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PROTOCOL

STRESS-L: STudy into the REversal of Septic Shock with Landiolol (Beta Blockade)

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University Hospitals Birmingham 
NHS Foundation Trust




**National Institute for
Health Research**

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/199828) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's SOPs and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

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	TABLE OF CONTENTS	PAGE
	SIGNATURE PAGE	2
	CONTACT NAMES AND NUMBERS	2
	TABLE OF CONTENTS	5
1.	TRIAL SUMMARY	9
	LIST OF ABBREVIATIONS/GLOSSARY	12
2.	BACKGROUND	14
2.1	Lay Scientific Summary.....	14
2.2	Epidemiology and burden of the condition	15
2.3	Existing knowledge	15
2.4	Hypothesis	17
2.5	Need for a trial	18
2.6	Exploratory mechanistic studies	18
2.7	Ethical considerations	19
2.8	CONSORT	20
2.9	Assessment and management of risk	20
3.	TRIAL DESIGN.....	21
3.1	Trial summary and flow diagram.....	21
3.2	Aims and objectives.....	24
3.2.1	Primary objective	24
3.2.2	Secondary objectives.....	24
3.3	Outcome measures	24
3.3.1	Efficacy.....	24
3.3.2	Safety.....	25
3.4	Eligibility criteria	25

3.4.1	Inclusion criteria	25
3.4.2	Exclusion criteria	26
3.5	Participant identification.....	26
3.6	Informed consent	27
3.7	Randomisation.....	28
3.7.1	Randomisation	28
3.7.2	Post-randomisation withdrawals, exclusions and moves out of region	29
3.8	Trial treatments.....	29
3.8.1	Intervention.....	29
3.8.2	Dose modification for side-effects	30
3.8.3	Stopping the study drug infusion	30
3.8.4	Control / Usual Care	30
3.8.5	Definition of End of Noradrenaline Treatment (EONT) visit	32
3.9	Details of Investigational Medicinal Product	32
3.9.1	Description and manufacture	32
3.9.2	Dosage and excipients.....	32
3.9.3	Packaging and labelling	33
3.9.4	Storage, dispensing and returns.....	33
3.9.5	Known side effects	34
3.9.6	Contraindications, special warnings and precautions in the context of septic shock	34
3.9.7	Compliance/contamination.....	34
3.10	Concomitant illness and medication	35
3.10.1	Concomitant illness	35
3.10.2	Concomitant medication.....	35
3.11	End of trial	35
4.	METHODS AND ASSESSMENTS.....	36
4.1	Schedule of delivery of intervention and data collection	36
4.2	Transport and storage of research samples.....	39

4.3	Assessment of protocol compliance	40
5.	ADVERSE EVENT MANAGEMENT / PHARMACOVIGILANCE	40
5.1	Definitions	40
5.1.1	Adverse Events (AE).....	40
5.1.2	Adverse Reaction (AR).....	40
5.1.3	Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Events (SUSARS)	40
5.2	Reporting SAEs and SUSARs	41
5.3	Responsibilities.....	43
5.4	Procedures in case of overdose	44
5.5	Procedures in case of pregnancy	45
5.6	Notification of deaths.....	45
5.7	Reporting urgent safety measures.....	45
6.	DATA MANAGEMENT	46
6.1	Data collection and management	46
6.2	Database.....	46
6.3	Data storage	46
6.4	Data access and quality assurance.....	47
6.5	Data Shared with Third Parties.....	48
6.6	Archiving.....	48
7.	STATISTICAL ANALYSIS.....	48
7.1	Power and sample size	48
7.2	Planned recruitment rate	48
7.3	Statistics and data analysis.....	48
7.4	Decision making for subsequent trial.....	49
7.5	Methodological analysis.....	49

8.	TRIAL ORGANISATION AND OVERSIGHT	49
8.1	Sponsor and governance arrangements	49
8.2	Regulatory authorities/ethical approval	49
8.3	Trial Registration	50
8.4	Notification of serious breaches to GCP and/or trial protocol	50
8.5	Indemnity	51
8.6	Trial timetable and milestones.....	51
8.7	Administration.....	51
8.8	Trial Management Group (TMG).....	51
8.9	Trial Steering Committee (TSC)	51
8.10	Data Monitoring Committee (DMC).....	52
8.11	Essential Documentation	52
9.	MONITORING AND QUALITY ASSURANCE OF TRIAL PROCEDURES	52
10.	PATIENT AND PUBLIC INVOLVMENT (PPI).....	53
11.	DISSEMINATION AND PUBLICATION	53
12.	REFERENCES	54
13.	APPENDICES.....	61

LIST OF TABLES

PAGE

Table 1: Trial Assessments.....	38
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LIST OF FIGURES

PAGE

Figure 1: Trial CONSORT Flow Diagram	23
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1. TRIAL SUMMARY

Trial title	STudy into the REversal of Septic Shock with Beta Blockade Landiolol (Beta Blockade)
Acronym	STRESS-L
Chief Investigator	Dr Tony Whitehouse
Clinical Phase	Phase IIb
Trial Design	Open-label randomised controlled trial. No placebo
Sample size	340 participants
Primary objective	To assess the efficacy, tolerability, safety and mechanisms of beta-blockade in patients with septic shock requiring prolonged (>24 hours) support with high-dose vasopressor agents.
Population	Adult patients in an intensive care unit (ICU) diagnosed with septic shock as defined by consensus criteria (Sepsis-3) who, having received adequate fluid resuscitation, are receiving noradrenaline treatment at $\geq 0.1 \text{ mcg/kg/min}$ continuously for longer than 24 hours (but less than 48 hours) to maintain a predefined mean arterial pressure (usually of 65 mmHg) and continue to have a heart rate (HR) more than 94 bpm ($\geq 95 \text{ bpm}$).
IMP	Landiolol infusion (1 – 40 $\mu\text{g/kg/min}$) to maintain heart rate of 80-94 beats per minute
Treatment Duration	Landiolol infusion should continue until the HR is consistently below 95 bpm. Landiolol infusion should continue whilst in ICU only and even if vasopressor support has finished. Once Landiolol has been discontinued for 12 hours it should not be restarted.
Follow up Duration	Participants will be followed up on the study for up to 90 days
Planned Trial Period	51 months
Eligibility criteria	Inclusion criteria <ul style="list-style-type: none"> • Male or female aged 18 years or above • Being treated on an ICU • Septic shock according to internationally accepted definitions* • Heart rate $\geq 95 \text{ bpm}$ (24 hours after start of vasopressor therapy) • Receiving vasopressor support with noradrenaline to maintain a target blood pressure for $\geq 24 \text{ hours}$

- Are being treated with noradrenaline at a rate $\geq 0.1\text{mcg/kg/min}$

*Sepsis -3 definitions:

- confirmed or suspected infection requiring antibiotic therapy
- new organ dysfunction, as evidenced by an increase in Sequential Organ Failure Assessment (SOFA) score ≥ 2
- a blood lactate $>2\text{ mmol/l}$ at any point during shock resuscitation
- vasopressor therapy to maintain mean arterial pressure (MAP) $\geq 65\text{ mmHg}$

In particular the presence of a blood lactate $> 2\text{ mmol/l}$ is only necessary for the diagnosis of septic shock and is NOT necessary for randomisation 24 hours later.

Exclusion criteria

- Noradrenaline dose $<0.1\text{ mcg/kg/min}$
- >48 hours after start of vasopressor therapy
- Having pre-existing severe cardiac dysfunction (NYHA grade 4 or more)
- Having pre-existing severe pulmonary hypertension (mean PA pressures $> 55\text{mmHg}$)
- Acute severe bronchospasm (due to asthma or COPD)
- Untreated second or third degree heart block
- Untreated pheochromocytoma
- Prinzmetal's angina
- A past history of ischaemic stroke or transient ischaemic attack (TIA) or untreated severe carotid stenosis
- Advanced liver disease
- Have been treated with any beta-blocker drug in the seventy two hours prior to screening
- Known sensitivity to beta-blockers
- Patient / legal representative unwilling to provide written informed consent
- Known to be pregnant
- Terminal illness other than septic shock with a life expectancy < 28 days
- Participants who have participated in another research trial involving an investigational medicinal product in the past 30 days
- Patients in whom the clinical team feel are about to finish their noradrenaline therapy

Outcome measures	<p><u>Primary endpoint</u></p> <p>Mean SOFA score whilst on ICU after randomisation (up to a maximum of 14 days)</p> <p><u>Secondary endpoints</u></p> <p>Patient-centered outcomes:</p> <ul style="list-style-type: none"> • 28-day, hospital and 90-day survival • Individual organ failure-days in ICU survivors through measures of oxygenation, renal, hepatic and coagulation function; dose and duration of vasopressor treatment (total daily administered doses of adrenaline, dobutamine, phosphodiesterase inhibitors) • ICU and hospital length of stay <p>Exploratory mechanistic outcomes:</p> <ul style="list-style-type: none"> • Myocardial Injury – Troponin-T, Beta Natriuretic Peptide, Creatine Kinase-MB, Arrhythmia, Changes in ECG between Randomisation and End of ICU • Metabolic Function – changes in plasma lactate concentration, plasma free fatty acid concentration, control of serum blood glucose, changes in insulin requirements • Immune Function – Plasma concentrations of cytokines, plasma C-reactive concentration protein, neutrophil phagocytic and oxidative burst activity (selected sites) <p>Safety outcomes:</p> <ul style="list-style-type: none"> • Number of episodes of bradycardia (HR <50 bpm) • Bradycardia with haemodynamic compromise requiring intervention • Significant hypotension requiring intervention • Heart block • Arrhythmia with haemodynamic compromise requiring intervention.
Randomisation and blinding	<p>Participants will be randomised strictly sequentially as participants are eligible for randomisation using a 1:1 ratio. Randomisation will be stratified by recruiting site and noradrenaline dose. A web-based system will be used.</p> <p>It is not possible for this trial to be blinded as the dose of landiolol must be titrated to achieve a target HR.</p>

LIST OF ABBREVIATIONS/GLOSSARY

Abbreviation	Explanation
AE	Adverse Event
AR	Adverse Reaction
BNP	Beta Naturetic Protein
BPM	Beats Per Minute
CK-MB	Creatine Kinase (MB Fraction)
CI	Chief Investigator
CI	Confidence Interval
CONSORT	<i>Consolidated Standards of Reporting Trials</i>
COPD	Chronic Obstructive Airways Disease
CRF	Case Report Form
CRP	C-Reactive Protein
CTA	Clinical Trials Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
CTRG	Clinical Trials and Research Governance
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EONT	End of Noradrenaline Treatment
EOT	End of Treatment
FBC	Full Blood Count (Haemoglobin [HB], White Cell Count [WCC], Platelets [Plt])
GCP	Good Clinical Practice
GP	General Practitioner (Family Doctor)
HMGB-1	High Mobility Group Box 1
HRA	Health Research Authority
HR	Heart Rate
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IL-6	Interleukin-6
IMP	Investigational Medicinal Product
INR	International Normalised Ratio
IRAS	Integrated Research Application System

Abbreviation	Explanation
MAP	Mean Arterial Pressure
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
PI	Principal Investigator
PIL	Participant/Patient Information Leaflet
PPI	Patient & Public Involvement
QoL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R&D	Research and Development
RR	Relative Risk
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SOFA	Sequential Organ Failure Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSC	Trial Steering Committee
WCTU	Warwick Clinical Trials Unit

2. BACKGROUND

2.1 Lay Scientific Summary

Septic shock (blood poisoning) is a life-threatening condition caused by severe infection. For reasons still poorly understood, in some patients, their inflammation system remains excessively activated. Instead of fighting the infection, an ongoing inflammatory state results in widespread injury and failure of normal functioning of the body's vital organs, such as the lungs, heart, brain and kidneys. A hallmark of septic shock is a very low blood pressure that does not improve with an intravenous fluid drip.

According to the UK Sepsis Trust (www.sepsistrust.org), septic shock kills 37,000 patients per year on wards and ICUs in the UK (more than bowel cancer, breast cancer and prostate cancer put together). Yet despite huge research efforts over the last 20-30 years, the death rate from this most severe manifestation of sepsis has remained unchanged. Outcomes have improved for sepsis in general through earlier recognition and intervention with antibiotics, however once the patient is in established shock, the risk of dying remains very high.

For many years, we have routinely used in clinical practice a group of drugs known as 'catecholamines' to increase the patient's blood pressure back to normal. The objective is that this will help their vital organs to function properly and to recover. The most commonly used catecholamine is noradrenaline, a synthetic form of a hormone produced by the body to deal with stressful situations. Noradrenaline does however carry side-effects when given at high doses and for extended periods of time, including adverse effects on the heart, the immune system and the patient's metabolism. Thus, the drug treatment itself, augmenting the body's own production of these hormones, may achieve the short-term goal of increasing blood pressure though at the possible expense of a worsened outcome. The role of catecholamines is therefore being questioned.

A group in Italy recently performed a study in their hospital in Rome. They selected patients with septic shock and fast heart rates; they were receiving high doses of noradrenaline. This subset of patients carries a particularly high mortality (over 60%). Half their patients were randomly allocated to receive a 'beta-blocking' drug infusion intravenously. These beta-blockers are already widely used for counteracting the stressful long-term actions of catecholamines, for example high blood pressure, chronic heart failure, abnormally fast heart rates and cardiac rhythms, and tremor. The Italian group gave enough drug to reduce, and then maintain, the patients' heart rate at between 80-94 beats per minute. They found this strategy was not only safe but was associated with big improvements in survival and time in intensive care. However, their study was relatively small and from a single site so did not provide enough information to make the use of beta blockers a mainstream recommendation. They did not study the way in which the beta blocker was acting in their patients.

We propose to repeat their study in multiple (approx. 30-35) intensive care units throughout the UK to see if we can confirm the safety and benefits found in Rome but also to extend it by taking blood samples to measure effects of the drug on the patient's immune system, metabolism and heart function so that we may better understand its mechanisms of action. We also propose to store blood samples for analysis of the genes and proteins that may predispose patients to become so severely septic and to identify those who respond to beta blocker therapy.

2.2 Epidemiology and burden of the condition

The mortality from septic shock remains very high (>40% in 3 randomised trials reported in the New England Journal of Medicine in 2014 (1-3)). To date, therapeutic strategies using immunomodulatory or vasoactive interventions have failed to make any significant impact on this high mortality. Recently, interest has grown in the use of beta-adrenergic blockade following supportive results in animal and preliminary human studies.

