STRESS-L TRIAL

Study into the Reversal of Septic Shock with Landiolol (Beta Blockade)

CASE RECORD FORM (CRF)

Participant ID: | | | | | |

Participant Initials: | | | |

Site number: | | |

CRF Version: FINAL Version 7.0 26 November 2020

EudraCT Number: 2017-001785-14

Study Coordinating Centre: Warwick Clinical Trials Unit

Participant initials: | | | |

Participant ID: | | | | | |

Participant Form

INCLUSION CRITERIA

*Participants will be excluded if **ANY** of the following are No:*	YES	NO
Aged 18 years or above	☐	☐
Being treated on an ICU	☐	☐
Septic shock according to internationally accepted definitions*	☐	☐
Heart rate ≥95 bpm (at the time of randomisation)	☐	☐
Receiving vasopressor support to maintain a target blood pressure for ≥24 hours	☐	☐
Are being treated with noradrenaline at a rate ≥ 0.1mcg/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.

EXCLUSION CRITERIA

*Participants will be excluded if **ANY** of the following are Yes:*	YES	NO
Tachycardia as a result of pain, discomfort from medical devices (including endotracheal tubes), during interventions or other patient distress	☐	☐
Any form of vasodilatory shock that is not caused by sepsis	☐	☐
Noradrenaline infusion <0.1mcg/kg/min	☐	☐
> 72 hours after start of vasopressor therapy	☐	☐
<12 hours since noadrenaline to treat a medical condition other than septic shock stopped	☐	☐
Having pre-existing severe cardiac dysfunction (NYHA grade 4 or more)	☐	☐
Having pre-existing severe pulmonary hypertension (mean PA pressures > 55mmHg)	☐	☐
Acute severe bronchospasm (due to asthma or COPD)	☐	☐
Untreated second or third degree heart block	☐	☐
Untreated phaeochromocytoma	☐	☐
Prinzmetal's angina	☐	☐
A past history of ischaemic stroke or transient ischaemic attack (TIA) or untreated severe carotid stenosis	☐	☐
Advanced liver disease with Child-Pugh Score of ≥B	☐	☐
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 been administered an investigational medicinal product for another research trial in the past 30 days	☐	☐
Patients in whom the clinical team feel are about to finish their noradrenaline therapy	☐	☐
Decision of withdrawal of care is in place or imminently anticipated	☐	☐
Receiving extracorporeal membrane oxygenation (ECMO) treatment	☐	☐

'I confirm that this patient is eligible for enrolment in this trial'

Form completed by (*print name*):	Signature (approved investigator only):	Date:

Participant initials: ☐☐☐	**Participant Form**
Participant ID: ☐☐☐☐☐	

INFORMED CONSENT			
Consent Type	**Was written Informed Consent obtained?**		**Date and time of Informed Consent**
	No	**Yes**	
Trial Informed Consent	☐	☐	☐☐/☐☐☐/☐☐☐☐ DD/MMM/YYYY
Informed Consent for Collection of Research Blood Samples (mandatory)	☐	☐	
Informed Consent for Storage and Use in Possible Future Genomic / Metagenomic Research (HBRC/Biobank at the University of Birmingham)	☐	☐	

Consent obtained from:	Patient ☐ ☐ Personal LR ☐ Professional LR ☐

Participant initials: ☐☐☐	**Randomisation Form**
Participant ID: ☐☐☐☐☐	

CALLER AND SITE INFORMATION		
Randomisation site/hospital:		
Callers first name (please print):		
Callers surname (please print):		
Caller's role in trial:		
Callers contact details	Telephone:	Email:

PARTICIPANT DETAILS		
Initials	**Gender**	**Date of Birth**
☐☐☐	Female ☐ Male ☐	☐☐/☐☐☐/☐☐☐☐ DD/MMM/YYYY

TO RANDOMISE, CALL THE IVR SYSTEM on 02476 932036
(24 hour / 7 day a week service)

RANDOMISATION (IVR SYSTEM QUESTIONS)		
Please enter site number:	☐☐	
Does the patient fulfil all of the eligibility criteria?	Yes ☐	No ☐
Has an approved investigator signed the eligibility form?	Yes ☐	No ☐
Has written informed consent been gained?	Yes ☐	No ☐
What is the current noradrenaline dose?	0.1 - 0.3 mcg/kg/min ☐	>0.3 mcg/kg/min ☐

You will be given the participant's ID and treatment allocation. **The patient will be identified by their participant ID from now on.** Please ensure that these are clearly recorded below.

TRIAL ARM ALLOCATION:

☐ **Landiolol Plus** Standard Treatment

☐ Standard Treatment **Only**

PARTICIPANT TRIAL NUMBER:

☐☐☐☐☐

Randomisation completed by (*print name*):	Signature:	Date signed:

Please note: you must be signed off on the trial delegation log.
If the IVR system is inaccessible, dial 02476 150402 during standard business hours to perform a randomisation.

Participant initials: ☐☐☐

Participant ID: ☐☐☐☐☐

Baseline - DAY 0

BASELINE CHARACTERISTICS	
Patient ethnicity	**White** ☐ British ☐ Irish ☐ Any other White background **Mixed** ☐ White and Black Caribbean ☐ White and Black African ☐ White and Asian ☐ Any other Mixed background Asian ☐ Indian ☐ Pakistani ☐ Bangladeshi ☐ Any other Asian background **Black / African / Caribbean / Black British** ☐ African ☐ Caribbean ☐ Any other Black / African / Caribbean / Black British background. Any other ethnic group. ☐ Chinese ☐ Any other Ethnicity not given ☐
Patient Postcode	☐☐ ☐☐☐
Date and time of hospital admission:	☐☐/☐☐☐/☐☐☐☐ DD/MMM/YYYY ☐☐:☐☐ HH/MM

