STRESS-L Protocol Version Control Log

Protocol Version 2.0 (31/07/2018) Summary of Changes

Page(s)	Section	Previous wording	New Wording
3-4	Contact Names and Numbers	Trial Coordinator: Nafisa Boota Warwick Clinical Trials Unit, Tel: 02476 572905 Email: stress-l@warwick.ac.uk	Trial Manager: Emma Skilton Warwick Clinical Trials Unit, Tel: 02476 572905 Email: stress-l@warwick.ac.uk
		Senior Project Manager: Dr Sukhi Dosanjh	Senior Project Manager: Scott Regan
		Trial Steering Committee: TBD – Lay Independent Member	Keith Young – Lay independent member
		Fax: TBD	Fax: 02476151136
		Clinical queries should be directed to the Study Coordinator as above who will direct the query to the appropriate person.	Clinical queries should be directed to the Trial Manager as above who will direct the query to the appropriate person.
31-33	Details of Investigational Medicinal	Final trial labelling and QP release of trial drug will be carried out by Laboratorio Reig Jofré (Spain) and distributed to sites by a UK based distribution company.	Final trial labelling and QP release of trial drug will be carried out by CSM Germany and distributed to sites by Mawdlseys a UK based distribution company.
		Laboratorio Reig Jofré (Spain) will label the primary (vials) and secondary (outer carton) packaging according to the requirements of the STRESS-L trial and Annex 13 of EU Guidelines to Good Manufacturing Practice.	CSM Germany will label the primary (vials) and secondary (outer carton) packaging according to the requirements of the STRESS-L trial and Annex 13 of EU Guidelines to Good Manufacturing Practice.
		The final product will be QP released for use in the STRESS-L trial by the designated person at Laboratorio Reig Jofré (Spain).	The final product will be QP released for use in the STRESS-L trial by the designated person at AOP Orphan Pharmaceuticals (Austria).

		Laboratorio Reig Jofré (Spain) will ship bulk trial supplies to a third party distributor in the UK for storage and distribution to UK sites.	CSM Germany will ship bulk trial supplies to Mawdsleys in the UK for storage and distribution to UK sites.
		Storage of trial drug at site will be in a secure location, in a temperature controlled environment, with a temperature log maintained for each working day.	Storage of trial drug at site will be in a secure location. The initial batch of drug will be stored in a temperature controlled environment, with a temperature log maintained for each working day.
		N/A.	Subsequent batches to be used will follow these storage conditions or comply with section 6.4 of the Summary Product of Characteristics.

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Protocol Version 3.0 (18/10/2018) Summary of Changes

Page(s)	Section	Previous wording	New wording
4	Contact names and numbers	Trial Steering Committee: Nafisa Boota, Trial Coordinator	Trial Steering Committee: Emma Skilton, Trial Manager
9	Trial Summary – Treatment duration	less than 48 hours	less than 72 hours
		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.
10 24-25	Trial Summary – Eligibility Criteria 3.4 Eligibility Critiera	Receiving vasopressor support with noradrenaline to maintain a target blood pressure for ≥ 24 hours	Receiving vasopressor support to maintain a target blood pressure for ≥24 hours
		>48 hours after start of vasopressor therapy	>72 hours in the current cause of septic shock after start of vasopressor therapy
		Untreated pheochromocytoma	Untreated phaeochromocytoma
		Advance Liver Disease	Advanced Liver Disease with Child-Pugh Score of ≥B
		Have been treated with any beta-blocker drug in the seventy two hours prior to screening.	Have been treated with any beta-blocker drug in the seventy two hours prior to randomisation.
		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.
18	Need for a trial	By targeting patients with persisting tachycardia and vasopressor requirement, the study group is a particular	By targeting patients with spontaneous persisting tachycardia and vasopressor requirement, the study group is a particular at-risk cohort.