Beta blockade represents a paradigm shift in patient management but its use arises from observations in both animal models (4-8) and patients (9;10) of harm induced by excessive sympathetic activation and benefit from beta-adrenergic blockade. Excess beta-adrenergic activation may be both endogenous (related to the severity and duration of the underlying infection) and exogenous due to the catecholamine therapy which has hitherto been the mainstay of management of hypotension caused by septic shock. A combination of beta2 agonism with beta1 blockade improves sepsis-induced immune, cardiovascular and coagulation dysfunction in established sepsis (11). It is unclear whether the benefits of beta-blockade lie entirely in improved cardiovascular function.

A recent randomised single centre study of 154 patients from Rome (12) reported the use of beta-adrenergic blockade using the short-acting agent esmolol in patients with septic shock and tachycardia who required vasopressor therapy for >24 hours. The dosing endpoint was a reduction in heart rate to 80-94 beats/min (bpm). Though this study was not powered to detect a change in outcome, marked improvements were seen in survival (adjusted hazard ratio, 0.39; 95% CI, 0.26-0.59; $p < 0.001$). Improvements were also seen in the beta-blocker-treated group in the duration of vasopressor treatment, and in measures of renal and cardiac function.

2.3 Existing knowledge

Interaction between sympathetic nervous and immune systems in response to invading pathogens is mediated with effector arms consisting of catecholamines and inflammatory cytokines. In the first instance, sympathetic activation is an appropriate **physiological** response but for reasons still poorly understood there comes a point at which such an effector system becomes **pathological**, resulting in injury to the host (13;14). There is a correlation between high levels of plasma catecholamines and critically ill patients (14;15) whilst tachycardia, a clinical surrogate of excessive sympathetic activation, is also an important prognosticator of mortality in septic shock (16). There is a downregulation of the total number and a relative change in the ratio of beta1:beta 2 adrenoceptors with excessive catecholamine exposure which contributes immune and cardiac dysfunction (11).

There may be an important iatrogenic contribution to this. The extent and duration of catecholamine therapy are all independently associated with poor outcomes in critically ill patients, after adjustment for disease severity (14;16-18). Catecholamines are associated with adverse effects including direct myocardial damage, insulin resistance, thrombogenicity, immunosuppression, and enhanced bacterial growth (19). Notwithstanding these data, international sepsis management guidelines currently recommend noradrenaline as the first-line treatment for fluid-unresponsive hypotension (20).

Pre-Clinical studies: It was noted many years ago that epinephrine enhanced bacterial infections (21) and decreased the number of bacteria necessary for a lethal dose in both Clostridia species and pathogenic aerobic organisms. Catecholamines have been demonstrated to enhance biofilm formation and stimulate bacterial growth (22-24). Certain beta blocking agents have been shown to inhibit bacterial growth in vitro (25). Reduction in bacterial growth has been proposed as one mechanism for a lower incidence of spontaneous bacterial peritonitis seen in patients with liver cirrhosis treated with propranolol (26).

As long ago as 1969, propranolol was used in a canine lipopolysaccharide (LPS) model of Gram-negative sepsis and found that the beta blocker significantly improved survival when it was started 60 minutes after LPS infusion (4). Propranolol prevented hypotension and reduced fluid requirements. In the intervening years, animal models have been disparate, varying in the beta blocker used, way in which sepsis is initiated, outcome studied and length of study and beta blocker treatment. Consequently, pathways defining the mechanism for beta blockade are far from clear.

Continuous infusion of esmolol initiated after septic insult improved survival at 5 days in a murine model (27) associated with an increase in the NFkappa B pathway. Pre-treatment with atenolol or metoprolol did not alter survival in a caecal ligation and puncture (CLP) rat model (7) given 2 hours before CLP but the median time to death was increased by 33 hours in metoprolol-treated rats ($P = 0.03$). Metoprolol pre-treatment reduced hepatic expression of proinflammatory cytokines and lowered plasma IL-6 (both $P < 0.05$). Myocardial protein expression of IL-18 and monocyte chemoattractant protein-1, key mediators of cardiac dysfunction in sepsis, were also reduced ($P < 0.05$). In another study, atenolol had an anti-inflammatory effect by increasing IL-10 but had no effect on TNF-alpha or IL-6 concentrations in an ovine model with E. coli septicaemia (28).

Clinical studies: A heart rate >95 bpm is associated with major cardiac events and increased mortality in the critically ill (16). Whether this is directly due to direct cardiac toxicity and/or a reflection of whole body injury resulting from the hyperadrenergic state remains uncertain. Beta-blockade reduces pro-inflammatory cytokines in heart failure (29), in critically ill patients after trauma (30;31) and had a beneficial effect on the T helper 1:2 ratio (32).

Heart rate is the key determinant of myocardial oxygen consumption and tachycardia substantially increases myocardial oxygen demand (33), although cardiac ischaemia is rarely the cause of dysfunction (34), tachycardia is associated with myocardial events (non-fatal myocardial infarction, non-fatal cardiac arrest, and cardiac related death) (16). Clinical evidence suggests a strong association between tachycardia and mortality in a short-term model such as the peri-operative period (35); (36) and over a longer period (hypertensive patients) (37); (38).

Vasoactive and inotropic drugs can induce cardiac arrhythmias in a dose-dependent manner (39) and Gandhi noted increased mortality associated with new onset atrial fibrillation (RR for in-hospital mortality 1.45 95 % CI 1.32-1.60, $p < 0.00001$) (40). Landiolol has been successfully used to curtail supraventricular tachyarrhythmias in septic patients (41).

A retrospective analysis examining patients either already treated with, or commencing beta-blockers in hospital for other conditions such as hypertension and tachyarrhythmias reported a significant decrease in fatal outcome and recovery time (42). Beta blocker therapy prior to ICU was also associated with lower ICU mortality (43) whether non-selective beta-blockers

(OR 0.99 [95%CI: 0.67 -1.47]) or cardioselective (OR 0.70 [95%CI: 0.58-0.83]). Herndon et al used propranolol to reduce heart rate by 20% in burned septic children and demonstrated attenuated hypermetabolism and reversal of muscle-protein catabolism both in the short-term (44), and over 12 months (45).

Two studies from Europe (9;10) and two case series in China (46;47) have reported the safe use of esmolol in septic patients. In a follow-on study, Morelli et al (12) randomised patients admitted with vasopressor-dependent septic shock and persisting tachycardia for >24h to receive placebo or an esmolol infusion targeting to reduce HR to 80-94 bpm. This target was safely achieved and, in addition, there were significant reductions in noradrenaline requirements and in metabolic acidaemia. Notably, although not powered to discover a mortality difference, the Morelli study reported a substantial reduction in 28-day mortality rate with esmolol from 80.5% to 49.4% ($p<0.05$) and significant reductions in serum markers of renal (creatinine) and myocardial (troponin) injury.

Landirolol (Rapibloc®, AOP Orphan Pharmaceuticals, Vienna, Austria) is a new ultra-short acting beta blocker that has a half-life of 2.3 to 4 minutes (48) and is about 8 times more selective for the beta 1 receptor than esmolol (49). Landiolol offers advantages over esmolol as it is metabolised by plasma pseudocholinesterase and liver carboxylesterase to inactive metabolites yet its metabolism is unaffected by liver impairment (50). Landiolol does not exacerbate hyperreactive airways, unlike propranolol which significantly increases pulmonary airway resistance and decreases dynamic lung compliance (51).

Several studies have shown that landiolol attenuates the increase in heart rate associated with tracheal intubation (52;53) and bronchoscopy (54), without adversely affecting blood pressure or other haemodynamic parameters. Landiolol has been well tolerated in clinical trials of patients with tachyarrhythmias including following cardiac surgery, with a relatively low risk of hypotension and bradycardia (55). Cardiovascular stability has also been demonstrated during extubation (56).

Landirolol has been used safely and successfully in a septic patient with atrial fibrillation (57). Landiolol has been approved in Japan since 2002 for the treatment of intraoperative and postoperative tachyarrhythmias. To date it has been given to 2.4 million patients (personal communication, AOP Orphan).

A few preclinical studies have examined landiolol in sepsis. It decreased circulating levels of the cytokines, TNF-alpha, IL-6, and high mobility group box (HMGB)-1, and reduced histological lung damage in a rat endotoxin model (8). Landiolol was also cardio-protective in septic rats by normalising the expression of cardiac vasoactive peptide endothelin-1 (58).

2.4 Hypothesis

We hypothesise that a reduction in heart rate using landiolol infusion in patients with septic shock and tachycardia improves organ failure as measured by the Sequential Organ Failure Assessment (SOFA) score (59) during the 14 days after study drug administration through a reduction in cardiac and immune dysfunction.

2.5 Need for a trial

The deleterious effects of prolonged adrenergic stress on cardiac, immune, inflammatory, metabolic, coagulant and bioenergetic pathways may be attenuated in septic shock patients at high-risk of mortality by beta-blockade.

Morelli's study (12) has been criticised for being single centre and for the high mortality seen in the control group. Early data using esmolol and landiolol have suggested that beta blockade is possible and safe in this sick and physiologically deranged population. The use of an ultra-short-acting agent in our study will enhance the safety profile of the use of this therapeutic strategy in such patients.

By targeting patients with persisting tachycardia and vasopressor requirement, the study group is a particular at-risk cohort. It is crucial to discover if the safety and efficacy Morelli described can be reproduced in a prospective randomised multicentre study in which mechanisms of action can also be explored.

2.6 Exploratory mechanistic studies

Conflicting animal data and a paucity of well-controlled clinical studies mean that the mechanisms defining the role of beta blockade in sepsis are far from clear. It is highly unlikely there is a single pathway that underlies the effects and our focus will be changes in cardiac and immune systems. In order to define the extent to which these systems are altered by beta blocker therapy, a variety of markers defining these broad pathways will be measured. Their lack of selectivity reflects the state of understanding of beta blockade in septic shock.

Our hypothesis is that exposure to catecholamines (either endogenously generated or administered as part of recommended blood pressure management) is damaging to the myocardium and / or is immunosuppressive.

Investigation of cardiac protection by beta-blockade

Prolonged hypotension, defined as a mean arterial pressure (MAP) of less than 60 to 65 mmHg for more than 12 hours, is associated with poor outcome (60) but a greater mortality has been noted in patients where higher mean BP values were generated using progressively higher catecholamine doses (15). The mechanism for this in sepsis is unknown but these findings leave the clinician in an impossible dilemma of when to increase the rate of vasopressor.

Up to 40% of septic patients develop reversible cardiomyopathy (61) to which endogenous and exogenous adrenergic agonism contributes. Beta blockers reduce HR and ventricular workload in severe sepsis (62) and may reduce myocardial damage (63). This proportion may be higher in the tachycardic group of study and so cardiomyocyte damage will be assessed using plasma creatine kinase (CK-MB) and troponin-T (64). B-type natriuretic peptide, identified as a screening tool for left ventricular dysfunction (65) and prognostic of poor outcomes at high levels in sepsis will also be measured (61) (66). We will also record the number of hours that patients are in atrial fibrillation.

The source of beta-blocker cardiac protection will be assessed by recording cardiovascular variables (heart rate, blood pressure, inotrope use) and analysing plasma catecholamine levels with plasma cardiac-derived creatine kinase (CK-MB) and troponin-T and B-type

natriuretic peptide. The rates, type and duration of arrhythmias will be recorded in each group.

Fatty acid oxidation is a preferred ATP source for the heart during sepsis but is critically dependent on the stage of sepsis. Fatty acid oxidation may be impaired relative to circulating triglyceride levels (67;68), resulting in increased cycling between triglycerides and non-esterified fatty acids. Low levels of HDL cholesterol and hypertriglyceridaemia (69), and elevated plasma levels of fatty acids and ketone bodies (70) are poor prognostic indicators. We will investigate alterations in metabolism using blood glucose, insulin infusion use (often used in ICU to treat stress hyperglycaemia) and free fatty acid profiles in order to further define the changes in bio-energetics.

Investigation of Immune Modulation

Since almost all immune cells express adrenergic receptors (71), catecholamines (and therefore their antagonists) exert substantial immunomodulating effects. Beta-blockade reduces pro-inflammation and may impact on anti-inflammatory cytokines (72).

High levels of IL-6 and IL-10 are known to be poor prognosticators in sepsis. Metoprolol treatment has been associated with reduced pro-inflammatory cytokine levels (7); landiolol reduced serum levels of high-mobility box group 1 (HMGB-1) and reduced NF-kappaB activity (8) both in LPS septic rats. We will therefore perform serial estimations of IL-6, -8, -10, and C-reactive protein to determine whether there are changes in inflammation associated with beta blockade. Changes in neutrophil phagocytic and oxidative burst activity will be measured in hospitals close to suitable analysers as these assays require fresh blood samples.

Aside from their immunomodulating effects, catecholamines increase in vivo growth of several gram positive and negative bacteria (21). Catecholamines have been implicated in increasing growth of intestinal commensal *E coli* and as a possible contributing factor in trauma-induced sepsis (24). Similarly, noradrenaline and dobutamine have been shown to stimulate *Staph epidermidis* growth and biofilm formation and may therefore increase catheter colonization and catheter-related bloodstream infections (22). We will therefore monitor the rates of post randomisation nosocomial (hospital acquired) infections including catheter-related blood stream infections and bacteraemias.

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. These will include analysis of the CysGlyGln haplotype of the ADRB2 (b2-adrenergic receptor) gene associated with a markedly worse survival in sepsis (73) and analysis of the proprotein convertase subtilisin/kexin type 9 (PCSK9) as the AA-genotype is associated with a significantly increased risk of death in sepsis (74;75).

2.7 Ethical considerations

The trial will be conducted in full conformance with the principles of the Declaration of Helsinki and to ICH Good Clinical Practice (GCP) guidelines. It will also comply with the Medicines for Human Use (Clinical Trials) Act 2004, subsequent amendments and Warwick Standard Operating Procedures (SOPs). All data will be stored securely and held in accordance with Data Protection Act 1998. Written informed consent will be gained prior to

entry in the study. Patient safety and well-being will be paramount and all patients will be treated with respect and dignity throughout the study.

The scientific rationale included in this protocol outlines the reasons why beta blockade may improve the current standard treatment for septic shock. In short, prolonged exposure to catecholamines is harmful (16) and beta blockade may well be protective (42). A single centre study (12) reported that beta blockade by esmolol infusion was safe and possible and associated with decreased mortality but that the mechanisms for this are unclear due to a mixture of models and perceived benefits (72).