Participant initials: ☐☐☐

Participant ID: ☐☐☐☐☐

Baseline - DAY 0

Diagnosis at admission to hospital:	
Date and time of ICU admission	☐☐/☐☐☐/☐☐☐☐ DD/MMM/YYYY ☐☐:☐☐ HH/MM
Main diagnosis at admission to ICU:	
Main site of infection (presumed or known):	Lungs ☐ Urine ☐ Abdomen ☐ Blood ☐ Other ☐ Specify:
Where was the infection acquired?	In the community ☐ Hospital (48 hours after admission to hospital) ☐
Date and time vasopressor support started (if another vasopressor preceded noradrenaline, for example metaraminol):	☐☐/☐☐☐/☐☐☐☐ DD/MMM/YYYY ☐☐:☐☐ HH/MM
Date and time noradrenaline started:	☐☐/☐☐☐/☐☐☐☐ DD/MMM/YYYY ☐☐:☐☐ HH/MM
Date and time of first lactate >2mmol/l:	☐☐/☐☐☐/☐☐☐☐ DD/MMM/YYYY ☐☐:☐☐ HH/MM
COVID status:	**Suspected** ☐ ☐☐/☐☐☐/☐☐☐☐ DD/MMM/YYYY **Confirmed** ☐ ☐☐/☐☐☐/☐☐☐☐ DD/MMM/YYYY **No** ☐

Participant initials: ☐☐☐

Participant ID: ☐☐☐☐☐

Baseline - DAY 0

BASELINE CHARACTERISTICS	
Date and time baseline ECG performed:	☐☐/☐☐☐/☐☐☐☐ DD/MMM/YYYY ☐☐:☐☐ HH/MM
Was a chest x-ray taken?	Yes ☐ No ☐
If yes, provide date and time of x-ray:	☐☐/☐☐☐/☐☐☐☐ DD/MMM/YYYY ☐☐:☐☐ HH/MM
Diffuse bilateral pulmonary infiltrates on chest x-ray?	Yes ☐ No ☐
Could the patient have ARDS?	Yes ☐ No ☐

Optional at discretion of site investigator	
Was a pregnancy test done? **Yes** ☐ **No** ☐	
PREGNANCY TEST	
Date of assessment:	☐☐/☐☐☐/☐☐☐☐ DD/MMM/YYYY
Pregnancy test result:	Negative ☐ Positive ☐

Participant initials: ☐☐☐

Participant ID: ☐☐☐☐☐

Baseline - DAY 0

BASELINE MEDICAL HISTORY	
Does the patient have any concomitant illnesses?	☐ **No** ☐ **Yes**, complete below

Condition / illness / surgical procedure	
Heart Disease58	☐ **No** ☐ **Yes**
Hypertension	☐ **No** ☐ **Yes**
Asthma/COPD	☐ **No** ☐ **Yes**
Diabetes	☐ **No** ☐ **Yes**
Parkinson's	☐ **No** ☐ **Yes**
Epilepsy	☐ **No** ☐ **Yes**
Renal Disease	☐ **No** ☐ **Yes**
Liver Disease	☐ **No** ☐ **Yes**
CVA/TIA	☐ **No** ☐ **Yes**
Peptic Ulcer	☐ **No** ☐ **Yes**
Malignancy	☐ **No** ☐ **Yes**
DVT/PE	☐ **No** ☐ **Yes**
Osteoarthritis	☐ **No** ☐ **Yes**
Rheumatoid Arthritis	☐ **No** ☐ **Yes**
Depression	☐ **No** ☐ **Yes**
Dementia	☐ **No** ☐ **Yes**

☐ **Tick if this form continues onto an additional page**

Participant initials: ☐☐☐

Participant ID: ☐☐☐☐☐

Baseline - DAY 0

DAY 0 = day of randomisation
T0 = time of randomisation

BASELINE ASSESSMENTS (DAY 0)

Day 0 date: ☐☐/☐☐☐/☐☐☐☐

DD/MMM/YYYY

MEASUREMENT	RESULT	UNIT
Weight	☐☐☐.☐	kg
Height	☐.☐☐	Metres

OTHER TREATMENT

STEROID	TOTAL DOSE	UNIT
	☐☐☐	mg

CARDIOVASCULAR

MEASUREMENT	RESULT	UNIT
ARTERIAL PaO_2	☐☐.☐	kPa
ARTERIAL $PaCO_2$	☐☐.☐	kPa

Optional cardiovascular assessments		
VENOUS PaO_2	☐☐.☐	kPa
VENOUS $PaCO_2$	☐☐.☐	kPa
CO	☐☐.☐	L/min
SV	☐☐☐	mL

Participant initials: ☐☐☐

Participant ID: ☐☐☐☐☐

Baseline - DAY 0

DAY 0 = day of randomisation
T0 = time of randomisation

BIOCHEMISTRY

MEASUREMENT	RESULT	UNIT
Glucose	☐☐.☐	mmol/L
Lactate (highest value last 48h)	☐☐.☐	mmol/L
Liver Function Tests	**AST** ☐☐☐☐ **ALT** ☐☐☐☐	U/L

CENTRAL LABORATORY SPECIMENS

	Was sample collected?		Date of assessment DD/MMM/YYYY	Time of assessment HH/MM	
	No	**Yes**			
Research Blood Sample (mandatory)	☐	☐	D D M M M Y Y Y Y	H H M M	
Number of plasma cryovials extracted	☐☐				

If No, please give reason	Y/N
Patient deceased	
Patient discharged	
Noradrenaline and Landiolol stopped	
COVID suspected or confirmed	
Other, please specify:	

PaxGene RNA sample 1	☐	☐	D D M M M Y Y Y Y	H H M M	

If No, please give reason	Y/N
Patient deceased	
Patient discharged	
Noradrenaline and Landiolol stopped	
COVID suspected or confirmed	
Other, please specify:	

PaxGene DNA sample 1	☐	☐	D D M M M Y Y Y Y	H H M M	

If No, please give reason	Y/N
Patient deceased	
Patient discharged	
Noradrenaline and Landiolol stopped	
COVID suspected or confirmed	
Other, please specify:	

Please note: Day 0 Research Blood Samples must be taken prior to patient starting Landiolol administration if randomised to Landiolol plus standard treatment arm.