		at-risk cohort.	
19	Investigation of Immune Modulation	Blood will also be drawn at study entry (D0), and at Day 1 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) analyses on these samples.	Blood will also be drawn at study entry (D0), 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 0,1 and EONT) analyses on these samples.
19 - 20	2.7 Ethical considerations	All data will be stored securely and held in accordance with Data Protection Act 1998.	All data will be stored securely and held in accordance with the new Data Protection Action 2018.
		N/A	Participant information sheets have been updated to include a data transparency statement in line with GDPR guidance from the HRA.
21	3.1 Trial summary and flow diagram	The trial will take place in 35 UK adult intensive care units (ICUs).	The trial will take place in approximately 35 UK adult intensive care units.
		;advanced liver disease;	;advanced liver disease with Child-Pugh Score of ≥B;
23	Secondary outcomes	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.	N/A – previous wording deleted.
26	3.5 Co-enrolment	N/A	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.
	3.6 Participant identification	N/A	Patients on ICU that develop sepsis after their arrival will be screened and included if the eligibility criteria are 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.
	3.6 Participant identification	Once eligibility criteria are met there is a 24 hour window for randomisation.	Once eligibility criteria are met there is a 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 hour mark and are no longer tachycardic they will not be eligible 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 48 hour mark and are no longer tachycardic they will not be eligible for randomisation.
27	3.7 Informed Consent	N/A	They will be asked to consider the wishes of the participant and if they agree to provide ongoing participation for their relative, partner or close friend in the trial. 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.
29	3.9.1 Intervention	'…the patient has reached the target mean arterial pressure pre-defined by the treating clinician	'…the patient has reached the target mean arterial pressure by the treating clinician overseeing care (suggested target 65-70 mmHg but

		overseeing care (suggested target 65-70 mmHg but this may be varied as detailed below) using vasopressors'.	this may be varied as detailed below) using vasopressors.
29 & 32	3.9.1 Intervention and 3.10.2 Dosage and excipients	N/A	Landiolol may be administered peripherally or centrally but MUST be on a dedicated line.
29	3.9.1 Intervention	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.
30	3.9.3 Stopping the study drug infusion	The study drug infusion should continue even when vasopressors have finished and the EONT visit has occurred whilst the patient remains tachycardic, without landiolol.	The study drug infusion should continue even when vasopressors have finished and the EONT visit has occurred whilst the patient remains tachycardic.
30	3.9.4 Control / Usual Care	N/A	If the treating clinician deems a beta blockade necessary, this will be captured on the Case Report Form and reported as a protocol deviation.
30	3.9.3 Stopping the study drug infusion	The study drug infusion should continue even when vasopressors have finished and the EONT visit has occurred whilst the patient remains tachycardic without landiolol.	The study drug infusion should continue even when vasopressors have finished and the EONT visit has occurred whilst the patient remains tachycardic.
30	3.9.4 Control / Usual Care	N/A	If the treating clinician deems beta blockade necessary, this will be captured on the Case Report Form and reported as a protocol

			deviation
31	3.9.4 Cardiovascular	In all patients we will compare oxygen delivery between treatment groups using central venous oxygen saturations ($ScvO_2$) and matched to the arterial saturations (SaO_2). This should be measured and recorded at baseline, and days 1, 2, 4 and 6 after randomisation if central venous access is available.	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, 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.	After fluid resuscitation, it should be titrated to maintain a target mean arterial pressure (MAP) by the clinician overseeing care.
		If used, vasopressin should be instigated at a fixed dose of 0.06 U/min as outlined in the vasopressor infusion protocol (APPENDIX C).	If used, vasopressin should be instigated at a fixed dose of 0.03 and stepping up to 0.06 U/min as outlined in the vasopressor infusion protocol (APPENDIX C).
32	3.10.1 Landiolol 300mg/50ml details	Final trial labelling and QP release of trial drug will be carried out by CSM Germany and distributed to sites by Mawdsleys.	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 distributed to sites by Mawdsleys.
32	3.10.4 Storage, dispensing and returns	The trial drug will be stored under temperature controlled conditions in the UK by a 3rd party contractor for distribution to participating trial centres.	The trial drug will be stored in the UK by a 3rd party contractor for distribution to participating trial centres.
33	3.20.4 Storage, dispensing and returns	It is envisaged between 2 and 4 vials will be required per participant for a 24 hour infusion.	N/A – previous wording deleted.
34	3.10.6 Contraindications, special warnings and precautions in the context of septic shock	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.