Whilst it could be argued that the lack of data from long-term septic shock animal models means that further information should be sought first, the long-term animal models themselves induce a great deal of animal suffering and are ethically questionable. At the same time, the finding of reduced mortality, albeit as a secondary outcome from Morelli's study brings the ethical dilemma of whether this finding can be ignored whilst waiting for the acquisition of more animal data. Furthermore, if the animal data do not support the systematic use of beta blockade in septic shock, how should we reconcile this with Morelli's study?

It is likely that most of the patients randomised to STRESS-L will not have capacity. Septic shock and multi-organ failure cause confusion and many patients will not have capacity to consent to inclusion in the trial. As usual with a clinical trial of an IMP, the trial is conducted because the available data suggest that patients could benefit from the intervention but that the current data is not overwhelmingly strong that beta blockade should be embedded as part of routine therapy.

2.8 CONSORT

The trial will be reported in line with the CONSORT (*Consolidated Standards of Reporting Trials*) statement (76).

2.9 Assessment and management of risk

This trial is categorised as:

Type B = somewhat higher than the risk of standard medical care

The use of beta blockade offers the possibility of altering the course of a condition that has previously proved highly resistant to treatments once established. It also allows the possibility of investigating novel mechanisms and pathways.

The major concern of giving a beta-blocker to a septic patient requiring noradrenaline to maintain an adequate blood pressure relates to its negative inotropic and hypotensive effects. However, Morelli (12) reported the safe administration of esmolol to a very sick cohort of septic shock patients; there have been other case reports (57) and by our own anecdotal use. Okajima and colleagues (41) used landiolol in septic patients and concluded that it safely reduced heart rate and, in part, converted to sinus rhythm in septic patients with supraventricular tachyarrhythmias.

Landiolol has a proven safety record in healthy subjects, patients with cardiac disease and following cardiac surgery (77). It has a rapid onset of action and is readily titratable with rapidly reversible effects (half-life of 2.3 to 4 minutes (48)) that are even faster than esmolol. Landiolol has been shown to exert a better cardiovascular profile in animals, healthy subjects and patients than esmolol (78-80). Landiolol should thus allow very tight control of the HR and rapid offset should unwanted cardiovascular effects occur.

3. TRIAL DESIGN

3.1 Trial summary and flow diagram

This is a multi-centre, randomised, controlled open label phase IIb trial comparing usual treatment with usual treatment plus landiolol infusion in a total of 340 patients.

Patients will be randomised to either usual care (control group) or usual care plus landiolol (intervention). There will be no placebo infusion or blinding as the infusion dose needs to be titrated to achieve a target heart rate of 80-94 bpm.

The trial will take place in 35 UK adult intensive care units (ICUs). Participating ICUs will have a typical case mix for UK critical care, a track record of recruitment to clinical trials, suitable support for screening and data collection and the means to store blood samples for transfer to the central analysis unit. They should also be willing to manage atrial fibrillation with correction of potassium, magnesium and amiodarone in the control group as the use of beta-blockers in these patients would risk making the trial results uninterpretable.

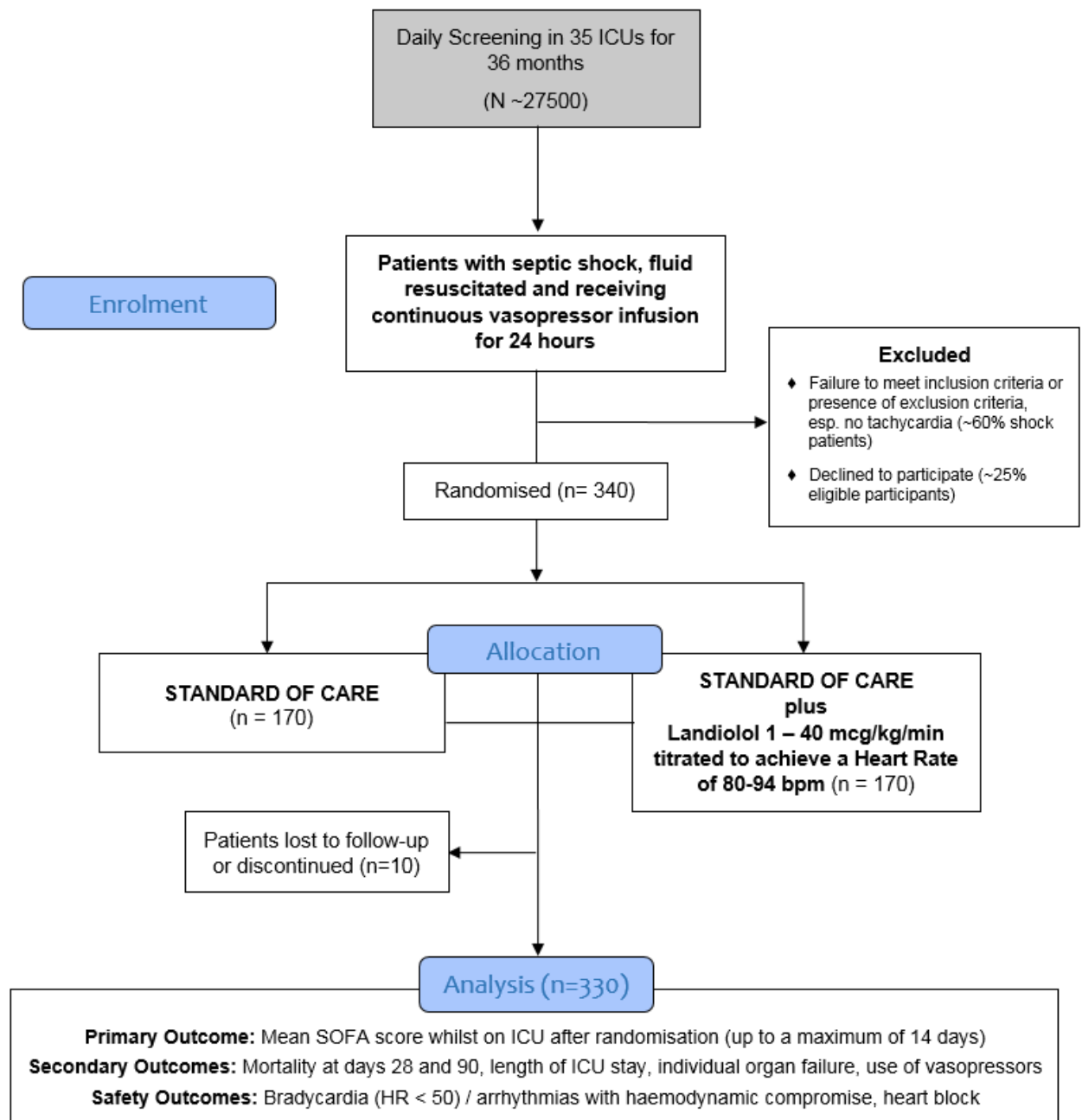
Adult patients in ICU with septic shock as defined by Sepsis-3 criteria who have required continuous vasopressor therapy for at least 24 hours, are being treated with 0.1 mcg/kg/min noradrenaline and a heart rate of 95bpm or greater will be eligible for entry. Patients having received beta-blocker therapy in the previous 72 hours; 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; with untreated pheochromocytoma; 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; terminal illness other than septic shock with a life expectancy of <28 days, will be excluded. Patients who have previously been in STRESS-L or are about to finish noradrenaline therapy or have been in an IMP trial in the previous 30 days will also be ineligible.

Once eligibility criteria are met there is a 24-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; 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.

Figure 1: Trial CONSORT Flow Diagram



3.2 Aims and objectives

3.2.1 Primary objective

The primary objective of this trial is to assess the efficacy, safety and mechanisms of beta-blockade in patients with septic shock and tachycardia requiring prolonged (>24 hours continuous treatment) support with high-dose vasopressor agents.

3.2.2 Secondary objectives

The secondary objectives of the trial are:

- 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 investigate the pathways that are altered by beta blockade in septic shock by examining the effects of landiolol on blood markers of inflammation, metabolism and cardiomyocyte damage.

3.3 Outcome measures

3.3.1 Efficacy

Primary outcome

The primary outcome will be the mean SOFA score over the first 14 days from entry to the trial and whilst in ICU. Measurement of the SOFA score will cease if the patient dies or is discharged from the ICU. It is assumed that delayed discharges will be evenly distributed between each group.

Mean SOFA score has a good correlation with ICU mortality and its predictive value is similar regardless of length of stay. This outcome will be used as an assessment of benefit so that should beta blockade prove to be beneficial, we will be able to propose a larger study with mortality alone as the primary endpoint.

Secondary outcomes

- Mortality at day 28 and day 90
- Length of ICU and hospital stay
- Individual organ failure-days in 28 day survivors through measures of oxygenation, renal, hepatic and coagulation function
- Reduction in dose and duration of vasopressor treatment (total doses of adrenaline, dobutamine, phosphodiesterase inhibitors)
- The Initial Pilot Phase 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.

Exploratory Mechanistic outcomes

Serial blood samples will be collected from patients as detailed in section 4.0. Assays will include markers of myocardial dysfunction and inflammation.

- Measurement of Total Catecholamine. It is unknown whether beta-blockade acts through altering the effects of extraneous catecholamines administered as treatment of septic shock or by modulating those produced by the patient. Serum catecholamines will be analysed in the context of the dose of inotropes being administered.
- Markers of myocardial dysfunction. Serum BNP has been demonstrated to be a reliable biomarker of myocardial injury, ischaemia and dysfunction in septic patients and also as a prognostic marker for a poor outcome (61;66). Serial measurements of Troponin-T will be made.
- Measurement of serum Free Fatty acids and markers of Fatty Acid Metabolism.
- Biomarkers of systemic inflammation. This will be measured using a multiplex inflammatory biomarker assay depending on the available technology at the time of analysis. A selection of cytokines will be analysed, all or some of which will include IL-1beta, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, TNF-alpha, TNF-beta, and IFN-gamma. This focused array will allow an assessment of the pro / anti-inflammatory balance over time in patients with septic shock and allow more detailed study of the other potential mechanisms of action of landiolol. Cortisol assays will measure the influence of beta blockade on the adrenal cortex
- In addition samples will be stored for subsequent analysis (e.g. genetics / proteomics / metabolomics) as appropriate.

3.3.2 Safety

The episodes of Bradycardia (HR <50 bpm), Bradycardia with haemodynamic compromise requiring intervention, significant hypotension requiring intervention (not including temporarily stopping the infusion), heart block, arrhythmia with haemodynamic compromise requiring intervention will be reported.

3.4 Eligibility criteria

Patients are eligible to be included in the trial if they meet the following criteria:

3.4.1 Inclusion criteria

- Male or female aged 18 years or above
- Being treated on an ICU
- Septic shock according to internationally accepted definitions*
- Heart rate ≥ 95 bpm (24 hours after start of vasopressor therapy)
- Receiving vasopressor support with noradrenaline to maintain a target blood pressure for ≥ 24 hours
- Are being treated with noradrenaline at a rate ≥ 0.1 mcg/kg/min

*Sepsis -3 definitions:

- confirmed or suspected infection requiring antibiotic therapy
- new organ dysfunction, as evidenced by an increase in SOFA score ≥ 2
- a blood lactate >2 mmol/l at any point during shock resuscitation
- vasopressor therapy to maintain mean arterial pressure (MAP) ≥ 65 mmHg

In particular the presence of a blood lactate > 2 mmol/l is only necessary for the diagnosis of septic shock and is NOT necessary for randomisation 24 hours later.

3.4.2 Exclusion criteria

The participant may not enter the trial if any of the following apply:

- Noradrenaline infusion <0.1 mcg/kg/min
- >48 hours after start of vasopressor therapy
- Having pre-existing severe cardiac dysfunction (NYHA grade 4 or more)
- Having pre-existing severe pulmonary hypertension (mean PA pressures > 55 mmHg)
- Acute severe bronchospasm (due to asthma or COPD)
- Untreated second or third degree heart block
- Untreated pheochromocytoma
- Prinzmetal's angina
- A past history of ischaemic stroke or transient ischaemic attack (TIA) or untreated severe carotid stenosis.
- Advanced liver disease
- Having been treated with any beta-blocker drug in the seventy two hours prior to screening.
- Known sensitivity to beta-blockers
- Patient / legal representative unwilling to provide written informed consent
- Known to be pregnant
- Terminal illness other than septic shock with a life expectancy < 28 days
- Participants who have participated in another research trial involving an investigational medicinal product in the past 30 days.
- Patients in whom the clinical team feel are about to finish their noradrenaline therapy.

3.5 Participant identification

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.

Once eligibility criteria are met there is a 24-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 remains tachycardic. 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.

3.6 Informed consent

Eligible patients who are deemed competent will be provided with a copy of the patient information sheet before informed consent is sought. However, due to the nature of the underlying condition and its treatment, the majority of patients will be unable to give informed consent. The vulnerability of this patient group is fully appreciated and every effort must be undertaken to protect their safety and well-being. To ensure this, consenting will be obtained in accordance with the Medicines for Human Use Regulations and the Health Research Authority ethics guide on medical research involving adults who cannot consent (<http://www.hra.nhs.uk/resources/before-you-apply/consent-and-participation/adults-unable-to-consent-for-themselves/>).

Patient Consent

If possible, written informed consent will be obtained from the patient. The investigator or their suitably trained nominee, e.g. from the research team, will inform the patient of all aspects pertaining to participation in the study. The investigator or their nominee will answer any questions that the patient has concerning study participation. In order to avoid overwhelming patients already facing a life-threatening condition we will provide the potential participant with a short study information sheet. If the potential participant wants to see the full detailed patient information sheet this will be provided, or this will be provided later when the patient is feeling better. If needed, local centres should ensure that hospital interpreter and translator services will be available to assist with discussion of the study. Local arrangements may be made for the participant information sheets (PIS) and consent forms to be available in other languages. Informed patients will be given an adequate amount of time to consider their participation in the trial. If the patient decides to participate in the trial, they will be asked to sign the informed consent form which will then be countersigned by the investigator or their nominee. The patient will retain one copy of the signed consent form. Another copy will be placed in the patient's medical records whilst the original will be retained in the Investigator Site File.

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 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.

Professional Legal Representative Consent

If the patient is unable to give informed consent and attempts to meet and discuss with a PerLR have failed then a doctor who is not connected with the conduct of the trial may act as a Professional Legal Representative (ProLR). The doctor will be informed about the trial by a member of the research team and given a copy of the PIS. 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. The doctor will retain one copy of the signed Consent Form. A second copy will be placed in the patient's medical records; the original will be retained in the Investigator Site File.

