperature excursion rule applying to individual excursions.
Pharmacy IMP Inventory Log	**1.0**	**01/12/2017**	N/A	N/A		
ICU IMP Inventory Log	**1.0**	**01/12/2017**	N/A	N/A		
Pharmacy IMP Destruction Log	**1.0**	**01/12/2017**	N/A	N/A		
ICU IMP Destruction Log	**1.0**	**22/07/2018**	N/A	N/A		
ISF Section 8: Laboratory						
Lab Manual	1.0	12/03/2018	N/A	N/A		

Name	Version number	Document Date	Submission Date	REC Approval Date	Reason for change	Summary of changes made
Lab Manual	2.0	21/12/2018	N/A	N/A	Protocol amendment	• Addition of PaxGene RNA Blood Tube to be taken at EONT
Lab Manual	3.0	06/07/2020	N/A	N/A	Updated in response to the ongoing COVID-19 pandemic	• If patient has suspected or confirmed COVID-19, blood samples will not be taken to minimise risk of viral transmission.
Lab Manual	**4.0**	**02/03/2021**	N/A	N/A	Updated to clarify blood sampling guidance	• Blood samples should continue to be taken regardless of whether the patient has stopped landiolol treatment and/or discontinued noradrenaline treatment for more than 12 hours reaching the EONT visit time point.
Blood Sample Storage Form	1.0	26/03/2018	N/A	N/A		
Blood Sample Storage Form	**1.1**	**25/06/2018**	N/A	N/A	Addition of missing field	• Addition of stored by column
Blood Sample Transport Form	1.0	26/03/2018	N/A	N/A		
Blood Sample Transport Form	1.1	25/06/2018	N/A	N/A	Addition of missing field	• Addition of initials of receiver
Blood Sample Transport Form POST COVID	**2.0**	**07/10/2020**	N/A	N/A	Addition of confirmation of -ve COVID test	• Addition of confirmation of -ve COVID test
Blood Sample Schedule Information	1.0	31/01/2020	N/A	N/A	N/A	• Aide memoir for blood sample schedule
Blood Sample Schedule Information	**2.0**	**06/07/2020**	N/A	N/A	Updated in response to the ongoing COVID-19 pandemic	• Blood samples should not be taken for suspected or confirmed positive COVID-19 patients.
Section 10: Data Collection						
Screening Log	1.0	07/12/2017	N/A	N/A		
Screening Log	2.0	04/04/2018	N/A	N/A		
Screening Log	3.0	14/09/2018	N/A	N/A		
Screening Log	4.0	04/10/2018	N/A	N/A		
Screening Log	5.0	13/12/2018	N/A	N/A	Amended following feedback	• Addition of further information regarding patients' ineligibility
Screening Log	6.0	08/02/2019	N/A	N/A	Amended following feedback	• Addition of profile of patients to screen

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						• Streamlining of information regarding patient's ineligibility
Screening Log	7.0	26/07/2019	N/A	N/A	Protocol amendment	• Changes to eligibility criteria
Screening Log	**8.0**	**30/07/2020**	N/A	N/A	Protocol amendment	• Changes to eligibility criteria
Enrolment Log	**1.0**	**07/12/2017**	N/A	N/A		
Initial Serious Adverse Event Form	1.0	19/12/2017	N/A	N/A		
Initial Serious Adverse Event Form	1.1	28/02/2018	N/A	N/A	Amended following feedback	Formatting changes & addition of CI confirmation.
Initial Serious Adverse Event Form	2.0	**14/05/2019**	N/A	N/A	Protocol amendment	• Removal of instruction to fax SAE forms • Expectedness and event classification now completed by WCTU
Follow-up Serious Adverse Event Form	1.0	19/12/2017	N/A	N/A		
Follow-up Serious Adverse Event Form	1.1	28/02/2018	N/A	N/A	Amended following feedback	Formatting changes & addition of CI confirmation.
Follow-up Serious Adverse Event Form	2.0	**14/05/2019**	N/A	N/A	Protocol amendment	• Removal of instruction to fax SAE forms • Expectedness and event classification now completed by WCTU
Serious Adverse Event Continuation Form	1.0	19/12/2017	N/A	N/A		
Serious Adverse Event Continuation Form	**2.0**	**26/06/2019**	N/A	N/A	Protocol amendment	• Removal of instruction to fax SAE forms
CRF Booklet	1.0	20/12/2017	N/A	N/A		
CRF Booklet	2.0	24/05/2018	N/A	N/A	Refined following feedback	• Formatting changes • Data validations refined • Collecting date and time vasopressor support started (if another vasopressor preceded noradrenaline, for example metaraminol • Venous PaO2 and PaCO2 are optional assessments • Day 0 lactate will be highest value in last 48