35	3.12 End of Trial	This study will end when the specified number of patients have been recruited, all patients have completed 6 month follow-up and the database is locked.	This study will end when the specified number of patients have been recruited, all patients have completed 3 month follow-up and the database is locked.
36-37	4.1 Schedule of delivery of intervention and data collection	Randomisation should not occur until noradrenaline therapy has been running for >24 hours and the patient remains tachycardic.	Randomisation should not occur until 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 (Day 0)	Baseline visit – 24 hours prior and up to the time of randomisation (Day 0)
		Echocardiogram	Electrocardiogram
		The rates of noradrenaline infusion and landiolol infusion (if randomised to this group) should be recorded hourly until day 7 to allow comparison of noradrenaline dosing.	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.
		The serum will be removed and stored as per detailed instructions provided in the trial Laboratory manual.	The plasma 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.	N/A – previous wording deleted.
		A biobank blood sample will be collected on Day 0 and Day 1 if the patient (or their legal representative) has consented to provide these.	A biobank blood sample will be collected on Day 0, 1 and EONT visit if the patient (or their legal representative) has consented to provide these.

38	Table 1: Trial Assessments	Baseline	Baseline (Day 0 -24hr – T0)
		Day 1	Day 1(T0+24)
		Glucose time points: Baseline, Days 1 – 14 and EONT.	Altered time points: Baseline, Days 1, 2, 4, 6 and EONT.
		Lactate time points: Baseline, Days 1 – 14 and EONT.	Altered time points: Baseline, Days 1, 2, 4 6 and EONT.
		N/A	Liver Function Tests (ALT or AST): Baseline, Days 1, 2, 4, 6 and EONT.
		Venous Blood Gas	Central Venous Blood Gas / Arterial Blood Gas, altered time points: Baseline, Days 1, 2, 4, 6 and EONT.
		Atrial Fibrillation (Hourly: T0+7 days): Baseline, Days 1-14 and EONT.	Altered time points: Baseline, Days 1, 2, 3, 4 and 5.
		Blood Pressure (Hourly: T0+ 7 days): Baseline, Days 1 – 14 and EONT	Altered time points: Baseline, Days 1, 2, 3, 4 and 5.
		Rate of vasopressor	Rate of vasopressor / inotropes
		Steroid use: Baseline, Days 1 – 14 and EONT	Altered time points: Baseline, Days 1, 2, 4, 6 and EONT.
39	4.2 Transport and storage of research samples	The blood samples will be centrifuged and the serum isolated will be temporarily stored at-20 °C or -70 °C at the respective sites.	The blood samples will be centrifuged and the plasma isolated will be temporarily stored at -20 °C or -80 °C/-70 °C at the respective sites.
		N/A	Freezer temperature excursions will be monitored in accordance with local Trust policy.
		Regular frozen shipments of serum will be arranged to the University Hospitals of Birmingham NHS Foundation Trust (UHB) for subsequent analysis.	Batch frozen shipments of plasma will be arranged to the University of Birmingham for storage and subsequent analysis.
		Specifically chosen participating sites, close to suitable analysers, will retain part of the fresh blood samples	N/A – previous wording deleted.

		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 (5ml) will be collected on Day 0 and Day 1 if the patient (or their legal representative) has consented to provide these.	A Biobank blood sample (5ml) will be collected on Day 0, Day 1 and EONT visit, if the patient (or their legal representative) has consented to provide these.
		As with the research blood samples these will be centrifuged and the serum isolated will be temporarily stored at -20°C or -70°C at the respective sites.	Whole blood will be temporarily stored at –20°C and then transferred to -80°C/-70°C at the respective sites.
		The frozen serum will be sent in batches to the Human Biomaterials Resource Centre (HBRC) at the University of Birmingham.	The frozen blood 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.	Samples stored at the University of Birmingham will be stored in accordance with the Human Tissue Act 2004.
41	5.1.3 Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Events (SUSARs)	Hepatic impairment as measured by Transaminases <1000 IU/L.	Hepatic impairment as measured by Transaminases 10xULN (Upper Limit Normal)
42 & 43	5.2 Reporting SAEs and SUSARs	SAEs and SUSARs will be reporting using the SAE form in the participant's eCRF.	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 Summary of Product Characteristics (SPC) for landiolol will be used to assess expectedness of events (known as the reference safety information).	Section 4.8 of the Summary of Product Characteristics (SPC) for landiolol will be used to assess expectedness of events (known as the reference safety information).