If a relative, partner or close friend should subsequently visit the patient after enrolment and before the patient has regained capacity they should be informed about the patient's participation. Similarly, if a patient regains capacity they will be informed of their participation in the trial and if they agree consent for ongoing participation will be sought.

The right of the participant to refuse to participate without giving reasons must be respected. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

Trial procedures including baseline assessments will not be undertaken until the informed consent form has been signed and dated by the participant/legal representative.

Should there be any subsequent amendment to the final protocol, which might affect their participation in the trial, then these will be discussed with the participant and, if applicable, continuing consent will be obtained using an amended consent form.

The process for obtaining informed consent will be in accordance with the REC guidance, and GCP and any other applicable regulatory requirements, which may be introduced.

3.7 Randomisation

3.7.1 Randomisation

This is an open label trial with no blinding of the treatment allocation. Blinding is not possible due to the requirement for the landiolol dose to be titrated to achieve a target HR.

We will use a computerised minimisation randomisation system, created by the Warwick Clinical Trials Unit (WCTU) in accordance with their standard operating procedure and held on a secure server, with the allocation generated per individual (participant). Participants will be randomised strictly sequentially as they become eligible for randomisation using a 1:1 ratio. A unique trial number for each participant will be generated sequentially per participant across the whole trial.

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 - 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 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.

The sequence and decode of treatment allocations will be concealed until interventions have all been assigned and recruitment, data collection, and all other trial-related assessments are complete.

3.7.2 Post-randomisation withdrawals, exclusions and moves out of region

Participants may be withdrawn from the trial at the discretion of the investigator and/or Trial Steering Committee due to safety concerns.

Participants may be discontinued from the trial treatment and/or the trial at any time without prejudice. Unless a participant explicitly withdraws their consent, they should be followed-up wherever possible and data collected as per the protocol until the end of the trial. Data collected up to the point of withdrawal will be retained.

Patients will be followed post-hospital discharge by the local research teams to determine their survival status, this will be done in the first instance by contacting their GP. We therefore expect loss to follow-up to be low.

3.8 Trial treatments

Participants will be randomised to either the intervention group or control group.

3.8.1 Intervention

The study drug should not be started until the treating physician is confident that adequate fluid resuscitation has been achieved and the patient has reached the target mean arterial pressure pre-defined by the treating clinician overseeing care (suggested target 65-70 mmHg but this may be varied as detailed below) using vasopressors. Adequate fluid resuscitation should be achieved using repeated fluid challenges. Examples of appropriate targets include any or all of the following:

- Good peripheral perfusion on clinical examination

- Other measures of cardiac output / flow, e.g. cardiac output, stroke volume variability (SVV), global end-diastolic volume index (GEDVI)
- No decrease in vasopressor infusion rate and no change in heart rate or mean blood pressure following fluid challenge
- Central venous pressure ≥ 8 mmHg (≥ 12 mmHg in mechanically ventilated patients)

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 has an elimination half-life of 2.3 to 4 minutes (48) 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 should begin to be reduced when all vasopressor agents (noradrenaline, vasopressin) have stopped for 12 hours (see also section 3.8.5 DEFINITION OF END OF NORADRENALINE TREATMENT (EONT) VISIT) but should continue according to the landiolol infusion protocol (APPENDIX B: STRESS-L Study Drug Infusion Protocol) until the patient's heart rate is persistently below 95 bpm. Once the landiolol infusion has been stopped for more than 12 hours, it should not be recommenced. Landiolol infusion should not be stopped during procedures including trips to theatre, percutaneous tracheostomy, central line insertions etc.

The EONT visit should occur once the noradrenaline infusion has been stopped for 12 hours.

3.8.2 Dose modification for side-effects

The flowsheet (APPENDIX B: STRESS-L Study Drug Infusion Protocol and APPENDIX C: STRESS-L Vasopressor Infusion Protocol) should be followed to manage the expected pharmacodynamic effects of landiolol, in particular bradycardia and hypotension.

3.8.3 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 without landiolol. 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.

3.8.4 Control / Usual Care

The control group will receive usual care only but not receive any beta blockade for the duration of their ICU stay. There will be no placebo infusion. Participants randomised to this arm will receive standard care for septic shock, namely:

- Timely treatment of the source of sepsis (e.g. drainage of infected fluid collections)

- Prompt and appropriate empiric antibiotic treatment, and modification, if needed, on the basis of culture results
- Appropriate fluid resuscitation to correct hypovolaemia.

All other general ICU management should be based on the latest guidance from the surviving sepsis campaign (20) and UK national critical care guidelines (e.g. ventilator and central line care bundles). However, outlined below are specific recommendations to ensure compliance with the STRESS-L protocol.

Cardiovascular

Fluids

Crystalloid infusions (e.g. 0.9% saline or compound sodium lactate) should be used for intravenous fluid resuscitation. Starch containing colloid solutions (e.g. Voluven and Volulyte) should NOT be used in view of evidence that they may be associated with adverse outcomes and increased rates of acute kidney injury (82), (83). Gelatin based solutions and human albumin solution may be used as alternative resuscitation fluids.

Fluid resuscitation should be given based on repeated assessment of volume status as detailed above.

In all patients we will compare oxygen delivery between treatment groups using central venous oxygen saturations (ScvO₂) and matched to the arterial saturations (SaO₂). This should be measured and recorded at baseline, and days 1, 2, 4 and 6 after randomisation if central venous access is available.

Vasoactive drugs - vasopressors

Noradrenaline is the initial vasopressor of choice. After fluid resuscitation, it should be titrated to maintain a target mean arterial pressure (MAP) that is pre-defined by the clinician overseeing care. This should usually be 65-70mmHg. In individual patients, a higher MAP target may be chosen, for instance if the patient is known to be hypertensive; similarly, in a young patient who is normally normotensive, a lower MAP may be chosen. However, it is important to ensure that the lowest dose of vasopressor is used to maintain an acceptable MAP to allow tissue perfusion in that patient.

Vasopressin, or any of its analogues, may be used as an alternative vasopressor or in addition to noradrenaline. **If used, vasopressin should be instigated at a fixed dose of 0.06 U/min** as outlined in the vasopressor infusion protocol (APPENDIX C).

Vasoactive drugs – inotropes

Additional inotropic agents may be administered as part of the STRESS-L protocol to optimise the cardiac output. Specifically, the use of beta agonists is not prohibited as this constitutes current recommended practice according to the Surviving Sepsis campaign guidelines (20).

Management of Atrial Fibrillation

Patients who develop atrial fibrillation (AF) **should not be treated with beta-blockade** as this will confound the analysis of STRESS-L. In the first instance, AF should be managed by ensuring that the serum potassium is at least 4.5 mmol/l. A dose of 20 mmol magnesium sulphate may be administered. If AF continues the patient should be treated with

amiodarone (300mg loading administered over 1 hour followed by a continuous infusion of 900 mg for 24 hours). DC cardioversion may be attempted if the treating clinician deems it appropriate.

Renal support

High volume haemofiltration for the management of sepsis (i.e. RRT not to treat kidney failure) **should not be used**.

3.8.5 Definition of End of Noradrenaline Treatment (EONT) visit

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. The EONT visit can occur at any point between day 1 and 14. If the patient has been randomised to the intervention group, then the infusion should begin to be reduced; the heart rate should be maintained between 80 and 94 bpm with further landiolol infusion as required and according to the protocol (APPENDIX B: STRESS-L Study Drug Infusion Protocol).

3.9 Details of Investigational Medicinal Product

3.9.1 Description and manufacture

Landiolol is a beta blocker used for supraventricular tachycardia and for the rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative, postoperative, or other circumstances where short-term control of the ventricular rate with a short acting agent is desirable. Landiolol is also indicated in non-compensatory sinus tachycardia where, in the physician's judgment the rapid heart rate requires specific intervention. Landiolol is not intended for use in chronic conditions.

Landiolol 300mg/50ml details

AOP Orphan Pharmaceuticals (Austria) will supply the study drug for STRESS-L free of charge for the duration of the trial.

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. All sites involved have the appropriate licenses in place.

3.9.2 Dosage and excipients

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 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 (based on 40 mcg/kg/min in a 24 hour infusion). **See section 3.8. and APPENDIX B for full dosing requirements**

Drug Name	Dosage	Description
Landiolol	1 – 40µg/kg/min	Supplied as lyophilisate in vials with a nominal filling volume of 50 ml containing 300mg landiolol hydrochloride (which is equivalent to 280 mg landiolol) and inactive ingredients Mannitol E421 and Sodium hydroxide (for pH adjustment).

3.9.3 Packaging and labelling

Laboratorio Reig Jofré 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.

Laboratorio Reig Jofré will ship bulk trial supplies to a 3rd party distributor in the UK for storage and distribution.

3.9.4 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.

Participating centres will be allocated a supply of trial treatment at site activation. Drug supplies across participating centres will be monitored by the coordinating centre using a web-based system created by WCTU. When the supplies at the participating centre reach a pre-determined level then a re-order is triggered and a further supply of trial treatment is sent to the corresponding participating site.

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. Any temperature incursions must be reported to the coordinating centre as soon as they are identified.

The local site investigator is responsible for ensuring trial drug accountability, including reconciliation of trial treatment and maintenance of trial treatment records, throughout the course of the study in accordance with UK regulatory requirements. Trial drug may be dispensed only by specifically authorised personnel. Responsibility for certain tasks related to the management of the trial drug can be delegated to the site pharmacy clinical trials staff and other members of the site trial team.

Landiolol supplied for use in the STRESS-L Trial must only be prescribed for participants randomised into this trial. The trial drug should be prescribed on the participant's inpatient chart and clearly identified as for the STRESS-L Trial. Sites may use local prescribing systems, including paper and electronic systems. Prescriptions should be made available for review as source data, if required.

It is envisaged between 2 and 4 vials will be required per participant for a 24 hour infusion. The prepared infusion solution can be used only for a maximum of 24 hours. Dispensing will

be recorded on the appropriate trial specific accountability forms. Trial drug must not be used for any other purpose than the present study. Trial drug that has been dispensed and prepared for administration to a participant must not be re-dispensed or re-issued to a different participant. Unused vials at the end of the trial or which has expired will be returned to the local pharmacy to be recorded and final accountability performed before local destruction is approved by the trial coordinating centre.

Further details regarding the IMP will be provided in the IMP Management Manual.

3.9.5 Known side effects

The most common (>1/100 to <1/10) side effects of the IMP are bradycardia and hypotension. For the full list of undesirable effects please refer to section 4.8 of the current Summary of Product Characteristics (SPC) for landiolol provided in the Investigator Site Files (ISF).

3.9.6 Contraindications, special warnings and precautions in the context of septic shock

Beta blockade treatment in septic shock represents a paradigm shift in patient management but its use arises from observations in both animal models (4-8) and patients (9;10) of harm induced by excessive sympathetic activation and benefit from beta-adrenergic blockade. Up to now, beta blockade has been regarded as contraindicated in patients with septic shock but Morelli's (12) study demonstrating cardiovascular stability in this group of patients has opened the prospect that beta blockade may benefit critically ill patients with septic shock.

The SPCs for beta blockers currently reflect the contraindications, precautions and warnings for their common indications of hypertension and tachyarrhythmias and not for their use in ICU. Contraindications in the SPC are diametrically opposed to the effects under study in STRESS-L; for example, conditions such as Severe Metabolic Acidosis (one of the inclusion criteria in STRESS-L) is marked as a contraindication in the SPC. Similarly, diabetic patients are advised not to take beta blocking tablets as these drugs mask the symptoms of hypoglycaemia but they do not interfere with the diabetes *per se*. Patients in ICU have their glucose controlled by continuous insulin infusion and it is routine to monitor the blood glucose regularly; STRESS-L patients will be managed according to this standard of care.

As landiolol is cleared by plasma cholinesterases, its metabolism should be unaffected by renal insufficiency. Protocolisation of the management of HR and BP outlined in Appendices B and C adjust the dose of infusions according to the individual response of the patient. As a result, if the clearance of landiolol is affected, lower infusion rates will be used because the patient response will be stronger

3.9.7 Compliance/contamination

Compliance for ICU patients will be assessed from their medication chart. The dosage of landiolol and noradrenaline will be recorded frequently on the case report form. Number of vials of landiolol issued per participant will be monitored on the site pharmacy records.

3.10 Concomitant illness and medication

3.10.1 Concomitant illness

Details of any concomitant illness (any illness present at the start of the trial) should be recorded at trial entry. If a change influences the participant's eligibility to continue in the trial, the investigator must be informed.

Septic shock is a serious disease with a high mortality. The standard management of septic shock involves the use of vasoactive drugs that may exacerbate or compromise concomitant conditions. The presence of peripheral vascular disease (PVD) is a risk for increased mortality in septic shock; while the SPC states that beta blockade should be avoided in patients with PVD, the vasodilation induced by sepsis means that any possible adverse effects of landiolol will be reduced and so it will be possible to administer the IMP in these patients.

3.10.2 Concomitant medication

Concomitant administration of landiolol with verapamil or diltiazem is not recommended in patients with atrioventricular conduction abnormalities. Participants on the control arm will not be prescribed any beta blockade for the duration of their ICU stay, similarly those on the intervention arm will not be prescribed any other beta blocker.

Antihypertensive agents should be used with caution in patients treated with landiolol.

Catecholamine-depleting agents or antisympathomimetic agents (e.g. clonidine, dexmedetomidine, reserpine) may have an additive effect when concomitantly administered with landiolol with marked hypotension and bradycardia. There is a possibility of 'rebound' hypertension in patients treated with clonidine although this was not observed after landiolol was administered for 24 hours.

Anaesthetists should be made aware that landiolol enhances the hypotensive effects of anaesthetic agents and that because of its degradation by plasma esterases, drugs such as suxamethonium can decrease the metabolism of landiolol leading to an increased plasma landiolol concentration and enhanced bradycardic effects.

All other drugs should be prescribed as clinically indicated based on the guidance in protocol section 3.8.

3.11 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.

The trial will be stopped prematurely if:

- Mandated by the Ethics Committee
- Mandated by the Medicines and Healthcare products Regulatory Agency (MHRA)
- Following recommendations from the Data Monitoring Committee (DMC)
- Funding for the trial ceases

Recruitment at individual sites may be terminated due to poor recruitment or serious breaches of GCP.

The Research Ethics Committee and MHRA will be notified in writing within 90 days when the trial has been concluded or within 15 days if terminated early.