Participant initials:	☐☐☐
Participant ID:	☐☐☐☐☐

Start of Landiolol Treatment

LANDIOLOL ARM ONLY	
Date and time landiolol started:	☐☐/☐☐☐/☐☐☐☐ DD/MMM/YYYY ☐☐:☐☐ HH/MM

Participant initials:	
Participant ID:	

Baseline - DAY 0
DAY 0 = day of randomisation
T0 = time of randomisation

	CARDIOVASCULAR DATA – PRE-RANDOMISATION (D0)

MEASURE	**UNIT**	**CARDIOVASCULAR MEASURE (RELATIVE TO T0)**					
		-24h	**-18h**	**-12h**	**-6h**	**T0**	
MAP	mmHg						
HR	beats/min						
AF	Y/N						

NAME OF IONOTROPE	**UNIT**	**Received Y/N** **If yes, enter dose**	**RATE OF INOTROPE**				
			-24h	**-18h**	**-12h**	**-6h**	**T0**
Norad	mcg/kg/min						
Vasopressin	units/min						
Ino1	mcg/kg/min						
Ino2	mcg/kg/min						

Participant initials: | | | |

Participant ID: | | | | | |

SOFA SCORE (DAILY UP TO DAY 14)

DAY 0 = day of randomisation

SOFA SCORE (DAILY DATA COLLECTION)

Day	RESPIRATION			COAGULATION	LIVER	CARDIOVASCULAR		RENAL	
	Lowest PaO_2 / FiO_2 Ratio (kPa)	OR O_2 Saturation %	Assisted Ventilation ? (Y/N)	Lowest Platelets (x 10^9/L)	Highest Bilirubin (µmol/L)	Lowest MAP (mmHg)		Highest Creatinine (µmol/L)	Urine Output (mL/24 hours)
0									
1									
2									
3									
4									
5									
6									
7									

OTHER OUTCOME DATA

WCC	Delirium?	CRP
(x 10^9/L)	Y/N/Sedation/Unknown	mg/L

Participant initials: | | | |

Participant ID: | | | | | |

SOFA SCORE (DAILY UP TO DAY 14)

DAY 0 = day of randomisation

SOFA SCORE (DAILY DATA COLLECTION)

Day	RESPIRATION			COAGULATION	LIVER	CARDIOVASCULAR	RENAL		OTHER OUTCOME DATA		
	Lowest PaO_2 / FiO_2 Ratio (kPa)	OR O_2 Saturation %	Assisted Ventilation? (Y/N)	Lowest Platelets (x 10^9/L)	Highest Bilirubin (µmol/L)	Lowest MAP (mmHg)	Highest Creatinine (µmol/L)	Urine Output (mL/24 hours)	WCC (x 10^9/L)	Delirium? Y/N/ Sedation/ Unknown	CRP mg/L
8											
9											
10											
11											
12											
13											
14											
EONT											

Participant initials: | | | |

Participant ID: | | | | | |

SOFA SCORE (DAILY UP TO DAY 14)

DAY 0 = day of randomisation

INOTROPE DOSE

Day		Noradrenaline (Norepinephrine)	Adrenaline (Epinephrine)	Dopamine	Dobutamine	Vasopressin
1	Y/N					
	If yes, highest dose over 24 hour period					
2	Y/N					
	If yes, highest dose over 24 hour period					
3	Y/N					
	If yes, highest dose over 24 hour period					
4	Y/N					
	If yes, highest dose over 24 hour period					
5	Y/N					
	If yes, highest dose over 24 hour period					
6	Y/N					
	If yes, highest dose over 24 hour period					
7	Y/N					
	If yes, highest dose over 24 hour period					

Participant initials: | | | |

Participant ID: | | | | | |

SOFA SCORE (DAILY UP TO DAY 14)

DAY 0 = day of randomisation

Day		Noradrenaline (Norepinephrine)	Adrenaline (Epinephrine)	Dopamine	Dobutamine	Vasopressin
8	Y/N					
	If yes, highest dose over 24 hour period					
9	Y/N					
	If yes, highest dose over 24 hour period					
10	Y/N					
	If yes, highest dose over 24 hour period					
11	Y/N					
	If yes, highest dose over 24 hour period					
12	Y/N					
	If yes, highest dose over 24 hour period					
13	Y/N					
	If yes, highest dose over 24 hour period					
14	Y/N					
	If yes, highest dose over 24 hour period					
EONT	Y/N					
	If yes, highest dose over 24 hour period					

Participant initials: | | | |

Participant ID: | | | | | |

OTHER BETA-BLOCKER (DAILY UP TO DAY 14)

DAY 0 = day of randomisation

Was the patient taking beta blockers 2 weeks prior to admission to the ICU?		☐ **No** ☐ **Yes**
Has patient received beta blockers on admission to ICU?		☐ **No** ☐ **Yes**
Has patient received beta blockers during ICU admission prior to randomisation?		☐ **No** ☐ **Yes**
Day 1	Has patient received beta blockers* within the last 24 hours?	☐ **No** ☐ **Yes****
Day 2	Has patient received beta blockers* within the last 24 hours?	☐ **No** ☐ **Yes****
Day 3	Has patient received beta blockers* within the last 24 hours?	☐ **No** ☐ **Yes****
Day 4	Has patient received beta blockers* within the last 24 hours?	☐ **No** ☐ **Yes****
Day 5	Has patient received beta blockers* within the last 24 hours?	☐ **No** ☐ **Yes****
Day 6	Has patient received beta blockers* within the last 24 hours?	☐ **No** ☐ **Yes****

Participant initials: ☐☐☐

Participant ID: ☐☐☐☐☐

OTHER BETA-BLOCKER (DAILY UP TO DAY 14)

DAY 0 = day of randomisation

Day 7	Has patient received beta blockers* within the last 24 hours?	☐ **No** ☐ **Yes****
Day 8	Has patient received beta blockers* within the last 24 hours?	☐ **No** ☐ **Yes****
Day 9	Has patient received beta blockers* within the last 24 hours?	☐ **No** ☐ **Yes****
Day 10	Has patient received beta blockers* within the last 24 hours?	☐ **No** ☐ **Yes****
Day 11	Has patient received beta blockers* within the last 24 hours?	☐ **No** ☐ **Yes****
Day 12	Has patient received beta blockers* within the last 24 hours?	☐ **No** ☐ **Yes****
Day 13	Has patient received beta blockers* within the last 24 hours?	☐ **No** ☐ **Yes****
Day 14	Has patient received beta blockers* within the last 24 hours?	☐ **No** ☐ **Yes****