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46-47	6. Data Management	N/A	New Data Protection Act 2018.
48	7.2 Planned recruitment rate	A maximum 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.	A 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.
49	7.3 Statistics and data analysis	Interim analyses will be conducted every 6 months to closely monitor the accumulating data.	The DMC will meet every 6 months to closely monitor the accumulating data, focusing on safety.
52	8.10 Data Monitoring Committee (DMC)	Confidential reports containing recruitment, protocol compliance, safety data and interim assessments of outcomes will be reviewed by the DMC.	Confidential reports containing recruitment, protocol compliance, safety and outcome data will be reviewed by the DMC.
63	Appendix C: STRESS-L Vasopressor Infusion Protocol	Consider starting Vasopressin infusion at 0.06 u/min.	Consider starting Vasopressin infusion at 0.03 u/min and stepping up to 0.06 u/min.
64	Appendix D: Landiolol Infusion Rate	N/A	For participants below 40 kg or over 100 kg ideal body weight will be used (method as per local practice). Additional body weight calculations added.

STRESS-L Protocol Version Control Log

Protocol Version 4.0 (02/04/2019) Summary of Changes

Page(s)	Section	Previous wording	New Wording
4	**Contact names and numbers**	Keith Young	Matthew Robinson
		Prof Rupert Pearce	Prof Rupert Pearse
09-11	**1. Trial Summary**	*N/A*	The maximum treatment duration is 14 days
		N/A	Any form of compensatory tachycardia
		N/A	Any form of vasodilatory shock that is not caused by sepsis
		Have been treated with any beta blocker drug in the seventy two hours prior to randomisation	*N/A – previous wording removed*
		N/A	Decision of withdrawal of care is in place or imminently anticipated
		Individual organ failure days in ICU survivors through measures of oxygenation, renal, hepatic and coagulation function	*N/A – previous wording removed*
		Dose and duration of vasopressor treatment (total daily administered doses of adrenaline, dobutamine, phosphodiesterase inhibitors)	Dose and duration of vasopressor treatment (total daily administered doses)
		Changes in ECG between Randomisation and End of ICU	*N/A – previous wording removed*
14	**2.1 Lay Scientific Summary**	We propose to repeat their study in multiple (approx. 40) intensive care units…	We propose to repeat their study in multiple (approx. 41) intensive care units...
20	**2.7 Ethical considerations**	Septic shock and multi-organ failure cause confusion and many patients will not have capacity to consent to inclusion in the trial.	Septic shock and multi-organ failure causes confusion and many patients will not have capacity to consent to inclusion in the trial.
21-23	**3.1 Trial summary and flow diagram**	The trial will take place in approximately 40 UK adult intensive care units (ICUs).	The trial will take place in approximately 41 UK adult intensive care units (ICUs).

		…patients with any form of vasodilatory shock that is not cause by sepsis…	…patients with any form of vasodilatory shock that is not caused by sepsis…
		Patients having received beta blocker therapy in the previous 72 hours	*N/A – previous wording removed*
		N/A	Patients with any form of compensatory tachycardia, patients with any form of vasodilatory shock that is not caused by sepsis
		Patients who are about to finish noradrenaline therapy or have been in an IMP trial in the previous 30 days will also be ineligible.	Patients who, in the opinion of the clinical staff, are about to finish noradrenaline therapy have been administered an IMP for another IMP trial in the previous 30 days or decision of withdrawal of care is in place or imminently anticipated will also be ineligible.
		Once eligibility criteria are met there is a 24 hour window for recruitment.	Once eligibility criteria are met there is a 48 hour window for recruitment.
		; individual organ failure days in 28 day survivors	*N/A – previous wording removed*
		Daily Screening in 35 ICUs for 36 months	Daily Screening in 41 ICUs for 36 months
24-25	**3.3.1 Efficacy Secondary outcomes**	Individual organ failure days in 28 day survivors through measures of oxygenation, renal, hepatic and coagulation function	*N/A – previous wording removed*
		Reduction in dose and duration of vasopressor treatment (total doses of adrenaline, dobutamine, phosphodiesterase inhibitors)	Reduction in dose and duration of vasopressor treatment (total daily administered doses)
		Changes in ECG between Randomisation and End of ICU	*N/A – previous wording removed*
		In addition samples will be stored for subsequent analysis (e.g. genetics / proteomics / metabolomics) as appropriate	In addition samples will be stored for subsequent analysis (e.g. genetics / proteomics / metabolomics) in order to investigate early cellular responses during the resolution of sepsis
26	**3.4.2 Exclusion criteria**	*N/A*	Any form of compensatory tachycardia