4. METHODS AND ASSESSMENTS

4.1 Schedule of delivery of intervention and data collection

Table 1 summarises the participant involvement and timelines.

Screening

All septic shock patients started on noradrenaline in ICU will be screened for trial eligibility. Once eligibility criteria are met there is a 24-hour window for randomisation. Due to this short window, informed consent may be sought during the first 24 hours of noradrenaline therapy. This will allow more time if legal representative consent is required. Randomisation should not occur until noradrenaline therapy has been running for ≥ 24 hours and the patient remains tachycardic. It will be made clear to the patient or their legal representative that if they no longer meet the eligibility criteria after the 24 hour mark the participant will not be randomised into the trial. Written informed consent must be obtained prior to any trial specific assessments or investigations taking place.

Baseline visit – start of infusion (Day 0)

Informed consent will be taken at (or leading up to) this visit and a final check against eligibility criteria will be undertaken. The patient's medical history will be taken, physical examination, basic demographic data and steroid use will be recorded. A pregnancy test will be carried out on women of childbearing potential at the discretion of the local investigator. An echocardiogram (ECG) will be recorded. The participant will be randomised, and if allocated to the landiolol arm, IMP will be dispensed and the infusion started. Any adverse events (AEs) will be recorded, and any Serious Adverse Events (SAEs) reported following randomisation. The elements of the SOFA score will be recorded along with routine clinical data (cardiovascular, respiratory and renal physiological variables as well as haematological, biochemical and microbiological sample test results). The rates of noradrenaline infusion and landiolol infusion (if randomised to this group) will be recorded hourly. The site and types of pathogens isolated following admission should be recorded on the eCRF

Day 1 up to day 14

As the Primary Outcome measure is the mean SOFA score whilst the patient is in ICU up to 14 days, the elements of the score will be recorded in the eCRF for every day that the patient remains in the ICU from randomisation. This may be performed retrospectively but participating centres should ensure that blood has been sent to the Local Hospital Laboratories for the domains that depend on Laboratory Tests (liver, renal and coagulation and C-Reactive Protein).

In addition, routinely collected clinical data (cardiovascular, respiratory and renal physiological variables as well as haematological, biochemical and microbiological sample test results) will be recorded whilst noradrenaline is being infused (see table 1).

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. Heart rate data

should be collected to allow assessment of landiolol infusion compliance. These data may be collected in retrospect by referring to the clinical data recorded on the ICU charts.

Other clinical data collected will be:

- 1) Haemodynamics: In addition to the standard measures such as heart rate, presence of atrial fibrillation and blood pressure outlined above, cardiac output and stroke volume may be recorded if used. Also, the most recent recordings prior to the Visit of superior vena caval oxygen saturation, haemoglobin, arterial oxygen saturation and blood lactate concentration.
- 2) The previous 24 hours' intravenous fluid intake, urine output, and need for renal replacement therapy
- 3) Respiratory variables, e.g. blood gases with the worst P/F ratio, type of ventilator support.

Adverse events and steroid use will be recorded on the eCRF. Any SAEs will be reported as per protocol section 5.0. The site and types of pathogens isolated should be recorded on the eCRF.

End of Noradrenaline Treatment (EONT) Visit

As detailed above clinical data will also be recorded 12 hours (or as soon as possible) after noradrenaline has been stopped. This is called the End of Noradrenaline Treatment (EONT) Visit. Additionally IMP accountability will be undertaken; and AEs and steroid use will be recorded in the eCRF.

Follow Up Visits – Day 28 and Day 90

Participants will also be followed up to ascertain survival status at 28 days and at 90 days post-randomisation. The participant's GP will be contacted in the first instance to ascertain if the patient is alive; the participant may then be contacted by telephone. SAEs will be reported up to day 90 following randomisation.

Blood samples

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). The serum 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.

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

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

Transport and storage requirements have been outlined in section 4.2. Full requirements are detailed in the trial Laboratory Manual provided with the Investigator Site File.

Table 1: Trial Assessments

Procedure (Time (T) in days/hours)	Screening (T0-12)	Baseline- Start of Infusion (Day 0; T0)	Day 1 (T0+24)	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	EONT Visit ¹	FU Visit Day 28	Final visit Day 90
Eligibility assessment	•																		
Informed consent		•																	
Demographics		•																	
Medical History		•																	
Physical examination		•																	
ECG		•	According to clinical need or if AE/SAE																
Pregnancy test ²		•																	
Randomisation		•																	
IMP		Dispense															Return		
Blood sample		•	•	•		•		•									•		
Biobank blood sample (optional)		•	•																
Transport of stored serum																	Batch		
Local laboratory tests:		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•		
C-Reactive Protein (CRP)		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•		
Glucose		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•		
Lactate		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•		
Worst PaO ₂ /FiO ₂		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•		
Platelets		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•		
Creatinine		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•		
Bilirubin		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•		
INR		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•		
White Cell Count		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•		
Central Venous Blood Gas (ScvO ₂)		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•		
Arterial Blood Gas		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•		
Microbiology results from local lab		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•		
Heart Rate (Hourly: T0+7 days)		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•		
Atrial Fibrillation (Hourly: T0+7 days)		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•		
Blood Pressure (Hourly: T0+7 days)		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•		
Rate of Vasopressor (Hourly: T0+7 days)		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•		
In/Out Fluids		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•		
SOFA score		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•		
Adverse Events (SAEs up to Day 90)		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Steroid use		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•		
Compliance		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•		
Mortality status																		•	•
End of Trial																			•

1. End of all vasopressor infusions +12 hours (may occur at any point between day 1 and day 14); see protocol section 3.8.5 for full details. The maximum duration of landiolol treatment is 14 days.

2. Pregnancy test on women of childbearing potential at the discretion of local investigator

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). These research blood samples are mandatory as the results will help us to define the mechanisms involved in treating sepsis with beta blockade (as part of the secondary outcomes). The following tests will likely be carried out on these samples but will be dependent on available technology: catecholamines, Troponin-T, creatine kinase (CK-MB), beta natriuretic peptide (BNP), cytokine analysis (probably IL-1 beta, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, TNF-alpha, TNF-beta, and IFN-gamma). The blood samples will be centrifuged and the serum isolated will be temporarily stored at -20°C or -70°C at the respective sites. Sites will receive detailed procedures relating to processing, storage and shipment of samples in the STRESS-L Laboratory Manual provided as part of the Investigator Site File. Regular frozen shipments of serum will be arranged to the University Hospitals of Birmingham NHS Foundation Trust (UHB) for subsequent analysis.

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

A Biobank blood sample (5ml) will be collected on Day 0 and Day 1, if the patient (or their legal representative) has consented to provide these. These are optional blood samples and will be used for potential genetic research in future ethically approved studies by the research team. 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. The frozen serum will be sent in batches to the Human Biomaterials Resource Centre (HBRC) at the University of Birmingham.

Samples stored at UHB and the University of Birmingham will be stored in accordance with the Human Tissue Act 2004. Disposal will be according to local laboratory procedures.

Full requirements and contact details for the laboratories are detailed in the trial Laboratory Manual provided with the Investigator Site File.

4.3 Assessment of protocol compliance

The Local Research Team (PI, CIs and/or Research Nurses) at the Site will review heart rate data daily from the ICU charts and record the amount of time the patient has achieved the target HR. They will feedback to the clinical team whether target heart rate was achieved successfully. 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.

The Local Research Team will also ensure that landiolol is discontinued according to the Appendix.

The Local Research Team will ensure adequate supply of the IMP for the duration of the patient's inclusion in the trial. The Local Research Team will ensure return of unused IMP to pharmacy at the end of the infusion.

The Local Research Team will ensure that STRESS-L study bloods are taken and processed according to the schedule (TABLE 1).

5. ADVERSE EVENT MANAGEMENT / PHARMACOVIGILANCE

5.1 Definitions

5.1.1 Adverse Events (AE)

An Adverse Event (AE) is defined as any untoward medical occurrence in a participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment/intervention.

All AEs following randomisation up to day 14 (end of landiolol infusion) should be collected and recorded in the AE section of the eCRF.

Adverse event data will be reviewed by the STRESS-L Trial TMG and by the Data Monitoring Committee.

5.1.2 Adverse Reaction (AR)

An Adverse Reaction (AR) is: 'All untoward and unintended responses to an investigational medicinal product related to any dose administered'.

5.1.3 Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Events (SUSARS)

A Serious Adverse Event is an AE that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation

- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical condition.

Suspected Unexpected Serious Adverse Reactions (SUSARs) are SAEs that are considered to be related to the administration of the trial drug and are also unexpected i.e. their nature or severity is not consistent with the Summary of Product Characteristics (SPC).

Clinical outcomes

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 Serious Adverse Events:

- Death related to sepsis
- Cardiovascular failure, including the need for vasopressors / inotropes
- Respiratory failure, including mechanical ventilation and acute lung injury
- Hepatic impairment as measured by Transaminases <1000 IU/L
- Renal failure, including the need for renal replacement therapy
- Haematological / Coagulation failure, including thrombocytopaenia and Disseminated Intravascular Coagulopathy

Delirium / confusion

Clinical details about these clinical outcomes will be routinely collected in the case record form.

5.2 Reporting SAEs and SUSARs

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 to the coordinating centre within **24 hours** of the research staff becoming aware of the event. 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.

For each **SAEs / SUSARs** the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to trial drug / investigation), in the opinion of the investigator

- whether the event would be considered expected or unexpected.

Any change of condition or other follow-up information should be faxed 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 using the SAE form 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 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.

The causality of SAEs (i.e. relationship to trial treatment) will be assessed by the investigator(s) on the SAE form.

Relationship to trial medication	Description
Unrelated	There is no evidence of any causal relationship
Unlikely to be related	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication or device). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible relationship	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication or device). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable relationship	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Events which are possibly, probably or definitely related will be reported immediately.

The Summary of Product Characteristics (SPC) for landiolol will to be used to assess expectedness of events (known as the reference safety information).

Participants will be followed up at days 28 and 90 to ascertain mortality status. The local research teams will contact the participant's GP in the first instance to determine this.

5.3 Responsibilities

The safety of landiolol has been noted in Section 2.8.

Individual SAEs and trends in SAEs will be independently reviewed for STRESS-L as detailed below:

- Clinical review in real time of each SAE and within 24 hours of being reported to the coordinating centre
- Cumulative review of all safety information by the DMC on a 6 monthly basis and the TMG on a monthly basis

Principal Investigator (PI):

Checking for AEs and ARs when participants attend for treatment / follow-up.

1. Using medical judgement in assigning seriousness, causality and expectedness [in Phase III and late Phase II CTIMPs] using the Reference Safety Information approved for the trial.
2. Ensuring that all SAEs and SARs (including SUSARs) are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs and SARs (including SUSARs) are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.
3. Ensuring that AEs and ARs are recorded and reported to the Sponsor in line with the requirements of the protocol.

Chief Investigator (CI) / delegate or independent clinical reviewer:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment.
3. Immediate review of all SUSARs.
4. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
5. Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs.
6. Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).

Sponsor:

1. Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol.
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
3. Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring Committee (DMC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
4. Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC within required timelines.
5. Notifying Investigators of SUSARs that occur within the trial.
6. Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial.
7. Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC.

Trial Steering Committee (TSC):

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMC regarding safety issues.

Data Monitoring Committee (DMC):

In accordance with the Trial Terms of Reference for the DMC, periodically reviewing unblinded overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

5.4 Procedures in case of overdose

Overdoses come under 'Patient Safety Incidents' and are defined as 'any unintended or unexpected incident which could have or did lead to harm for one or more patients' (also may be referred to as adverse incidents, clinical errors or near-miss). Although not a requirement of the CT regulations, the PI at each centre should ensure their NHS Trust is notified of any patient safety incidents, according to local policy. NHS Trusts should report all incidents to the National Patient Safety Agency.

The maximum recommended daily dosage of landiolol for this patient population is 57.6mg/kg (based on 40 mcg/kg/min in a 24 hour infusion). Rate of landiolol and noradrenaline will be recorded on the eCRF. Heart rate is closely monitored at the bedside, therefore an overdose is unlikely to occur. In the unlikely event that an overdose does occur the infusion will be reduced accordingly.

Overdoses should be notified to the sponsor with immediate effect and recorded on the deviation/violation log. If a SAE is associated with the overdose ensure the overdose is fully described in the SAE report form.

5.5 Procedures in case of pregnancy

There are no available data from the use of landiolol in pregnant women. A participant that is known to be pregnant will be excluded from the trial.

It is not routine practice to test women of child-bearing age with sepsis. Furthermore, sepsis in women of this age group is very uncommon. In these cases, the sepsis itself and its usual treatment (cardiovascular drugs, antibiotics etc) will already be in place and of themselves place the woman and her pregnancy at risk.

There are few studies into the effects of landiolol in pregnancy. Suehiro published that landiolol reduced maternal BP and HR changes during induction of anaesthesia for Caesarean section but found no adverse effects on uterine contraction or the foetus were seen (53).

For the purposes of this trial a urine pregnancy or equivalent test will be carried out at the discretion of the local investigator for women of child bearing potential, following the attainment of written informed consent. If a pregnancy test is done and found to be positive the patient will be excluded from the trial and will not be eligible for randomisation.

As the half-life of the IMP is between 2.3 to 4 minutes, the EONT visit (12 hours following the end of noradrenaline infusion) is a more than adequate wash out period. The likelihood that a participant will become pregnant following discharge from ICU is unlikely as these patients remain very ill. However guidance in case of pregnancy has been provided below.

Patients found to be pregnant despite being randomised to receive landiolol should be reported as a serious adverse incident and the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the participant was discontinued from the trial.

If a pregnancy occurs following discharge from hospital during the follow up period the coordinating centre will be notified. All reports of congenital abnormalities/birth defects must be reported and followed up as a SAE.

5.6 Notification of deaths

All deaths will be reported to the sponsor irrespective of whether the death is related to disease progression, the IMP, or an unrelated event. Deaths will be reported on the relevant eCRF up to the end of the follow up period of 90 days.

5.7 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

6. DATA MANAGEMENT

Personal data collected during the trial will be handled and stored in accordance with the 1998 Data Protection Act.

Participants will be identified using a unique trial number, initials and date of birth only.

6.1 Data collection and management

The electronic Case Report Forms (eCRFs) will be developed to collect all required trial data.