**NOT including Landiolol*

***Complete protocol deviation form on STRESS-L database*

Participant initials: | | | |

Participant ID: | | | | | |

IN/OUT FLUIDS (DAILY UP TO DAY 14)

DAY 0 = day of randomisation

Day	TOTAL OF FLUIDS IN				TOTAL OF FLUIDS OUT			BALANCE (mL)
	ORAL (mL)	CRYSTALLOID (mL)	COLLOID (mL)	OTHER (mL)	URINE (mL)	CVVHF BALANCE (mL)	OTHER (mL)	
0								
1								
2								
3								
4								
5								
6								
7								

Participant initials: | | | |

Participant ID: | | | | | | |

IN/OUT FLUIDS (DAILY UP TO DAY 14)

DAY 0 = day of randomisation

Day	TOTAL OF FLUIDS IN				TOTAL OF FLUIDS OUT			BALANCE (mL)
	ORAL (mL)	CRYSTALLOID (mL)	COLLOID (mL)	OTHER (mL)	URINE (mL)	CVVHF BALANCE (mL)	OTHER (mL)	
8								
9								
10								
11								
12								
13								
14								

Please complete this for <u>every day</u> that the patient is in ICU from the point of randomisation

Participant initials: | | | |

Participant ID: | | | | | |

LANDIOLOL INFUSION (DAILY UP TO DAY 14)

LANDIOLOL INFUSION DETAILS															
Date prepared DD/MMM/YYYY									**Time prepared** HH/MM				**Number of vials used**	**Batch number**
D	D	M	M	M	Y	Y	Y	Y	H	H	M	M		
D	D	M	M	M	Y	Y	Y	Y	H	H	M	M		
D	D	M	M	M	Y	Y	Y	Y	H	H	M	M		
D	D	M	M	M	Y	Y	Y	Y	H	H	M	M		
D	D	M	M	M	Y	Y	Y	Y	H	H	M	M		
D	D	M	M	M	Y	Y	Y	Y	H	H	M	M		
D	D	M	M	M	Y	Y	Y	Y	H	H	M	M		
D	D	M	M	M	Y	Y	Y	Y	H	H	M	M		
D	D	M	M	M	Y	Y	Y	Y	H	H	M	M		
D	D	M	M	M	Y	Y	Y	Y	H	H	M	M		
D	D	M	M	M	Y	Y	Y	Y	H	H	M	M		
D	D	M	M	M	Y	Y	Y	Y	H	H	M	M		
D	D	M	M	M	Y	Y	Y	Y	H	H	M	M		
D	D	M	M	M	Y	Y	Y	Y	H	H	M	M		
D	D	M	M	M	Y	Y	Y	Y	H	H	M	M		
D	D	M	M	M	Y	Y	Y	Y	H	H	M	M		
D	D	M	M	M	Y	Y	Y	Y	H	H	M	M		
D	D	M	M	M	Y	Y	Y	Y	H	H	M	M		
D	D	M	M	M	Y	Y	Y	Y	H	H	M	M		
D	D	M	M	M	Y	Y	Y	Y	H	H	M	M		
D	D	M	M	M	Y	Y	Y	Y	H	H	M	M		
D	D	M	M	M	Y	Y	Y	Y	H	H	M	M		
D	D	M	M	M	Y	Y	Y	Y	H	H	M	M		
D	D	M	M	M	Y	Y	Y	Y	H	H	M	M		
D	D	M	M	M	Y	Y	Y	Y	H	H	M	M		
D	D	M	M	M	Y	Y	Y	Y	H	H	M	M		

☐ **Tick if this form continues onto an additional page**

Participant initials: | | | |

Participant ID: | | | | | |

DAY 1

CARDIOVASCULAR DATA – DAY 1

MEASURE	UNIT	CARDIOVASCULAR MEASURE (HOURLY POST RANDOMISATION)																						
		T+ 1h	T+ 2h	T+ 3h	T+ 4h	T+ 5h	T+ 6h	T+ 7h	T+ 8h	T+ 9h	T+ 10 h	T+ 11 h	T+ 12 h	T+ 13 h	T+ 14 h	T+ 15 h	T+ 16 h	T+ 17 h	T+ 18 h	T+ 19 h	T+ 20 h	T+ 21 h	T+ 22 h	T+ 23 h	T+ 24h
MAP	mmHg																								
HR	b/min																								
AF	Y/N																								

NAME OF DRUG	UNIT	Received Y/N If yes, enter dose	RATE OF INOTROPE / LANDIOLOL (HOURLY POST RANDOMISATION)																							
			T+ 1h	T+ 2h	T+ 3h	T+ 4h	T+ 5h	T+ 6h	T+ 7h	T+ 8h	T+ 9h	T+ 10 h	T+ 11 h	T+ 12 h	T+ 13 h	T+ 14 h	T+ 15 h	T+ 16 h	T+ 17 h	T+ 18 h	T+ 19 h	T+ 20 h	T+ 21 h	T+ 22 h	T+ 23 h	T+ 24 h
Norad	mcg/ kg/min																									
Landiolol	mcg/ kg/min																									
Vasopressin	units/ min																									
Ino1	mcg/ kg/min																									
Ino2	mcg/ kg/min																									

Participant initials: ☐☐☐

Participant ID: ☐☐☐☐☐

DAY 1

DAY 1 – ADDITIONAL ASSESSMENTS

Date of assessments: ☐☐/☐☐☐/☐☐☐☐

DD/MMM/YYYY

OTHER TREATMENT

STEROID	TOTAL DOSE	UNIT
	☐☐☐	mg

CARDIOVASCULAR

MEASUREMENT	RESULT	UNIT
ARTERIAL PaO_2	☐☐.☐	kPa
ARTERIAL $PaCO_2$	☐☐.☐	kPa

Optional cardiovascular assessments		
VENOUS PaO_2	☐☐.☐	kPa
VENOUS $PaCO_2$	☐☐.☐	kPa
CO	☐☐.☐	L/min
SV	☐☐☐	mL