		N/A	Any form of vasodilatory shock that is not caused by sepsis
		Having been treated with any beta blocker during in the seventy two hours prior to randomisation	*N/A – previous wording removed*
		N/A	Decision of withdrawal of care is in place or imminently anticipated.
27	**3.6 Participant identification**	Patients may also be included if the recommence noadrenaline treatment for a new bout of sepsis 72 hours after the previous noradrenaline treatment.	Patients may also be included fi they recommence noradrenaline treatment for a new bout of sepsis more than 72 hour after the previous noradrenaline treatment has ended.
		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.	If the patient recommences noradrenaline treatment less than 72 hours following the previous round of noadrenaline, the coordinating centre should be contacted to advise eligibility.
		Randomisation should not occur until noradrenaline therapy has been running for ≥24 hours and the patient remains tachycardic.	Randomisation should not occur until noradrenaline therapy has been running for ≥24 hours and the patient must be 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 hour mark and are no longer tachycardic they will not be eligible 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 72 hour mark and are no longer tachycardic they will not be eligible for randomisation.
27-28	**3.7 Informed consent**	The PerLR will be informed about the trial by the Investigator or their nominee and provided with a copy of the Covering Statement for Personal Legal Representative with an attached PerLR Information Sheet and asked to give an opinion as to whether the patient would object to taking part in such medical research.	The PerLR will be informed about the trial by the Investigator or their nominee and provided with a copy of the PerLR Information Sheet and asked to give an opinion as to whether the patient would object to taking part in such medical research.

		If the PerLR decides that the patient would have no objection to participating in the trial, they will be asked to sign the PerLR Consent Form which will then be countersigned by the Investigator or their nominee.	If the PerLR decides that the patient would have no objection to participating in the trial, they will be asked to sign the Legal Rep Consent Form which will then be countersigned by the Investigator or their nominee.
		If the doctor decides the trial is in the best interests of the patient, taking into consideration any advanced statements, they will be asked to sign the ProLR Consent Form.	If the doctor decides the trial is in the best interests of the patient, taking into consideration any advanced statements, they will be asked to sign the Legal Rep Consent Form.
30-31	**3.9.1 Intervention**	*N/A*	**3.9.1.1 Starting Landiolol Infusion**
		N/A - New wording added combined with old wording to clarify Landiolol Infusion administration process.	**3.9.1.2 Administering Landiolol Infusion** 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 landiolol infusion and noradrenaline protocol (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.

		N/A - New wording added combined with old wording to clarify Stopping Landiolol Infusion process.	**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 end of Day 14 and eventually stopped. The use of alternative beta blockade is at the discretion of the treating clinician.

33	**3.10.2 Dosage and excipients**	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.	*N/A – previous wording removed (duplication)*
		The maximum recommended daily dose of landiolol for this patient population is 57.6mg/kg (based on 40 mcg/kg/min in a 24 hour infusion)	The maximum recommended daily dosage of landiolol for this patient population is 57.6mcg/kg per day (based on 40 mcg/kg/min)
36-39	**4.1 Schedule of delivery of intervention and data collection**	The rates of noradrenaline infusion and landiolol infusion (if randomised to this group) will be recorded hourly.	The rates of noradrenaline infusion will be recorded hourly.
		Day 1 up to day 14	Day 1 (time of randomisation to post 24 hours)
		Research blood samples will be collected on Days 0, 1, 2, 4 and 6 and EONT visit (if this does not fall on a blood sampling day).	Research blood samples will be collected on Days 0, 1, 2, 4 and 6 and EONT visit.