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						hours. Later lactate measurements will be most recent assessments. • Glucose measurements will be most recent assessment.
CRF Booklet	3.0	11/01/2019	N/A	N/A	Protocol amendment	• Inclusion and exclusion criteria updated on eligibility form in line with protocol amendment (v3.0, 18 October 2018).
CRF Booklet	4.0	12/03/2019	N/A	N/A	Addition of missing field	• Additional Assessments: inclusion of optional Biobank sample at EONT time point
CRF Booklet	5.0	18/04/2019	N/A	N/A	Amendment of error	• Landiolol unit on paper CRF corrected from ml/hr to mcg/kg/min • Addition of blood sample guidance • Clarification of cardiovascular form completion timelines
CRF Booklet	5.1	26/07/2019	N/A	N/A	Protocol amendment	• Inclusion and exclusion criteria updated on eligibility form in line with protocol amendment (v4.0, 02 April 2019). • Day 28 Follow Up SOFA score data removed
CRF Booklet	5.2	14/01/2020	N/A	N/A	Correction to exclusion criteria	• Advanced liver disease with Child-Pugh Score of ≥B (greater than or equals to)
CRF Booklet	6.0	06/07/2020	N/A	N/A	Protocol amendment	• Inclusion and exclusion criteria updated on eligibility form in line with protocol amendment (v5.0, 17 December 2019).
CRF Booklet	**7.0**	**26/11/2020**	N/A	N/A	Updated in align with updated electronic database capture	• Addition of patient ethnicity, patient postcode, COVID status, pre-set list of concomitant illnesses, height, number of plasma cryovials extracted & paxgene tubes taken and covid as a reason blood sample not taken questions. • Temporary Inotrope CRF questions moved to SOFA score CRF. Completion of the paper temporary inotrope CRF no longer required as data captured via e-CRF.

(Current versions in use are highlighted in yellow)

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						• Other Beta Blocker CRF moved to main CRF. Completion of the paper beta blocker CRF no longer required as data captured via e-CRF. • Addition of 'other' option for fluids in. • Addition of 'significant hypotension requiring intervention' event on cardiovascular safety outcome data CRF. • Addition of corrective and preventative action questions on protocol non-compliances CRF.
Eligibility Form	1.0	24/05/2018	N/A	N/A		
Eligibility Form	2.0	11/01/2019	N/A	N/A	Protocol amendment	• Inclusion and exclusion criteria updated on eligibility form in line with protocol amendment (v3.0, 18 October 2018).
Eligibility Form	3.0	26/07/2019	N/A	N/A	Protocol amendment	• Inclusion and exclusion criteria updated on eligibility form in line with protocol amendment (v4.0, 02 April 2019).
Eligibility Form	3.1	14/01/2020	N/A	N/A	Correction to exclusion criteria	• Advanced liver disease with Child-Pugh Score of ≥B (greater than or equals to)
Eligibility Form	**4.0**	**06/07/2020**	N/A	N/A	Protocol amendment	• Inclusion and exclusion criteria updated on eligibility form in line with protocol amendment (v5.0, 17 December 2019).
Randomisation Form	1.0	02/11/2017	N/A	N/A	N/A	N/A
Randomisation Form	**2.0**	**26/11/2020**	N/A	N/A	IVR system update	• What is the current noradrenaline dose question response option updated from ≤0.1 to '≤0.1-0.3 mcg/kg/min' to provide a range.
End of Trial and Sign off statement	**1.0**	**24/05/2018**	N/A	N/A	N/A	N/A
Temporary Inotrope Dose Form	**1.0**	**07/11/2018**	N/A	N/A	N/A	N/A **DOCUMENT NO LONGER VALID AS DATA IS CAPTURED VIA e-CRF ON DATABASE**

(Current versions in use are highlighted in yellow)