Access to the online eCRF will be provided by the Warwick CTU, with paper versions made available to sites if required prior to electronic data entry. All paper CRF pages which have entries will be transcribed to the online eCRF by a member of the local research team, and any changes on the paper CRFs must also be made online, where all data will be stored in a secure dedicated server with access restricted to authorised users only. Original paper CRFs where utilised, will remain with the investigator as a permanent record. The Principal Investigator at each centre must ensure that their worksheets are kept in a secure location (i.e. in a locked cabinet or cupboard, or a locked room).

Each participant will be assigned a trial identity code number, allocated at randomisation, for use on eCRFs and other trial documents.

eCRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log.'

All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.

Procedures for chasing missing eCRFs and data will be detailed in the STRESS-L Data Management Plan.

The local Principal Investigator shall sign a declaration ensuring accuracy of data recorded in the eCRF.

6.2 Database

The database will be developed by the Programming Team at WCTU and all specifications (i.e. database variables, validation checks, screens) will be agreed between the programmer and appropriate trial staff.

6.3 Data storage

All essential documentation and trial records will be stored by WCTU in conformance with the applicable regulatory requirements and access to stored information will be restricted to authorised personnel.

Study documents and data storage

The investigator will retain essential documents until notified by the Sponsor, and for at least ten years after study completion, as per WCTU SOPs. Subject files and other source data (including copies of protocols, eCRFs, original reports of test results, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be kept for the maximum period of time permitted by the institution. Documents will be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

6.4 Data access and quality assurance

Participants' identification data (initials and date of birth) will be required for the registration process. The WCTU will preserve the confidentiality of participants taking part in the study. The University of Warwick is registered under the Data Protection Act.

The investigator must ensure that the participant's privacy is maintained. On the eCRF or other documents submitted to the coordinating centre, participants will be identified by a unique participant ID number only. Documents that are not submitted to the coordinating centre (e.g. signed informed consent form) should be kept strictly confidential by the investigator.

The investigator will make a separate confidential record of the participant's name and Participant ID number (the trial Enrolment Log), to permit identification of all participants enrolled in the trial in accordance with regulatory requirements and for follow-up as required.

The investigator shall permit direct access to participant's records and source document for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor and Regulatory Authorities.

Any samples transferred from the site will be identified by the trial identification number and one other identifier (initials or date of birth).

Databases will only be accessed by authorised personnel using specific passwords. Electronic participant data will only be identified by their trial identification number. All data will be handled in accordance with the Data Protection Act 1998.

Participants will not be identified in any trial reports or publications.

Quality Control will be performed according to Warwick Clinical Trials Unit internal procedures. The study may be audited by a Quality Assurance representative of the Sponsor or the relevant NHS Trust's governance team. All necessary data and documents will be made available for inspection by external authorities.

6.5 Data Shared with Third Parties

The trial statisticians/analysts and DMC will have access to the data set for the analysis of trial outcomes. The Chief Investigator (Dr Tony Whitehouse) will have access to the data and will take full responsibility for the analysis and publication of the results. Once the main analyses have been undertaken, data will be available to principal and other investigators subject to approval of data analysis plans by the steering committee and compliance with the University of Warwick Standard Operating Procedures on Data Transfer. We will comply with Data Sharing Policies that may be instituted by the Funder (NIHR EME) during the lifetime of the project.

6.6 Archiving

Trial documentation and data will be archived for at least ten years after completion of the trial. The PI or designee must maintain adequate and accurate records to enable the conduct of the Trial to be fully documented and the Trial data to be subsequently verified. After trial closure the PI will maintain all source documents and trial related documents. The WCTU will maintain specific trial related documents. All source documents will be retained for a minimum period of ten years following the end of the Trial. The WCTU will authorise and advise of the archiving requirements as part of the site closure process (on behalf of the Sponsor).

7. STATISTICAL ANALYSIS

7.1 Power and sample size

The primary outcome is the mean SOFA score over the first 14 days in ICU. In data for 324 patients from UHB satisfying the trial eligibility criteria, the mean SOFA score over the first 14 days in ICU was 6.3, with standard deviation 2.4. Assuming (conservatively) a standard deviation of 2.8, and a difference of 1 point between the beta blocker and control groups, obtaining a p-value less than 0.05 (two-sided) with 90% power would require outcome data on 330 patients. To allow for 3% withdrawals and losses, the proposed sample size is 340.

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. Compared to other similar trials we believe this to be an achievable target. The target recruitment rate for the trial has been discussed with and agreed by the Trial Management Group (TMG).

7.3 Statistics and data analysis

Results will be reported in accordance with Consolidation Standards of Reporting Trials (CONSORT) guidelines for randomised controlled trials (84). The primary analysis will be conducted according to intention to treat, comparing all those allocated to beta blocker with

all of those allocated to standard care, regardless of treatment actually received. Regression models will be used to estimate the treatment effects (with 95% confidence intervals), and the models will be adjusted for clinically important covariates. Subgroup effects for baseline severity measured using the dose of noradrenaline will be assessed using formal statistical tests for interaction for the primary outcome and mortality. If there is substantial non-compliance we will conduct CACE (complier average causal effect) analyses to estimate the treatment effect among those who received the treatment as allocated. Interim analyses will be conducted every 6 months to closely monitor the accumulating data. If required, multiple imputation techniques will be applied to deal with missing data as a sensitivity analysis. A detailed statistical analysis plan (SAP) will be written by the study statistical team and then finalised and approved by the DMC and TSC before any analysis is undertaken.

7.4 Decision making for subsequent trial

The purpose of this trial is to establish whether there is likely to be any treatment benefit to beta-blockers, whether this is influenced by noradrenaline dose, and hence to determine whether a subsequent trial to evaluate the treatment's effects on mortality is justified. This decision will be based on (a) evidence of benefit in the trial's primary and other intermediate outcomes (safety and cardiovascular stability) and (b) a sufficient probability that a subsequent trial would be able to detect a mortality benefit: if it is very unlikely that a mortality benefit would be found in a subsequent trial, the investment of time and resources may not be justified.

7.5 Methodological analysis

We plan to conduct some methodological work as part of the trial analysis and will be detailed in the SAP. This will explore different approaches to analysis of ICU trials, that allow incorporation of multiple relevant outcomes, including death, into a single overall measure (e.g. the win ratio (85), global ranking score (86) and weighted composite outcome (87)).

8. TRIAL ORGANISATION AND OVERSIGHT

8.1 Sponsor and governance arrangements

University Hospitals Birmingham NHS Foundation Trust (UHB) will act as the Sponsor for the trial with trial management being undertaken at the WCTU. WCTU SOPs will be adhered to. A collaborators agreement is in place between UHB and WCTU who will provide full research management services. Clinical Trial Agreements will also be in place between the Sponsor and each research site, with clear delegation of roles and responsibilities.

8.2 Regulatory authorities/ethical approval

This trial will seek a Clinical Trial Authorisation from the UK Competent Authority the Medicines and Healthcare products Regulatory Agency (MHRA).

This trial will also seek favourable opinion of a Research Ethics Committee.

All required ethical and regulatory approval(s) for the trial will be sought using the Integrated Research Application System.

Before enrolling participants into the trial, each trial site must ensure that the local conduct of the trial has the approval of the relevant NHS Trust Research & Development (R&D) department. Sites will not be permitted to enrol participants into the trial until capability and capacity has been confirmed and a fully signed site agreement has been received by the Warwick Clinical Trials Unit STRESS-L Trial Team and an official site opening letter has been issued.

Substantial protocol amendments will be provided to Principal Investigators and site staff and other relevant parties once the appropriate approvals have been obtained. Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to receiving Sponsor or IEC approval. However, in this case, approval must be obtained as soon as possible after implementation.

The regulatory authorities and REC will be offered annual progress reports and informed about the end of trial, within the required timelines.

The Chief Investigator will submit a final report to the required authorities with the results, including any publications within one year of the declared end of the trial.

8.3 Trial Registration

STRESS-L will be registered with EudraCT (2017-001785-14) and will also be registered with the International Standard Randomised Controlled Trial Number (ISRCTN) Register. We will also register the trial on clinicaltrials.gov.

8.4 Notification of serious breaches to GCP and/or trial protocol

A “serious breach” is a breach which is likely to effect to a significant degree –

- a) the safety or physical or mental integrity of the participants of the trial; or
- b) the scientific value of the trial

The sponsor shall be notified immediately of any case where the above definition applies during the trial conduct phase

The WCTU will on behalf of the sponsor will notify the licensing authority in writing of any serious breach of

- a) the conditions and principles of GCP in connection with that trial; or
- b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach

8.5 Indemnity

University Hospitals Birmingham NHS Foundation Trust, the Sponsor of the trial has civil liability insurance, which covers this study in all participating centres. UHB also holds insurance policy covering negligent harm.

8.6 Trial timetable and milestones

	Month	Recruitment
Set-up	1-5	n/a
Recruitment	6-41	36
Follow up	42-44	n/a
Analysis	45-51	n/a

8.7 Administration

The trial coordination will be based at WCTU, University of Warwick.

8.8 Trial Management Group (TMG)

The Trial Management Group, consisting of the project staff and co-investigators involved in the day-to-day running of the trial, will meet regularly throughout the project. Significant issues arising from management meetings will be referred to the Trial Steering Committee or Investigators, as appropriate.

8.9 Trial Steering Committee (TSC)

The trial will be guided by a group of respected and experienced personnel and trialists as well as at least one 'lay' representative. The TSC will have an independent Chairperson. Face to face meetings will be held at regular intervals determined by need but not less than once a year. Routine business is conducted by email, post or teleconferencing.

The Steering Committee, in the development of this protocol and throughout the trial will take responsibility for:

- Major decisions such as a need to change the protocol for any reason
- Monitoring and supervising the progress of the trial
- Reviewing relevant information from other sources
- Considering recommendations from the DMC

- Informing and advising on all aspects of the trial

The membership of the TSC is shown on page 4.

8.10 Data Monitoring Committee (DMC)

The DMC will consist of independent experts with relevant clinical research, and statistical experience. The DMC will meet every 6 months after the start of recruitment. Confidential reports containing recruitment, protocol compliance, safety data and interim assessments of outcomes will be reviewed by the DMC. The DMC will advise the TSC as to whether there is evidence or reason why the trial should be amended or terminated.

The membership of the DMC is shown on page 4.

DMC meetings will also be attended by the Chief Investigator and Trial Coordinator (for non-confidential parts of the meeting) and the trial statistician.

8.11 Essential Documentation

A Trial Master File will be set up according to WCTU SOP and held securely at the coordinating centre.

The coordinating centre will provide Investigator Site Files and Pharmacy Files to all recruiting centres involved in the trial.

9. MONITORING AND QUALITY ASSURANCE OF TRIAL PROCEDURES

Site initiation visits will be conducted for all participating centres to provide protocol procedural training.

A monitoring plan will be produced in line with the level of risk identified in the risk assessment. Appropriate WCTU staff members shall carry out central monitoring of trial data as an on-going activity. Data being recorded on the eCRF allows assessment of protocol compliance (see section 4.3). The TMG will regularly review serious adverse event data and protocol deviations.

On-site monitoring visits will be conducted as necessary and according to the monitoring plan for the trial. Monitoring and audits will be conducted in accordance with WCTU procedures. All trial related documents will be made available on request for monitoring and/or audit by WCTU, UHB and for inspection by the MHRA or other relevant bodies. The PI will allow the WCTU direct access to relevant source documentation for verification of data entered onto the eCRFs. Access should also be given to trial staff and relevant departments (i.e. pharmacy, laboratory).

Trial data and evidence of monitoring and systems audits will be made available for inspection by the regulatory authority as required.

10. PATIENT AND PUBLIC INVOLVMENT (PPI)

A PPI representative is a member of the Trial Management Group and has reviewed patient facing documentation prior to the ethics and regulatory submissions and their comments have been incorporated. Two PPI representatives will sit on the Trial Steering Committee and will provide input from a patient perspective at trial meetings. Both representatives will review and provide feedback on all relevant project documents.

11. DISSEMINATION AND PUBLICATION

The results of the trial will be reported first to trial collaborators. The main report will be drafted by the trial co-ordinating team, and the final version will be agreed by the Trial Steering Committee before submission for publication, on behalf of the collaboration.

The success of the trial depends on the collaboration of doctors, nurses and researchers from across the UK. Equal credit will be given to those who have wholeheartedly collaborated in the trial.

The trial will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org).

All publications and presentations relating to the study will be authorised by the Trial Management Group. Authorship will be determined according to the internationally agreed criteria for authorship (www.icmje.org).

12. REFERENCES

- (1) Asfar P, Meziani F, Hamel JF, Grelon F, Megarbane B, Anguel N, et al. High versus Low Blood-Pressure Target in Patients with Septic Shock. *N Engl J Med* 2014 Mar 18;370(17):1583-93.
- (2) Caironi P, Tognoni G, Masson S, Fumagalli R, Pesenti A, Romero M, et al. Albumin replacement in patients with severe sepsis or septic shock. *N Engl J Med* 2014 Apr 10;370(15):1412-21.
- (3) Holst LB, Haase N, Wetterslev J+, Wernerman J, Guttormsen AB, Karlsson S, et al. Lower versus Higher Hemoglobin Threshold for Transfusion in Septic Shock. *N Engl J Med* 2014 Oct 1;371(15):1381-91.
- (4) Berk JL, Hagen JF, Beyer WH, Gerber MJ, Dochat GR. The treatment of endotoxin shock by beta adrenergic blockade. *Ann Surg* 1969 Jan;169(1):74-81.
- (5) Suzuki T, Morisaki H, Serita R, Yamamoto M, Kotake Y, Ishizaka A, et al. Infusion of the beta-adrenergic blocker esmolol attenuates myocardial dysfunction in septic rats. *Crit Care Med* 2005 Oct;33(10):2294-301.
- (6) Aboab J, Sebillé V, Jourdain M, Mangalaboyi J, Gharbi M, Mansart A, et al. Effects of esmolol on systemic and pulmonary hemodynamics and on oxygenation in pigs with hypodynamic endotoxin shock. *Intensive Care Med* 2011 Aug;37(8):1344-51.
- (7) Ackland GL, Yao ST, Rudiger A, Dyson A, Stidwill R, Poputnikov D, et al. Cardioprotection, attenuated systemic inflammation, and survival benefit of beta1-adrenoceptor blockade in severe sepsis in rats. *Crit Care Med* 2010 Feb;38(2):388-94.
- (8) Hagiwara S, Iwasaka H, Maeda H, Noguchi T. Landiolol, an ultrashort-acting beta1-adrenoceptor antagonist, has protective effects in an LPS-induced systemic inflammation model. *Shock* 2009 May;31(5):515-20.
- (9) Balik M, Rulisek J, Leden P, Zakharchenko M, Otahal M, Bartakova H, et al. Concomitant use of beta-1 adrenoreceptor blocker and norepinephrine in patients with septic shock. *Wien Klin Wochenschr* 2012 Aug;124(15-16):552-6.
- (10) Morelli A, Donati A, Ertmer C, Rehberg S, Kampmeier T, Orecchioni A, et al. Microvascular effects of heart rate control with esmolol in patients with septic shock: a pilot study. *Crit Care Med* 2013 Sep;41(9):2162-8.
- (11) de ME, Aboab J, Mansart A, Annane D. Bench-to-bedside review: Beta-adrenergic modulation in sepsis. *Crit Care* 2009;13(5):230.
- (12) Morelli A, Ertmer C, Westphal M, Rehberg S, Kampmeier T, Ligges S, et al. Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical trial. *JAMA* 2013 Oct 23;310(16):1683-91.
- (13) Annane D, Bellissant E, Cavaillon JM. Septic shock. *Lancet* 2005 Jan 1;365(9453):63-78.