		N/A	Duplicate blood samples will not be required at EONT visit if the visit falls on a blood sampling day i.e. Days 0, 1, 2, 4 or 6. However, a biobank blood sample is still required at EONT visit if the visits falls on a blood sampling day. Day 0 blood samples must be taken prior to the 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.
		N/A	Blood samples do not need to be taken after the patient has reached the EONT visit and stopped Landiolol treatment.
40	**4.2 Transport and storage of research samples**	A research blood sample (up to 20 ml) will be collected on day 0, 1, 2, 4 and 6 and the end of vasopressor infusion (EONT) (if not a blood sampling day).	A research blood sample (up to 20 ml) will be collected on day 0, 1, 2, 4 and 6 and the end of vasopressor infusion (EONT).
		N/A	Duplicate blood samples will not be required at EONT visit if the visit falls on a blood sampling day i.e. Days 0, 1, 2, 4 or 6. However, a biobank blood sample is still required at EONT visit if the visit falls on a blood sampling day.
41	**4.3 Assessment of protocol compliance**	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 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.	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.
41-42	**5.1.3 Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Events (SUSARS)**	Clinical outcomes exempt from reporting	5.1.4 Clinical outcomes exempt from reporting
		The following events will be considered clinical outcomes and not liable for reporting as Serious Adverse Events.	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.

42-44	**5.2 Reporting SAEs and SUSARs**	'…faxed to the coordinating centre within 24 hours…'	'…emailed to the coordinating centre within 24 hours…'
		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 will liaise with the investigator to compile all the necessary information.	The trial manager will liaise with the investigator to compile all the necessary information.
48	**6.4 Data access and quality assurance**	All data will be handled in accordance with the new Data Protect Act 2018.	All data will be handled in accordance with the new Data Protection Act 2018.
50	**7.2 Planned recruitment rate**	A 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.	A 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 41 sites.
66	*N/A*	*N/A*	Appendix E: STRESS-L Timing and Weaning of the Study Drug

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Page(s)	Section	Previous wording	New Wording
3-4	**Contact Names and Numbers**	N/A	Sponsor: Clark Crawford 0121 371 4186 Trial Steering Committee: Clark Crawford
9-11	**1.0 Trial Summary – Treatment Duration**	It may be restarted at any point if noadrenaline continues.	It may be restarted at any point before the defined End of Noradrenaline Treatment (noadrenaline treatment has stopped for 12 hours).
	Eligibility criteria – Inclusion & Exclusion Criteria	Male of female aged 18 years or above	Aged 18 years or above
		Heart rate ≥95 bpm (24 hours after start of vasopressor therapy)	Heart rate ≥95 bpm (at the time of randomisation)
		Any form of compensatory tachycardia	Tachycardia as a result of pain, discomfort from medical devices (including endotracheal tubes), during interventions or other patient distress
		>72 hours in the current cause of septic shock after start of vasopressor therapy	>72 hours after start of vasopressor therapy
		N/A	<12 hours since noadrenaline to treat a medical condition other than septic shock stopped
		N/A	Receiving extracorporeal membrane oxygenation (ECMO) treatment

		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 with any form of compensatory tachycardia will be excluded. 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.	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 at the time of randomisation will be eligible for entry. Fast Atrial Fibrillation may be an indicator of septic shock; therefore, these patients will be eligible for the trial. Patients with any form of tachycardia as a result of pain, discomfort from medical devices (including endotracheal tubes), during interventions or other patient distress will be excluded Patients who have previously received noradrenaline treatment to treat a medical condition other than septic shock will also be excluded if it has been **less than 12 hours** since noadrenaline stopped. 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; receiving extracorporeal membrane oxygenation (ECMO) treatment will be excluded.
20	**2.7 Ethical Considerations**	Septic shock and multi-organ failure causes confusion and many patients will not have capacity to consent to inclusion in the trial.	Septic shock and multi-organ failure causes confusion and in addition, many patients will not have capacity to consent to inclusion in the trial due to their underlying condition.