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Beta-Blocker Collection Form	1.0	19/07/2019	N/A	N/A	N/A	N/A
Beta-Blocker Collection Form	**2.0**	**17/09/2019**	N/A	N/A	Amended following Data Analysis review	• Removal of beta blocker name, dose, unit and frequency. • Addition of patient taking beta-blockers 2 weeks prior to and on admission to ICU. **DOCUMENT NO LONGER VALID AS DATA IS CAPTURED VIA e-CRF ON DATABASE**
CRF Completion Guidelines	1.0	22/01/2018	N/A	N/A		
CRF Completion Guidelines	2.0	24/05/2018	N/A	N/A	Amended to reflect changes to CRF.	• Amended to reflect changes to CRF. • Clarification of highest inotrope. • Clarification of SOFA collection time points.
CRF Completion Guidelines	2.1	27/07/2018	N/A	N/A	Refined following feedback.	• Page 3: Addition of Paper CRF Instructions and Data Collection Time Point Guidelines. • Page 9: Clarification of date and time hospital and ICU admissions. • Page 11: Clarification that if noradrenaline has been discontinued for >12 hours but is restarted before you can complete the EONT Form, the form should still be completed. • Page 14: Clarification of SOFA score data collection.
CRF Completion Guidelines	2.2	18/04/2019	N/A	N/A	Amended to reflect changes to CRF	• Amended to reflect changes to CRF. • Page 12: Clarification of PI sign off form completion timelines.
CRF Completion Guidelines	2.3	18/09/2019	N/A	N/A	Amended to clarify guidance	• Addition of IN | OUT Fluids category guidance
CRF Completion Guidelines	3.0	06/07/2020	N/A	N/A	Updated in response to the ongoing COVID-19 pandemic	• Document positive COVID-19 infections in Microbiology Specimens CRF
CRF Completion Guidelines	**4.0**	**20/09/2021**	N/A	N/A	Updated to reflect database updates	• New guidance instructions on how to use updated database • Additional questions added to reflect CRF

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						booklet changes (v7.0 26 November 2020).
ISF Section 12: Trial Specific Working Instructions						
Frequently Asked Questions	1.0		N/A	N/A		
Frequently Asked Questions	2.0	25/01/2019	N/A	N/A	Amended following feedback	• Updated FAQs following feedback
Frequently Asked Questions	2.1	08/05/2019	N/A	N/A	Amended following feedback	Updates to • Inclusion criteria and screening section • IMP management section • Addition of new safety section
Frequently Asked Questions	3.0	31/07/2019	N/A	N/A	Amended following v4.0 Protocol Amendment	• Clarification regarding beta block usage and Landiolol administration
Frequently Asked Questions	**4.0**	**06/07/2020**	N/A	N/A	Amended following v5.0 Protocol Amendment and in response to COVID-19 pandemic	• Clarification regarding protocol v5.0 eligibility criteria • Blood samples will not be taken for suspected or confirmed COVID-19 patients.
Data Transfer Working Instructions	1.0	21/06/2018	N/A	N/A		
Data Transfer Working Instructions	**1.1**	**17/07/2018**	N/A	N/A	Updated	• Updated link to HSCIC website provided
Trial Participant Completion Checklist	1.0	09/08/2019	N/A	N/A		
Trial Participant Completion Checklist	2.0	27/01/2020	N/A	N/A	To clarify activities required for both arms	• Clarification blood samples and baseline ECG must be taken for both arms (interventional and standard care)
Trial Participant Completion Checklist	3.0	06/07/2020	N/A	N/A	Updated in response to the ongoing COVID-19 pandemic	• Blood samples will not be taken for suspected or confirmed COVID-19 patients.
Trial Participant Completion Checklist	4.0	24/02/2021	N/A	N/A	Updated to reflect new blood sampling guidance	• Blood samples should continue to be taken regardless of whether the patient has stopped landiolol treatment and/or discontinued noradrenaline treatment for more than 12 hours reaching the EONT visit time point. • Clarification current heart rate, noradrenaline dose and start of

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						vasoporessor therapy should be documented in the patients' medical notes at the time of the eligibility assessment alongside the presence of a persistent sepsis driven tachycardia.
Trial Participant Completion Checklist	**5.0**	**28/06/2021**	N/A	N/A	Correct typo error and clarify ECG timing	• IVR telephone number corrected to remove extra 6 digit. • Timing of ECG updated to clarify this can be taken up to 24 hours prior to randomisation.