BIOCHEMISTRY

MEASUREMENT	RESULT	UNIT
Glucose	☐☐.☐	mmol/L
Lactate	☐☐.☐	mmol/L
Liver Function Tests	**AST** ☐☐☐☐ **ALT** ☐☐☐☐	U/L

Participant initials: ☐☐☐

Participant ID: ☐☐☐☐☐

DAY 1

CENTRAL LABORATORY SPECIMENS

	Was sample collected?		Date of assessment DD/MMM/YYYY	Time of assessment HH/MM	
	No	**Yes**			
Research Blood Sample (mandatory)	☐	☐	D D M M M Y Y Y Y	H H M M	
Number of plasma cryovials extracted	☐☐				

If No, please give reason	**Y/N**
Patient deceased	
Patient discharged	
Noradrenaline and Landiolol stopped	
COVID suspected or confirmed	
Other, please specify:	

PaxGene RNA sample 2	☐	☐	D D M M M Y Y Y Y	H H M M	

If No, please give reason	**Y/N**
Patient deceased	
Patient discharged	
Noradrenaline and Landiolol stopped	
COVID suspected or confirmed	
Other, please specify:	

Participant initials: | | | |

Participant ID: | | | | | |

DAY 2

CARDIOVASCULAR DATA – DAY 2

MEASURE	UNIT	CARDIOVASCULAR MEASURE (HOURLY POST RANDOMISATION)																					
		T+ 25h	T+ 26h	T+ 27 h	T+ 28 h	T+ 29 h	T+ 30 h	T+ 31 h	T+ 32 h	T+ 33 h	T+ 34 h	T+ 35 h	T+ 36 h	T+ 37 h	T+ 38 h	T+ 39 h	T+ 40 h	T+ 41 h	T+ 42 h	T+ 43 h	T+ 44 h	T+ 45 h	T+ 46 h	T+ 47 h	T+ 48h
MAP	mmHg																								
HR	b/min																								
AF	Y/N																								

NAME OF DRUG	UNIT	Received Y/N If yes, enter dose	RATE OF INOTROPE / LANDIOLOL (HOURLY POST RANDOMISATION)																						
			T+ 25h	T+ 26 h	T+ 27 h	T+ 28 h	T+ 29 h	T+ 30 h	T+ 31 h	T+ 32 h	T+ 33 h	T+ 34 h	T+ 35 h	T+ 36 h	T+ 37 h	T+ 38 h	T+ 39 h	T+ 40 h	T+ 41 h	T+ 42 h	T+ 43 h	T+ 44 h	T+ 45 h	T+ 46 h	T+ 47 h	T+ 48 h
Norad	mcg/ kg/min																								
Landiolol	mcg/ kg/min																								
Vasopressin	units/min																								
Ino1	mcg/ kg/min																								
Ino2	mcg/ kg/min																								

Participant initials:	
Participant ID:	

DAY 2

DAY 2 - ADDITIONAL ASSESSMENTS

Date of assessments: ☐☐/☐☐☐/☐☐☐☐
DD/MMM/YYYY

OTHER TREATMENT

STEROID	TOTAL DOSE	UNIT
	☐☐☐	mg

CARDIOVASCULAR

MEASUREMENT	RESULT	UNIT
ARTERIAL PaO_2	☐☐.☐	kPa
ARTERIAL $PaCO_2$	☐☐.☐	kPa

Optional cardiovascular assessments		
VENOUS PaO_2	☐☐.☐	kPa
VENOUS $PaCO_2$	☐☐.☐	kPa
CO	☐☐.☐	L/min
SV	☐☐☐	mL

BIOCHEMISTRY

MEASUREMENT	RESULT	UNIT
Glucose	☐☐.☐	mmol/L
Lactate	☐☐.☐	mmol/L
Liver Function Tests	**AST** ☐☐☐☐ **ALT** ☐☐☐☐	U/L

Participant initials: ☐☐☐

Participant ID: ☐☐☐☐☐

DAY 2

CENTRAL LABORATORY SPECIMENS

	Was sample collected?		Date of assessment DD/MMM/YYYY	Time of assessment HH/MM	If No, please give reason
	No	Yes			
Research Blood Sample (mandatory)	☐	☐	D D M M M Y Y Y Y	H H M M	

CENTRAL LABORATORY SPECIMENS

	Was sample collected?		Date of assessment DD/MMM/YYYY	Time of assessment HH/MM	
	No	Yes			
Research Blood Sample	☐	☐	D D M M M Y Y Y Y	H H M M	
Number of plasma cryovials extracted	☐☐				

If No, please give reason	Y/N
Patient deceased	
Patient discharged	
Noradrenaline and Landiolol stopped	
COVID suspected or confirmed	
Other, please specify:	

Participant initials: | | | |

Participant ID: | | | | | |

DAYS 3, 4 & 5

CARDIOVASCULAR DATA – DAYS 3, 4 & 5

MEASURE	UNIT	CARDIOVASCULAR MEASURE											
		T+ 54h	T+ 60h	T+ 66h	T+ 72h	T+ 78h	T+ 84h	T+ 90h	T+ 96h	T+ 102h	T+ 108h	T+ 114h	T+ 120h
MAP	mmHg												
HR	b/min												
AF	Y/N												

NAME OF DRUG	UNIT	Received Y/N If yes, enter dose	RATE OF INOTROPE / LANDIOLOL											
			T+ 54h	T+ 60h	T+ 66h	T+ 72h	T+ 78h	T+ 84h	T+ 90h	T+ 96h	T+ 102h	T+ 108h	T+ 114h	T+ 120h
Norad	mcg/kg/min													
Landiolol	mcg/kg/min													
Vasopressin	units/min													
Ino1	mcg/kg/min													
Ino2	mcg/kg/min													

Participant initials: ☐☐☐

Participant ID: ☐☐☐☐☐

DAY 4

DAY 4 - ADDITIONAL ASSESSMENTS

Date of Assessments: ☐☐/☐☐☐/☐☐☐☐
DD/MMM/YYYY

OTHER TREATMENT

STEROID	TOTAL DOSE	UNIT
	☐☐☐	mg

CARDIOVASCULAR

MEASUREMENT	RESULT	UNIT
ARTERIAL PaO_2	☐☐.☐	kPa
ARTERIAL $PaCO_2$	☐☐.☐	kPa

Optional cardiovascular assessments		
VENOUS PaO_2	☐☐.☐	kPa
VENOUS $PaCO_2$	☐☐.☐	kPa
CO	☐☐.☐	L/min
SV	☐☐☐	mL