21	**3.1 Trial summary and flow diagram**	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 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.	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 at the time of randomisation will be eligible for entry. Fast Atrial Fibrillation may be an indicator of septic shock; therefore, these patients will be eligible for the trial. Patients with any form of tachycardia as a result of pain, discomfort from medical devices (including endotracheal tubes), during interventions or other patient distress will be excluded Patients who have previously received noradrenaline treatment to treat a medical condition other than septic shock will also be excluded if it has been **less than 12 hours** since noradrenaline stopped. 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; receiving extracorporeal membrane oxygenation (ECMO) treatment will be excluded.
24	**3.2.2 Secondary objectives**	To deliver an open-label, multi-centre randomised trial to determine whether infusion of the rapid-acting, ultra-short-lived and highly specific beta-adrenergic antagonist landiolol improves mean organ failure scores during an ICU admission compared with current best clinical practice, in patients who have septic shock.	To deliver an open-label, multi-centre randomised trial to determine whether infusion of the rapid-acting, ultra-short-lived and highly specific beta-adrenergic antagonist landiolol improves mortality and length of hospital stay during an ICU admission compared with current best clinical practice, in patients who have septic shock.

25	**3.3.2 Safety**	The episodes of Bradycardia (HR <50bpm), Bradycardia with haemodynamic compromise requiring intervention, significant hypotension requiring intervention (not including temporarily stopping the infusion), heart block, arrhythmia, arrhythmia with haemodynamic compromise requiring intervention will be reported.	The following events must be reported: • The episodes of Bradycardia (HR <50 bpm) • Bradycardia with haemodynamic compromise requiring **significant** intervention • Hypotension requiring **significant** intervention (not including temporarily stopping the infusion) • Heart block • Arrhythmia • Arrhythmia with haemodynamic compromise requiring intervention These events must be reported as a Serious Adverse Event if the delegated treating clinician deems this event fulfils the serious criteria or is **related to the drug.** If the event is not deemed to fulfil the serious criteria or is unrelated to the drug this should be reported on the Cardiovascular Safety Outcomes CRF.

26-27	**3.4 Eligibility criteria**	Male of female aged 18 years or above Heart rate ≥95 bpm (24 hours after start of vasopressor therapy) Any form of compensatory tachycardia >72 hours in the current cause of septic shock after start of vasopressor therapy N/A N/A	Aged 18 years or above Heart rate ≥95 bpm (at the time of randomisation) Tachycardia as a result of pain, discomfort from medical devices (including endotracheal tubes), during interventions or other patient distress >72 hours after start of vasopressor therapy <12 hours since noadrenaline to treat a medical condition other than septic shock stopped Receiving extracorporeal membrane oxygenation (ECMO) treatment
27	**3.5 Participant identification**	N/A 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 are met.	Fast Atrial Fibrillation may be an indicator of septic shock; therefore, these patients will be eligible for the trial. There is no restriction on the length of hospital or ICU stay prior to screening. Patients on ICU that develop sepsis after their arrival could also be screened and included if the eligibility criteria are met as long as they have not been previously enrolled in STRESS-L.
27	**3.7 Informed Consent**	However, due to the nature of the underlying condition and its treatment, the majority of patients will be unable to give informed consent.	However, due to the nature of their underlying condition or their treatment, the majority of patients will be unable to give informed consent.