- (14) Benedict CR, Rose JA. Arterial norepinephrine changes in patients with septic shock. *Circ Shock* 1992 Nov;38(3):165-72.
- (15) Boldt J, Menges T, Kuhn D, Diridis C, Hempelmann G. Alterations in circulating vasoactive substances in the critically ill--a comparison between survivors and non-survivors. *Intensive Care Med* 1995 Mar;21(3):218-25.
- (16) Sander O, Welters ID, Foex P, Sear JW. Impact of prolonged elevated heart rate on incidence of major cardiac events in critically ill patients with a high risk of cardiac complications. *Crit Care Med* 2005 Jan;33(1):81-8.
- (17) Dunser MW, Hasibeder WR. Sympathetic overstimulation during critical illness: adverse effects of adrenergic stress. *J Intensive Care Med* 2009 Sep;24(5):293-316.
- (18) Schmittinger CA, Torgersen C, Luckner G, Schroder DC, Lorenz I, Dunser MW. Adverse cardiac events during catecholamine vasopressor therapy: a prospective observational study. *Intensive Care Med* 2012 Jun;38(6):950-8.
- (19) Singer M. Catecholamine treatment for shock--equally good or bad? *Lancet* 2007 Aug 25;370(9588):636-7.
- (20) Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 2013 Feb;39(2):165-228.
- (21) EVANS DG, MILES AA, NIVEN JS. The enhancement of bacterial infections by adrenaline. *Br J Exp Pathol* 1948 Feb;29(1):20-39.
- (22) Lyte M, Freestone PP, Neal CP, Olson BA, Haigh RD, Bayston R, et al. Stimulation of *Staphylococcus epidermidis* growth and biofilm formation by catecholamine inotropes. *Lancet* 2003 Jan 11;361(9352):130-5.
- (23) Freestone PP, Haigh RD, Lyte M. Specificity of catecholamine-induced growth in *Escherichia coli* O157:H7, *Salmonella enterica* and *Yersinia enterocolitica*. *FEMS Microbiol Lett* 2007 Apr;269(2):221-8.
- (24) Freestone PP, Williams PH, Haigh RD, Maggs AF, Neal CP, Lyte M. Growth stimulation of intestinal commensal *Escherichia coli* by catecholamines: a possible contributory factor in trauma-induced sepsis. *Shock* 2002 Nov;18(5):465-70.
- (25) Takahashi N, Murota H, Sutoh I. Antimicrobial activity of topical beta-adrenergic blocking agents. *Ophthalmic Res* 1983;15(6):277-9.
- (26) Senzolo M, Cholongitas E, Burra P, Leandro G, Thalheimer U, Patch D, et al. beta-Blockers protect against spontaneous bacterial peritonitis in cirrhotic patients: a meta-analysis. *Liver Int* 2009 Sep;29(8):1189-93.
- (27) Ibrahim-Zada I, Rhee P, Gomez CT, Weller J, Friese RS. Inhibition of sepsis-induced inflammatory response by beta1-adrenergic antagonists. *J Trauma Acute Care Surg* 2014 Feb;76(2):320-7.

- (28) Calzavacca P, Lankadeva YR, Bailey SR, Bailey M, Bellomo R, May CN. Effects of selective Beta1-adrenoceptor blockade on cardiovascular and renal function and circulating cytokines in ovine hyperdynamic sepsis. *Crit Care* 2014 Nov 21;18(6):610.
- (29) Ohtsuka T, Hamada M, Hiasa G, Sasaki O, Suzuki M, Hara Y, et al. Effect of beta-blockers on circulating levels of inflammatory and anti-inflammatory cytokines in patients with dilated cardiomyopathy. *J Am Coll Cardiol* 2001 Feb;37(2):412-7.
- (30) Friese RS, Barber R, McBride D, Bender J, Gentilello LM. Could Beta blockade improve outcome after injury by modulating inflammatory profiles? *J Trauma* 2008 Apr;64(4):1061-8.
- (31) Bergmann M, Gornikiewicz A, Sautner T, Waldmann E, Weber T, Mittlbock M, et al. Attenuation of catecholamine-induced immunosuppression in whole blood from patients with sepsis. *Shock* 1999 Dec;12(6):421-7.
- (32) Tian X, Zhang L, Hou Y, Xu W, Dong Y, Liu J, et al. Effects of cAMP and beta-adrenergic receptor antagonists on the function of peripheral T helper lymphocytes in patients with heart failure. *Neuroimmunomodulation* 2011;18(2):73-8.
- (33) Habib G. Reappraisal of the importance of heart rate as a risk factor for cardiovascular morbidity and mortality. *Clin Ther* 1997;19 Suppl A:39-52.
- (34) Cunnion RE, Schaer GL, Parker MM, Natanson C, Parrillo JE. The coronary circulation in human septic shock. *Circulation* 1986 Apr;73(4):637-44.
- (35) Reich DL, Bennett-Guerrero E, Bodian CA, Hossain S, Winfree W, Krol M. Intraoperative tachycardia and hypertension are independently associated with adverse outcome in noncardiac surgery of long duration. *Anesth Analg* 2002 Aug;95(2):273-7, table.
- (36) Hartmann B, Junger A, Rohrig R, Klasen J, Jost A, Benson M, et al. Intra-operative tachycardia and peri-operative outcome. *Langenbecks Arch Surg* 2003 Sep;388(4):255-60.
- (37) Cook S, Togni M, Schaub MC, Wenaweser P, Hess OM. High heart rate: a cardiovascular risk factor? *Eur Heart J* 2006 Oct;27(20):2387-93.
- (38) Palatini P, Benetos A, Julius S. Impact of increased heart rate on clinical outcomes in hypertension: implications for antihypertensive drug therapy. *Drugs* 2006;66(2):133-44.
- (39) Indolfi C, Ross J, Jr. The role of heart rate in myocardial ischemia and infarction: implications of myocardial perfusion-contraction matching. *Prog Cardiovasc Dis* 1993 Jul;36(1):61-74.
- (40) Gandhi S, Litt D, Narula N. New-onset atrial fibrillation in sepsis is associated with increased morbidity and mortality. *Neth Heart J* 2015 Feb;23(2):82-8.

- (41) Okajima M, Takamura M, Taniguchi T. Landiolol, an ultra-short-acting beta1-blocker, is useful for managing supraventricular tachyarrhythmias in sepsis. *World J Crit Care Med* 2015 Aug 4;4(3):251-7.
- (42) Arbabi S, Champion EM, Hemmila MR, Barker M, Dimo M, Ahrns KS, et al. Beta-blocker use is associated with improved outcomes in adult trauma patients. *J Trauma* 2007 Jan;62(1):56-61.
- (43) Christensen S, Johansen MB, Tonnesen E, Larsson A, Pedersen L, Lemeshow S, et al. Preadmission beta-blocker use and 30-day mortality among patients in intensive care: a cohort study. *Crit Care* 2011;15(2):R87.
- (44) Herndon DN, Hart DW, Wolf SE, Chinkes DL, Wolfe RR. Reversal of catabolism by beta-blockade after severe burns. *N Engl J Med* 2001 Oct 25;345(17):1223-9.
- (45) Herndon DN, Rodriguez NA, Diaz EC, Hegde S, Jennings K, Mlcak RP, et al. Long-term propranolol use in severely burned pediatric patients: a randomized controlled study. *Ann Surg* 2012 Sep;256(3):402-11.
- (46) Chen JX, Sun J, Liu YY, Jia BH. [Effects of adrenergic beta-1 antagonists on hemodynamics of severe septic patients]. *Zhonghua Yi Xue Za Zhi* 2013 Apr 23;93(16):1243-6.
- (47) Yang S, Liu Z, Yang W, Zhang G, Hou B, Liu J, et al. [Effects of the beta-blockers on cardiac protection and hemodynamics in patients with septic shock: a prospective study]. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2014 Oct;26(10):714-7.
- (48) Atarashi H, Kuruma A, Yashima M, Saitoh H, Ino T, Endoh Y, et al. Pharmacokinetics of landiolol hydrochloride, a new ultra-short-acting beta-blocker, in patients with cardiac arrhythmias. *Clin Pharmacol Ther* 2000 Aug;68(2):143-50.
- (49) Iguchi S, Iwamura H, Nishizaki M, Hayashi A, Senokuchi K, Kobayashi K, et al. Development of a highly cardioselective ultra short-acting beta-blocker, ONO-1101. *Chem Pharm Bull (Tokyo)* 1992 Jun;40(6):1462-9.
- (50) Takahata T, Yasui-Furukori N, Sakamoto J, Suto K, Suto T, Tateishi T, et al. Influence of hepatic impairment on the pharmacokinetics and pharmacodynamics of landiolol hydrochloride, an ultra-short-acting beta1-blocker. *Drugs R D* 2005;6(6):385-94.
- (51) Yamakage M, Iwasaki S, Jeong SW, Satoh J, Namiki A. Beta-1 selective adrenergic antagonist landiolol and esmolol can be safely used in patients with airway hyperreactivity. *Heart Lung* 2009 Jan;38(1):48-55.
- (52) Goyagi T, Tanaka M, Nishikawa T. Landiolol attenuates the cardiovascular response to tracheal intubation. *J Anesth* 2005;19(4):282-6.
- (53) Suehiro K, Okutani R. Landiolol attenuates cardiovascular response at induction of general anesthesia for cesarean delivery. *J Anesth* 2012 Apr;26(2):200-5.

- (54) Tochikubo J, Adachi YU, Ejima T, Numaguchi A, Matsuda N, Sato S, et al. Landiolol reduces hemodynamic responses to bronchoscopy-assisted suctioning in intubated ICU patients. *J Intensive Care* 2014;2(1):6.
- (55) Plosker GL. Landiolol: a review of its use in intraoperative and postoperative tachyarrhythmias. *Drugs* 2013 Jun;73(9):959-77.
- (56) Yamazaki A, Kinoshita H, Shimogai M, Fujii K, Nakahata K, Hironaka Y, et al. Landiolol attenuates tachycardia in response to endotracheal intubation without affecting blood pressure. *Can J Anaesth* 2005 Mar;52(3):254-7.
- (57) Yoshida Y, Hongo T, Sakamoto A, Ogawa R. Successful management of tachycardiac atrial fibrillation in a septic patient with landiolol. *Anesth Analg* 2005 Jan;100(1):294.
- (58) Seki Y, Jesmin S, Shimojo N, Islam MM, Rahman MA, Khatun T, et al. Significant reversal of cardiac upregulated endothelin-1 system in a rat model of sepsis by landiolol hydrochloride. *Life Sci* 2014 Apr 13.
- (59) Vincent JL, Moreno R, Takala J, Willatts S, De MA, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996 Jul;22(7):707-10.
- (60) Dunser MW, Takala J, Ulmer H, Mayr VD, Luckner G, Jochberger S, et al. Arterial blood pressure during early sepsis and outcome. *Intensive Care Med* 2009 Jul;35(7):1225-33.
- (61) Charpentier J, Luyt CE, Fulla Y, Vinsonneau C, Cariou A, Grabar S, et al. Brain natriuretic peptide: A marker of myocardial dysfunction and prognosis during severe sepsis. *Crit Care Med* 2004 Mar;32(3):660-5.
- (62) Schmittinger CA, Dunser MW, Haller M, Ulmer H, Luckner G, Torgersen C, et al. Combined milrinone and enteral metoprolol therapy in patients with septic myocardial depression. *Crit Care* 2008;12(4):R99.
- (63) Schmittinger CA, Wurzing B, Deutinger M, Wohlmuth C, Knotzer H, Torgersen C, et al. How to protect the heart in septic shock: a hypothesis on the pathophysiology and treatment of septic heart failure. *Med Hypotheses* 2010 Mar;74(3):460-5.
- (64) Daubert MA, Jeremias A. The utility of troponin measurement to detect myocardial infarction: review of the current findings. *Vasc Health Risk Manag* 2010;6:691-9.
- (65) Atisha D, Bhalla MA, Morrison LK, Felicio L, Clopton P, Gardetto N, et al. A prospective study in search of an optimal B-natriuretic peptide level to screen patients for cardiac dysfunction. *Am Heart J* 2004 Sep;148(3):518-23.
- (66) Post F, Weilemann LS, Messow CM, Sinning C, Munzel T. B-type natriuretic peptide as a marker for sepsis-induced myocardial depression in intensive care patients. *Crit Care Med* 2008 Nov;36(11):3030-7.