BIOCHEMISTRY

MEASUREMENT	RESULT	UNIT
Glucose	☐☐.☐	mmol/L
Lactate	☐☐.☐	mmol/L
Liver Function Tests	**AST** ☐☐☐☐ **ALT** ☐☐☐☐	U/L

CENTRAL LABORATORY SPECIMENS

	Was sample collected?		Date of assessment	Time of assessment	
	No	Yes	DD/MMM/YYYY	HH/MM	

Participant initials: ☐☐☐

Participant ID: ☐☐☐☐☐

DAY 4

Research Blood Sample (mandatory)	☐	☐	D	D	M	M	M	Y	Y	Y	Y	H	H	M	M	
Number of plasma cryovials extracted	☐☐															

If No, please give reason	Y/N
Patient deceased	
Patient discharged	
Noradrenaline and Landiolol stopped	
COVID suspected or confirmed	
Other, please specify:	

Participant initials: | | | |

Participant ID: | | | | | |

CARDIOVASCULAR DATA
Day 6 - up to Day 14

CARDIOVASCULAR DATA CONTINUATION SHEET

MEASURE	UNIT	Received Y/N If yes, enter dose	DAY 6				DAY 7				DAY 8			
			T+ 126h	T+ 132h	T+ 138h	T+ 144h	T+ 150h	T+ 156h	T+ 162h	T+ 168h	T+ 174h	T+ 180h	T+ 186h	T+ 192h
HR	b/min													
Noradrenaline	mcg/kg/min													
Landiolol	mcg/kg/min													

MEASURE	UNIT	Received Y/N If yes, enter dose	DAY 9				DAY 10				DAY 11			
			T+ 198h	T+ 204h	T+ 210h	T+ 198h	T+ 204h	T+ 210h	T+ 198h	T+ 204h	T+ 210h	T+ 198h	T+ 204h	T+ 210h
HR	b/min													
Noradrenaline	mcg/kg/min													
Landiolol	mcg/kg/min													

MEASURE	UNIT	Received Y/N If yes, enter dose	DAY 12				DAY 13				DAY 14			
			T+ 270h	T+ 276h	T+ 282h	T+ 270h	T+ 276h	T+ 282h	T+ 270h	T+ 276h	T+ 282h	T+ 270h	T+ 276h	T+ 282h
HR	b/min													
Noradrenaline	mcg/kg/min													
Landiolol	mcg/kg/min													

Participant initials: ☐☐☐

Participant ID: ☐☐☐☐☐

DAY 6

DAY 6 – ADDITIONAL ASSESSMENTS

Date of Assessments: ☐☐/☐☐☐/☐☐☐☐

DD/MMM/YYYY

OTHER TREATMENT

STEROID	TOTAL DOSE	UNIT
	☐☐☐	mg

CARDIOVASCULAR

MEASUREMENT	RESULT	UNIT
ARTERIAL PaO_2	☐☐.☐	kPa
ARTERIAL $PaCO_2$	☐☐.☐	kPa

Optional cardiovascular assessments		
VENOUS PaO_2	☐☐.☐	kPa
VENOUS $PaCO_2$	☐☐.☐	kPa
CO	☐☐.☐	L/min
SV	☐☐☐	mL

BIOCHEMISTRY

MEASUREMENT	RESULT	UNIT
Glucose	☐☐.☐	mmol/L
Lactate	☐☐.☐	mmol/L
Liver Function Tests	**AST** ☐☐☐☐ **ALT** ☐☐☐☐	U/L

CENTRAL LABORATORY SPECIMENS

	Was sample collected?		Date of assessment	Time of assessment	
	No	Yes	DD/MMM/YYYY	HH/MM	

Participant initials: ☐☐☐

Participant ID: ☐☐☐☐☐

DAY 6

Research Blood Sample (mandatory)	☐	☐	D	D	M	M	M	Y	Y	Y	Y	H	H	M	M	
Number of plasma cryovials extracted	☐☐															

If No, please give reason	Y/N
Patient deceased	
Patient discharged	
Noradrenaline and Landiolol stopped	
COVID suspected or confirmed	
Other, please specify:	

Participant initials:		End of Noradrenaline Treatment (EONT)
Participant ID:		

EONT VISIT	
Date of assessment:	DD/MMM/YYYY

NORADRENALINE		
Date and time noradrenaline discontinued (for >12 hours):	DD/MMM/YYYY	HH/MM

OTHER TREATMENT		
STEROID	**TOTAL DOSE**	**UNIT**
		mg

CARDIOVASCULAR		
MEASUREMENT	**RESULT**	**UNIT**
ARTERIAL PaO_2	.	kPa
ARTERIAL $PaCO_2$	.	kPa

Optional cardiovascular assessments		
VENOUS PaO_2	.	kPa
VENOUS $PaCO_2$	.	kPa
CO	.	L/min
SV		mL

Participant initials:		End of Noradrenaline Treatment (EONT)
Participant ID:		

BIOCHEMISTRY		
MEASUREMENT	**RESULT**	**UNIT**
Glucose	.	mmol/L
Lactate	.	mmol/L
Liver Function Tests	**AST** **ALT**	U/L

CENTRAL LABORATORY SPECIMENS					
	Was sample collected?		**Date of assessment** DD/MMM/YYYY	**Time of assessment** HH/MM	
	No	**Yes**			
Research Blood Sample (mandatory)	☐	☐	D D M M M Y Y Y Y	H H M M	
Number of plasma cryovials extracted					

If No, please give reason	**Y/N**
Patient deceased	
Patient discharged	
Noradrenaline and Landiolol stopped	
COVID suspected or confirmed	
Other, please specify:	

PaxGene RNA sample 3	☐	☐	D D M M M Y Y Y Y	H H M M	

If No, please give reason	**Y/N**
Patient deceased	
Patient discharged	
Noradrenaline and Landiolol stopped	
COVID suspected or confirmed	
Other, please specify:	

Please note: If EONT visit falls on a sampling day (i.e. Days 0, 1, 2, 4 or 6) additional research blood samples for EONT are not required.