33	**3.9.3 Control /Usual Care – Management of Atrial Fibrillation** **Definition of End of Noradrenaline Treatment (EONT) visit**	N/A The Local Research Team at the site will perform the EONT visit once all vasopressor treatments (noradrenaline/vasopressin) have been stopped for 12 hours and the clinical team are of the opinion that they will not be restarted.	Fast Atrial Fibrillation may be an indicator of septic shock; therefore, these patients will be eligible for the trial. The Local Research Team at the site will perform the EONT visit once all vasopressor treatments (noradrenaline) have been stopped for 12 hours.
43	**5.1.4 Clinical outcomes exempt from reporting**	Cardiovascular failure, including the need for vasopressors/inotropes	Cardiovascular failure: The need for vasopressors, inotropic support including dobutamine, adrenaline and phosphodiesterase inhibitors **EXCEPT required cardiovascular safety outcome events (see page 25)**
43	**5.2 Reporting SAEs and SUSARs**	In particular, bradycardia (HR <50 bpm) with haemodynamic compromise requiring intervention, heart block, significant hypotension requiring intervention, arrhythmia with haemodynamic compromise requiring intervention should be recorded. Events will be followed up until the event has resolved or a final outcome has been reached.	In particular, bradycardia (HR <50 bpm) with haemodynamic compromise requiring intervention, heart block, significant hypotension requiring intervention, arrhythmia with haemodynamic compromise requiring intervention should be recorded (see page 26). Events **must** be reported for patients in the control and interventional arm. Events will be followed up until the event has resolved or a final outcome has been reached up until the final visit at Day 90.
66	**Appendix D: Landiolol Infusion rate**	Expansion of Landiolol dosing table	

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Page(s)	Section	Previous wording	New Wording
25	Safety	N/A	To protect staff safety and reduce risk of viral transmission, blood samples **should not be taken** for suspected or confirmed COVID-19 positive patients.
27-28	Informed Consent	N/A	Patient consent If the patient has capacity and has been provided with verbal information about the trial but there are concerns with regarding risk of infection transmission due to the COVID-19 pandemic, a witness will countersign the form alongside the investigator obtaining consent.
		Personal Legal Representative Consent If the patient is unable to give consent, written informed consent will be sought from the patient's 'Personal Legal Representative' (PerLR) who may be a relative, partner or close friend. The PerLR will be informed about the trial by the Investigator or their nominee and provided with a copy of the Covering Statement for Personal Legal Representative with an attached PerLR Information Sheet and asked to give an opinion as to whether the patient would object to taking part in such medical research. The Investigator or their nominee will answer any questions that the PerLR has concerning study participation. The PerLR will be given adequate time to consider the patient's wishes regarding participation in the study. If the PerLR decides that the patient would have no objection to participating in the trial, they will be asked to sign	Personal Legal Representative Consent If the patient is unable to give consent, informed consent will be sought from the patient's 'Personal Legal Representative' (PerLR) who may be a relative, partner or close friend. Significant limitations have been placed on the visitation of patients in hospital and therefore a personal legal representative is unlikely to be available to sign the consent form in person. The personal legal representative will be contacted by telephone or videoconference facilities and provided with information about the trial by the Investigator or their nominee. The PerLR will be asked to give an opinion as to whether the patient would object to taking part in such medical research. The Investigator or their nominee will answer any questions that the PerLR has concerning study participation. The PerLR will be given adequate time to consider the patient's wishes regarding participation in the study. If the PerLR decides that the patient would have no objection to participating in the trial, verbal consent will be

		the PerLR Consent Form which will then be countersigned by the Investigator or their nominee. The PerLR will retain a copy of the signed Consent Form. A second copy will be placed in the patients' medical records whilst the original will be retained in the Investigator Site File.	obtained only and the investigator obtaining consent alongside a witness will sign the consent form. A copy of the information sheet and consent form will be sent to the personal legal representative after the patient has been enrolled in the trial and this process will be documented in the patient's medical notes. A second copy of the consent form will be placed in the patients' medical records whilst the original will be retained in the Investigator Site File.
39	Schedule of Assessments	N/A	To protect staff safety and reduce risk of viral transmission, blood samples **should not be taken** for suspected or confirmed COVI9-19 positive patients.
54	Monitoring and quality assurance of trial procedures	N/A	On-site monitoring visits are currently not feasible due to restrictions on non-essential staff visiting hospitals with COVID-19 patients. A risk-based proportionate approach outlined in the monitoring plan for off-site remote monitoring has been developed through discussion with the trial sponsor, that takes account of the challenging circumstances in which this trial will operate and extreme pressure that will be placed on hospital staff. On-site monitoring visits will be conducted when possible and safe to do so as necessary and according to the monitoring plan for the trial.