- (67) Nordenstrom J, Carpentier YA, Askanazi J, Robin AP, Elwyn DH, Hensle TW, et al. Free fatty acid mobilization and oxidation during total parenteral nutrition in trauma and infection. *Ann Surg* 1983 Dec;198(6):725-35.
- (68) Gallin JI, Kaye D, O'Leary WM. Serum lipids in infection. *N Engl J Med* 1969 Nov 13;281(20):1081-6.
- (69) Nogueira AC, Kawabata V, Biselli P, Lins MH, Valeri C, Seckler M, et al. Changes in plasma free fatty acid levels in septic patients are associated with cardiac damage and reduction in heart rate variability. *Shock* 2008 Mar;29(3):342-8.
- (70) Levy B, Sadoune LO, Gelot AM, Bollaert PE, Nabet P, Larcan A. Evolution of lactate/pyruvate and arterial ketone body ratios in the early course of catecholamine-treated septic shock. *Crit Care Med* 2000 Jan;28(1):114-9.
- (71) Landmann R. Beta-adrenergic receptors in human leukocyte subpopulations. *Eur J Clin Invest* 1992 Oct;22 Suppl 1:30-6.
- (72) Pemberton P, Veenith T, Snelson C, Whitehouse T. Is It Time to Beta Block the Septic Patient? *Biomed Res Int* 2015;2015:424308.
- (73) Nakada TA, Russell JA, Boyd JH, Aguirre-Hernandez R, Thain KR, Thair SA, et al. beta2-Adrenergic receptor gene polymorphism is associated with mortality in septic shock. *Am J Respir Crit Care Med* 2010 Jan 15;181(2):143-9.
- (74) Thain KR, Nakada TA, Boyd JH, Walley KR. A Low Density Lipoprotein (LDL) Receptor Modulator, PCSK9, Is Associated With Increased Mortality In Septic Shock. *Am.J Respir.Crit Care Med.* 2012. 16-3-2016.
- (75) Walley KR, Thain KR, Russell JA, Reilly MP, Meyer NJ, Ferguson JF, et al. PCSK9 is a critical regulator of the innate immune response and septic shock outcome. *Sci Transl Med* 2014 Oct 15;6(258):258ra143.
- (76) Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010 Mar 23;340:c332.
- (77) Fujiwara H, Sakurai M, Namai A, Kawamura T. Effect of low-dose landiolol, an ultrashort-acting beta-blocker, on postoperative atrial fibrillation after CABG surgery. *Gen Thorac Cardiovasc Surg* 2009 Mar;57(3):132-7.
- (78) Sasao J, Tarver SD, Kindscher JD, Taneyama C, Benson KT, Goto H. In rabbits, landiolol, a new ultra-short-acting beta-blocker, exerts a more potent negative chronotropic effect and less effect on blood pressure than esmolol. *Can J Anaesth* 2001 Nov;48(10):985-9.
- (79) Mio Y. [New ultra-short-acting beta-blockers: landiolol and esmolol--the effects on cardiovascular system]. *Masui* 2006 Jul;55(7):841-8.
- (80) Taenaka N, Kikawa S. The effectiveness and safety of landiolol hydrochloride, an ultra-short-acting beta1-blocker, in postoperative patients with supraventricular

tachyarrhythmias: a multicenter, randomized, double-blind, placebo-controlled study. *Am J Cardiovasc Drugs* 2013 Oct;13(5):353-64.

- (81) Gordon AC, Perkins GD, Singer M, McAuley DF, Orme RM, Santhakumaran S, et al. Levosimendan for the Prevention of Acute Organ Dysfunction in Sepsis. *N Engl J Med* 2016 Oct 27;375(17):1638-48.
- (82) Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med* 2012 Nov 15;367(20):1901-11.
- (83) Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Aneman A, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med* 2012 Jul 12;367(2):124-34.
- (84) Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *JAMA* 1996 Aug 28;276(8):637-9.
- (85) Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. *Eur Heart J* 2012 Jan;33(2):176-82.
- (86) Felker GM, Maisel AS. A global rank end point for clinical trials in acute heart failure. *Circ Heart Fail* 2010 Sep;3(5):643-6.
- (87) Armstrong PW, Westerhout CM, Van de Werf F, Califf RM, Welsh RC, Wilcox RG, et al. Refining clinical trial composite outcomes: an application to the Assessment of the Safety and Efficacy of a New Thrombolytic-3 (ASSENT-3) trial. *Am Heart J* 2011 May;161(5):848-54.

13. APPENDICES

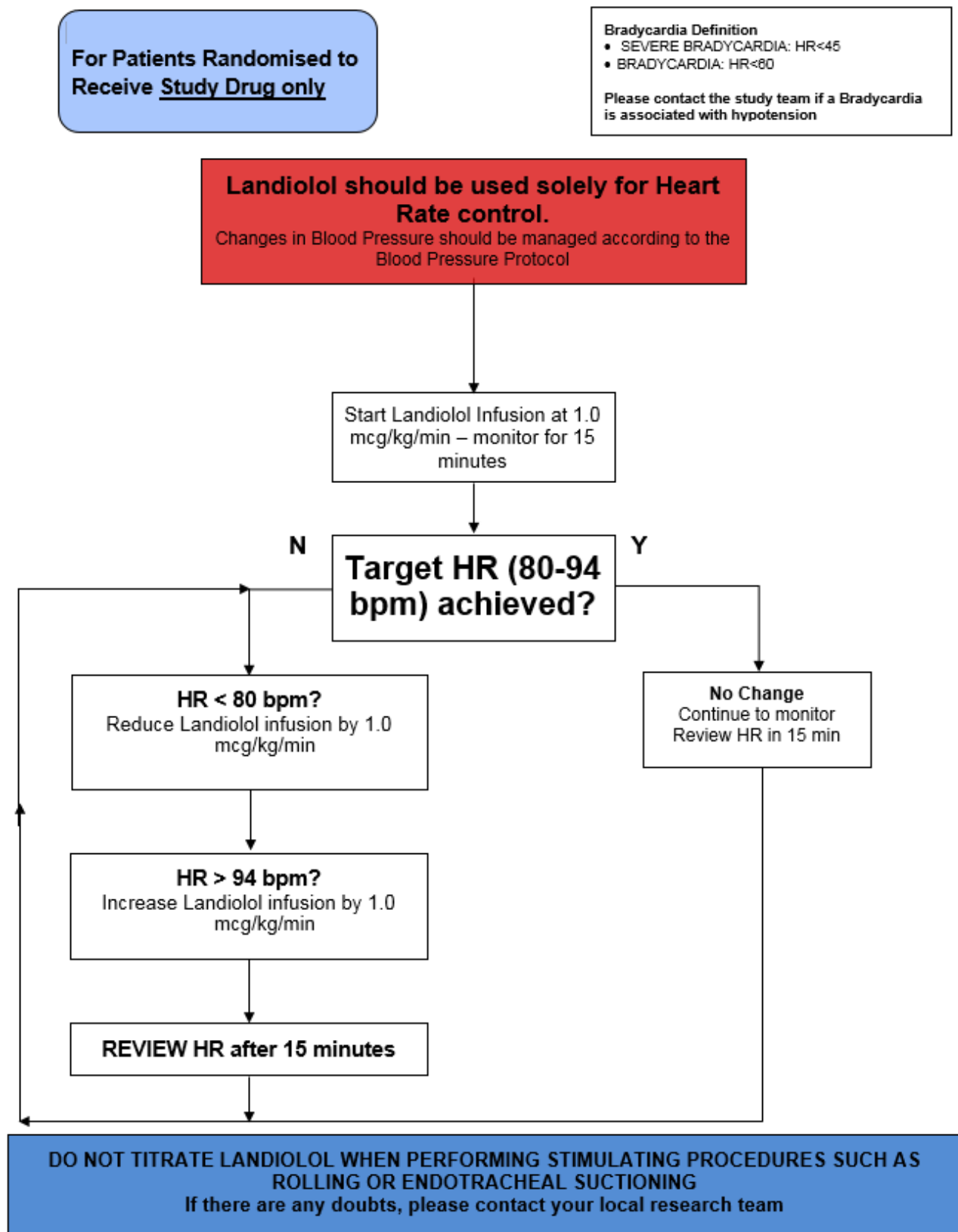
APPENDIX A: SOFA SCORE CALCULATION

System	Score				
	0	1	2	3	4
Respiration					
PaO ₂ / FiO ₂ Ratio (kPa)	≥53.3	<53.3	<40	<26.7 with Respiratory Support	<13.3 with Respiratory Support
Coagulation					
Platelets (x 10 ⁹ /L)	≥150	<150	<100	<50	<20
Liver					
Bilirubin (μmol/L)	<20	20-32	33-101	102-204	>204
Cardiovascular					
BP or Highest Inotrope (μg/kg/min)	MAP ≥ 70 mmHg	MAP < 70 mmHg	Dopamine ≤ 5 or Dobutamine (any dose)	Dopamine 5.1-15 OR Adrenaline ≤ 0.1 OR Noradrenaline ≤ 0.1	Dopamine > 15 OR Adrenaline >0.1 OR Noradrenaline >0.1
Renal					
Creatinine (μmol/L)	<110	110-170	171-299	300-440	>440
Urine Output (ml/day)				<500	<200
Neurological					
Glasgow Coma Scale	15	13-14	10-12	6-9	<6

Adapted from Vincent et al (59). Neurological will not be recorded in STRESS-L – it is here for the sake of completeness

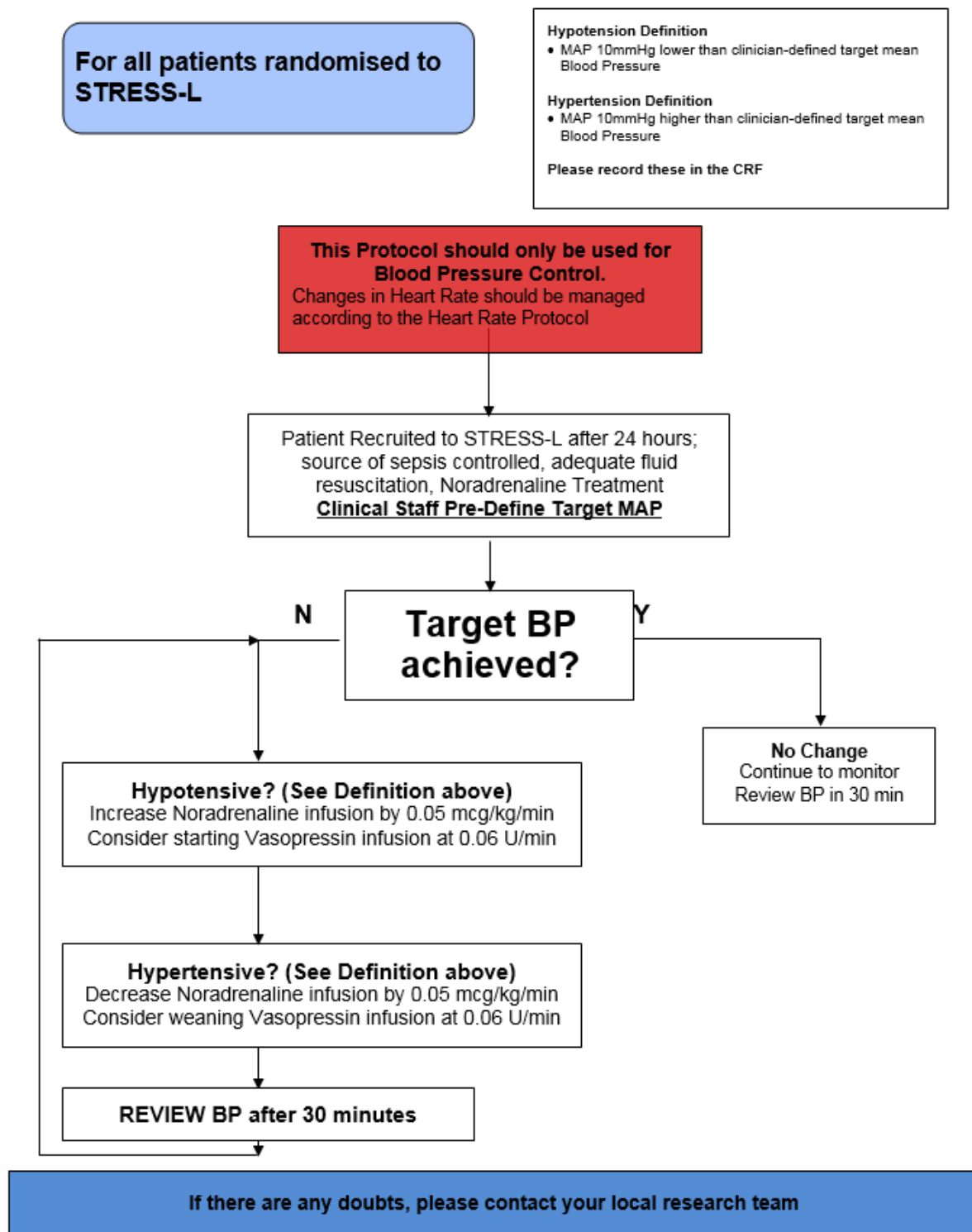
APPENDIX B: STRESS-L Study Drug Infusion Protocol

Landirolol is an ultra-short antagonist of the beta 1 adrenergic receptor



APPENDIX C: STRESS-L Vasopressor Infusion Protocol

STRESS-L is an Open-Labelled Trial and at risk of bias; the rate at which vasopressors should be weaned is protocolised



APPENDIX D: LANDIOLOL INFUSION RATE

Concentration of Landiolol:	300	mg per	50	ml	=	6	mg/ml
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Ideal Weight (kg)	Rate (mcg/kg/min)	Infusion Rate (ml/h)										
		1	1.5	2	2.5	3	4	5	10	20	30	40
40	Infusion Rate (ml/h)	0.4	0.6	0.8	1.0	1.2	1.6	2.0	4.0	8.0	12.0	16.0
45		0.5	0.7	0.9	1.1	1.4	1.8	2.3	4.5	9.0	13.5	18.0
50		0.5	0.8	1.0	1.3	1.5	2.0	2.5	5.0	10.0	15.0	20.0
55		0.6	0.8	1.1	1.4	1.7	2.2	2.8	5.5	11.0	16.5	22.0
60		0.6	0.9	1.2	1.5	1.8	2.4	3.0	6.0	12.0	18.0	24.0
65		0.7	1.0	1.3	1.6	2.0	2.6	3.3	6.5	13.0	19.5	26.0
70		0.7	1.1	1.4	1.8	2.1	2.8	3.5	7.0	14.0	21.0	28.0
75		0.8	1.1	1.5	1.9	2.3	3.0	3.8	7.5	15.0	22.5	30.0
80		0.8	1.2	1.6	2.0	2.4	3.2	4.0	8.0	16.0	24.0	32.0
85		0.9	1.3	1.7	2.1	2.6	3.4	4.3	8.5	17.0	25.5	34.0
90		0.9	1.4	1.8	2.3	2.7	3.6	4.5	9.0	18.0	27.0	36.0
95		1.0	1.4	1.9	2.4	2.9	3.8	4.8	9.5	19.0	28.5	38.0
100		1.0	1.5	2.0	2.5	3.0	4.0	5.0	10.0	20.0	30.0	40.0
105		1.1	1.6	2.1	2.6	3.2	4.2	5.3	10.5	21.0	31.5	42.0
110		1.1	1.7	2.2	2.8	3.3	4.4	5.5	11.0	22.0	33.0	44.0