Participant initials: ☐☐☐

Participant ID: ☐☐☐☐☐

End of Landiolol Treatment

LANDIOLOL TREATMENT	
Date and time landiolol discontinued:	☐☐/☐☐☐/☐☐☐☐ DD/MMM/YYYY ☐☐:☐☐ HH/MM

Participant initials: ☐☐☐

Participant ID: ☐☐☐☐☐

ICU Discharge Form

ICU DISCHARGE INFORMATION	
Date and time of ICU discharge:	☐☐/☐☐☐/☐☐☐☐ DD/MMM/YYYY ☐☐:☐☐ HH/MM
Diagnosis at end of ICU admission:	
Summary of ICU Admission:	
Discharged to:	HDU ☐ Ward ☐ Other hospital/care facility ☐

Participant initials: ☐☐☐

Participant ID: ☐☐☐☐☐

Hospital Discharge Form

HOSPITAL DISCHARGE INFORMATION	
Date and time of hospital discharge:	☐☐/☐☐☐/☐☐☐☐ DD/MMM/YYYY ☐☐:☐☐ HH/MM
If discharged from hospital, specify location:	Home (Unsupported) ☐ Home (Supported) ☐ Care Facility / Nursing Home ☐ Rehabilitation Facility ☐ Other ☐ **If other, specify:** _____

Participant initials: ☐☐☐

Participant ID: ☐☐☐☐☐

Follow up DAY 28

FOLLOW UP INFORMATION	
Date of assessment: ☐☐/☐☐☐/☐☐☐☐ DD/MMM/YYYY	**Mortality status at day 28:** Alive ☐ Deceased ☐

Participant initials: ☐☐☐ **Participant ID:** ☐☐☐☐☐	**Follow up DAY 90**

FOLLOW UP INFORMATION	
Date of assessment: ☐☐/☐☐☐/☐☐☐☐ DD/MMM/YYYY	
Mortality status at day 90:	Alive ☐ Deceased ☐

MICROBIOLOGY SPECIMENS (LOCAL LABORATORY)			
No.	**Specimen**	**Date of assessment** DD/MMM/YYYY	**Result**
1		D D M M M Y Y Y Y	
2		D D M M M Y Y Y Y	
3		D D M M M Y Y Y Y	
4		D D M M M Y Y Y Y	
5		D D M M M Y Y Y Y	
6		D D M M M Y Y Y Y	
7		D D M M M Y Y Y Y	
8		D D M M M Y Y Y Y	
9		D D M M M Y Y Y Y	
10		D D M M M Y Y Y Y	
☐ **Tick if this form continues onto an additional page**			

Participant initials: ☐☐☐

Participant ID: ☐☐☐☐☐

CARDIOVASCULAR SAFETY OUTCOME DATA COLLECTION

CARDIOVASCULAR SAFETY OUTCOME DATA							
DATE AND TIME OF EVENT	**TYPE OF EVENT**		**+/- LOW BLOOD PRESSURE ?**		**+/- INTERVENTION?**		
☐☐/☐☐☐/☐☐☐☐ DD/MMM/YYYY HH/MM ☐☐ : ☐☐	Bradycardia Heart block Other arrhythmia Significant hypotension requiring intervention	☐ ☐ ☐ ☐	Yes No	☐ ☐	Landiolol rate reduced Landiolol permanently stopped Noradrenaline increased Other	☐ ☐ ☐ ☐	Atropine/Glycopyrrolate ☐ Pacemaker ☐ CPR ☐ If other, please specify:
☐☐/☐☐☐/☐☐☐☐ DD/MMM/YYYY ☐☐ : ☐☐ HH/MM	Bradycardia Heart block Other arrhythmia Significant hypotension requiring intervention	☐ ☐ ☐ ☐	Yes No	☐ ☐	Landiolol rate reduced Landiolol permanently stopped Noradrenaline increased Other	☐ ☐ ☐ ☐	Atropine/Glycopyrrolate ☐ Pacemaker ☐ CPR ☐ If other, please specify:
☐☐/☐☐☐/☐☐☐☐ DD/MMM/YYYY ☐☐ : ☐☐ HH/MM	Bradycardia Heart block Other arrhythmia Significant hypotension requiring intervention	☐ ☐ ☐ ☐	Yes No	☐ ☐	Landiolol rate reduced Landiolol permanently stopped Noradrenaline increased Other	☐ ☐ ☐ ☐	Atropine/Glycopyrrolate ☐ Pacemaker ☐ CPR ☐ If other, please specify:

Participant initials: | | | |

Participant ID: | | | | | |

CARDIOVASCULAR SAFETY OUTCOME DATA COLLECTION

This form should be completed up until end of landiolol treatment or day 14

☐ **Tick if this form continues onto an additional page**

Participant initials: | | | |

Participant ID: | | | | | |

Adverse Events

ADVERSE EVENTS

Please make a separate entry for:

- *All new adverse events,*
- *All adverse events which have increased severity*
- *All adverse events with changes in treatment relationship,*
- *All medical conditions present at the baseline which have worsened*

Did the participant experience any adverse events during the trial? **No ☐** **Yes ☐** **Unknown ☐**

No.	**Adverse Event** (Diagnosis)	)	**Adverse Event Onset Date** (DD/MMM/YYYY)	**Relationship to Trial Medication** 1 = Definitely 2 = Probably 3 = Possibly 4 = Unlikely 5 = Unrelated	**CTCAE grade** (1-5)	**Action taken (IMP)** 0 = None 1 =Trt adjustment 2 = Trt permanent discontinuation	**Outcome** 1 = Recovered/Resolved 2 = Recovered/Resolved with Sequelae 3 = Ongoing at end of trial 4 = Fatal 5 = Unknown	**Adverse Event End Date** (DD/MMM/YYYY)
1			D D M M M **2 0** Y Y	☐	☐	☐	☐	D D M M M **2 0** Y Y
2			D D M M M **2 0** Y Y	☐	☐	☐	☐	D D M M M **2 0** Y Y
3			D D M M M **2 0** Y Y	☐	☐	☐	☐	D D M M M **2 0** Y Y
4			D D M M M **2 0** Y Y	☐	☐	☐	☐	D D M M M **2 0** Y Y
5			D D M M M **2 0** Y Y	☐	☐	☐	☐	D D M M M **2 0** Y Y
6			D D M M M **2 0** Y Y	☐	☐	☐	☐	D D M M M **2 0** Y Y
7			D D M M M **2 0** Y Y	☐	☐	☐	☐	D D M M M **2 0** Y Y
8			D D M M M **2 0** Y Y	☐	☐	☐	☐	D D M M M **2 0** Y Y
9			D D M M M **2 0** Y Y	☐	☐	☐	☐	D D M M M **2 0** Y Y
10			D D M M M **2 0** Y Y	☐	☐	☐	☐	D D M M M **2 0** Y Y

☐ **Tick if this form continues onto an additional page**

If a participant experiences a serious adverse event, this should be reported via the SAE Form and NOT recorded on the Adverse Event Form

Participant initials: ☐☐☐

Participant ID: ☐☐☐☐☐

Adverse Events

ADVERSE EVENTS

Please make a separate entry for:

- *All new adverse events,*
- *All adverse events which have increased severity*
- *All adverse events with changes in treatment relationship,*
- *All medical conditions present at the baseline which have worsened*

No.	**Adverse Event** (Diagnosis)		**Adverse Event Onset Date** (DD/MMM/YYYY)	**Relationship to Trial Medication** 1 = Definitely 2 = Probably 3 = Possibly 4 = Unlikely 5 = Unrelated	**CTCAE grade (1-5)**	**Action taken (IMP)** 0 = None 1 =Trt adjustment 2 = Trt permanent discontinuation	**Outcome** 1 = Recovered/Resolved 2 = Recovered/Resolved with Sequelae 3 = Ongoing at end of trial 4 = Fatal 5 = Unknown	**Adverse Event End Date** (DD/MMM/YYYY)
11			D D M M M 2 0 Y Y	☐	☐	☐	☐	D D M M M 2 0 Y Y
12			D D M M M 2 0 Y Y	☐	☐	☐	☐	D D M M M 2 0 Y Y
13			D D M M M 2 0 Y Y	☐	☐	☐	☐	D D M M M 2 0 Y Y
14			D D M M M 2 0 Y Y	☐	☐	☐	☐	D D M M M 2 0 Y Y
15			D D M M M 2 0 Y Y	☐	☐	☐	☐	D D M M M 2 0 Y Y
16			D D M M M 2 0 Y Y	☐	☐	☐	☐	D D M M M 2 0 Y Y
17			D D M M M 2 0 Y Y	☐	☐	☐	☐	D D M M M 2 0 Y Y
18			D D M M M 2 0 Y Y	☐	☐	☐	☐	D D M M M 2 0 Y Y
19			D D M M M 2 0 Y Y	☐	☐	☐	☐	D D M M M 2 0 Y Y
20			D D M M M 2 0 Y Y	☐	☐	☐	☐	D D M M M 2 0 Y Y

☐ **Tick if this form continues onto an additional page**

Protocol Deviations

Participant initials: | | | |

Participant ID: | | | | | |

Protocol Deviations

PROTOCOL NON-COMPLIANCES

Any protocol non-compliances to report?	Yes ☐	No ☐

EVENT DETAILS:
(Include full details of the non-compliance i.e. exact nature of the event, how and when you became aware, what investigations were undertaken, the implications of the findings, how this event has impacted (or had the potential to impact) either patient safety and/or scientific quality/data credibility, the root cause of the finding)

Date of event: | | | | / |

DD/MMM/YYYY

CORRECTIVE ACTIONS:
(Give details of what immediate corrective action(s) were taken to rectify the situation and minimise the impact of the finding. Consider person responsible, who will be involved, stipulate timelines, consider impact on other areas, additional approvals needed)

PREVENTATIVE ACTIONS: *(Give details of what actions will be/have been implemented to ensure the event does not happen again. Ensure actions relate to root cause. Consider if Quality Assurance procedures require updating, person responsible, who will be involved. Stipulate timelines, ensure actions are measurable)*		
FORM COMPLETED BY:		
Name (please print):		Date completed: / DD/MMM/YYYY
Signature:		

Participant initials: ☐☐☐	**Withdrawal Form**
Participant ID: ☐☐☐☐☐	

WITHDRAWAL FORM	
Date of withdrawal:	☐☐/☐☐☐/☐☐☐☐ DD/MMM/YYYY
Withdrawal status:	*Please select <u>one</u> option only:* **Participant has withdrawn from trial treatment but remains on follow up** ☐ **Participant has withdrawn from the trial entirely / withdrawn consent** ☐
Main reason for withdrawal:	Reason _____
Withdrawn by:	Participant ☐ Personal Legal Representative ☐ Professional Legal Representative ☐ Clinician ☐

Participant initials:	☐☐☐
Participant ID:	☐☐☐☐☐

Death Notification Form

DEATH INFORMATION	
Date of Death:	☐☐/☐☐☐/☐☐☐☐ DD/MMM/YYYY ☐☐:☐☐ HH/MM
Main cause of death: *(taken from the death certificate)*	
Please give brief details:	

Please ensure a Serious Adverse Event Report has been completed if applicable

END OF TRIAL	
Has the participant completed the trial? (All visits including the final follow up visit at day 90?)	Yes ☐ No ☐
Participant Status: If No, check the <u>primary</u> reason for Discontinuation *(tick <u>one</u> box):*	Lost to Follow Up ☐ Withdrawal of Consent ☐ *Please complete withdrawal form* Death ☐ *Please complete notification of death form and / or SAE report form as appropriate* Trial terminated by sponsor ☐ Other ☐ If other, please specify _____

Sign-off Statement

I confirm that I have made every reasonable effort to ensure that ALL of the data in this Case Record Form is a true, accurate and complete report. All log pages have been reviewed for completeness ensuring all records have end dates or are marked as ongoing.

Principal Investigator's Signature: _____ Date D D / M M M / 2 0 Y Y

DD/MMM/YYYY