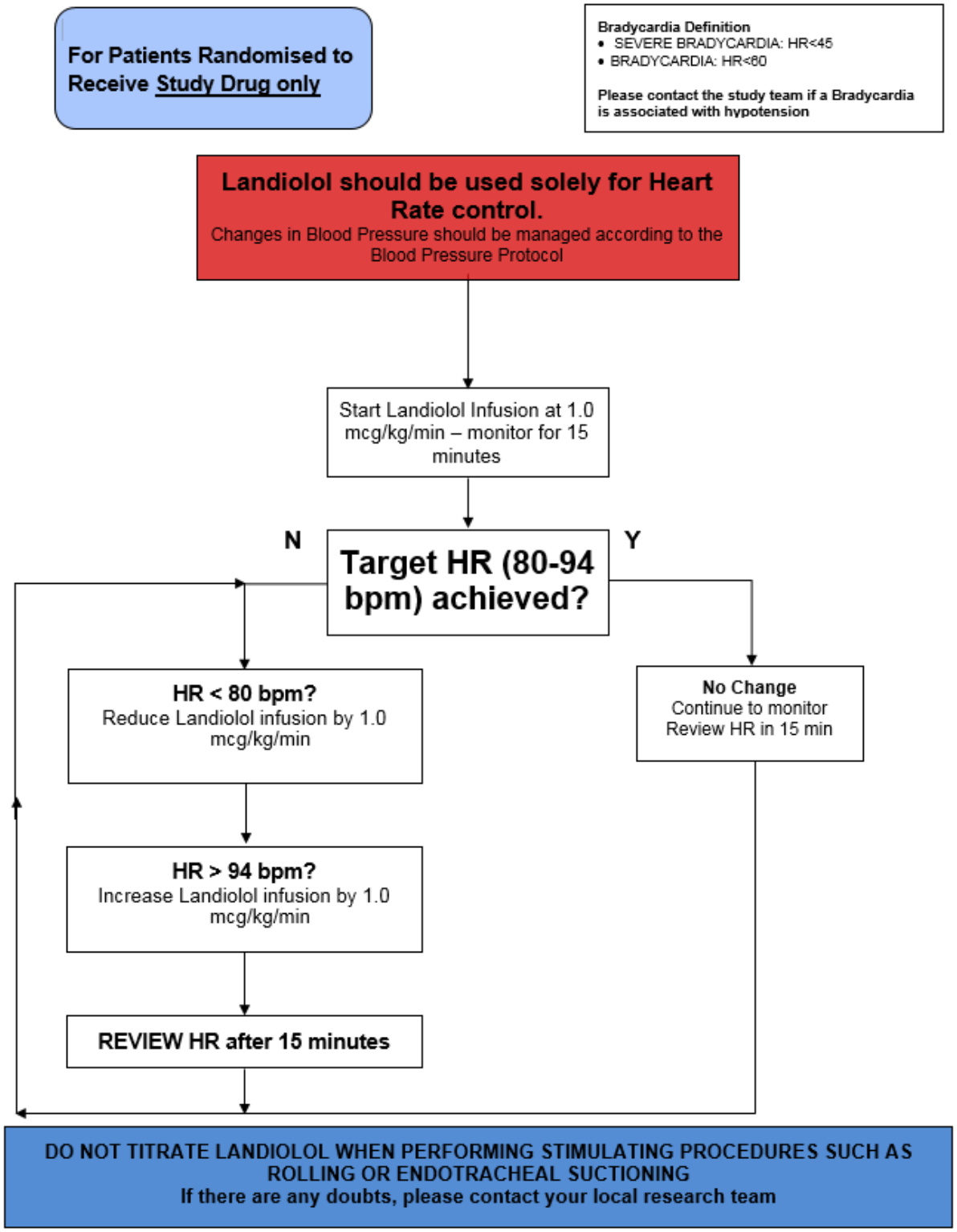
Supplemental Online Content

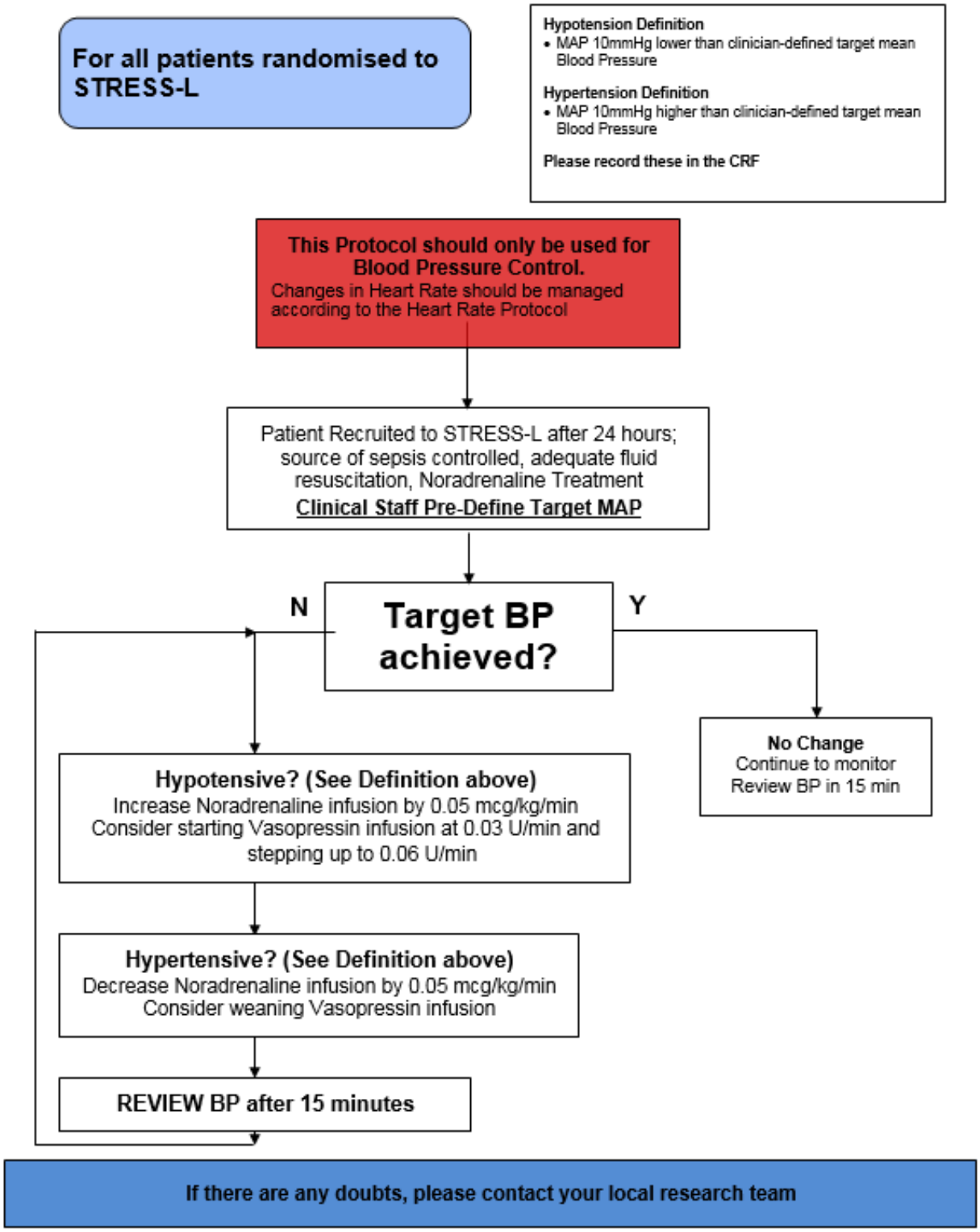
Whitehouse T, Hossain A, Perkins GD, et al; the STRESS-L Collaborators. Landiolol and organ failure in patients with septic shock: the STRESS-L randomized clinical trial. *JAMA*. doi:10.1001/jama.2023.20134

This supplemental material has been provided by the authors to give readers additional information about their work.

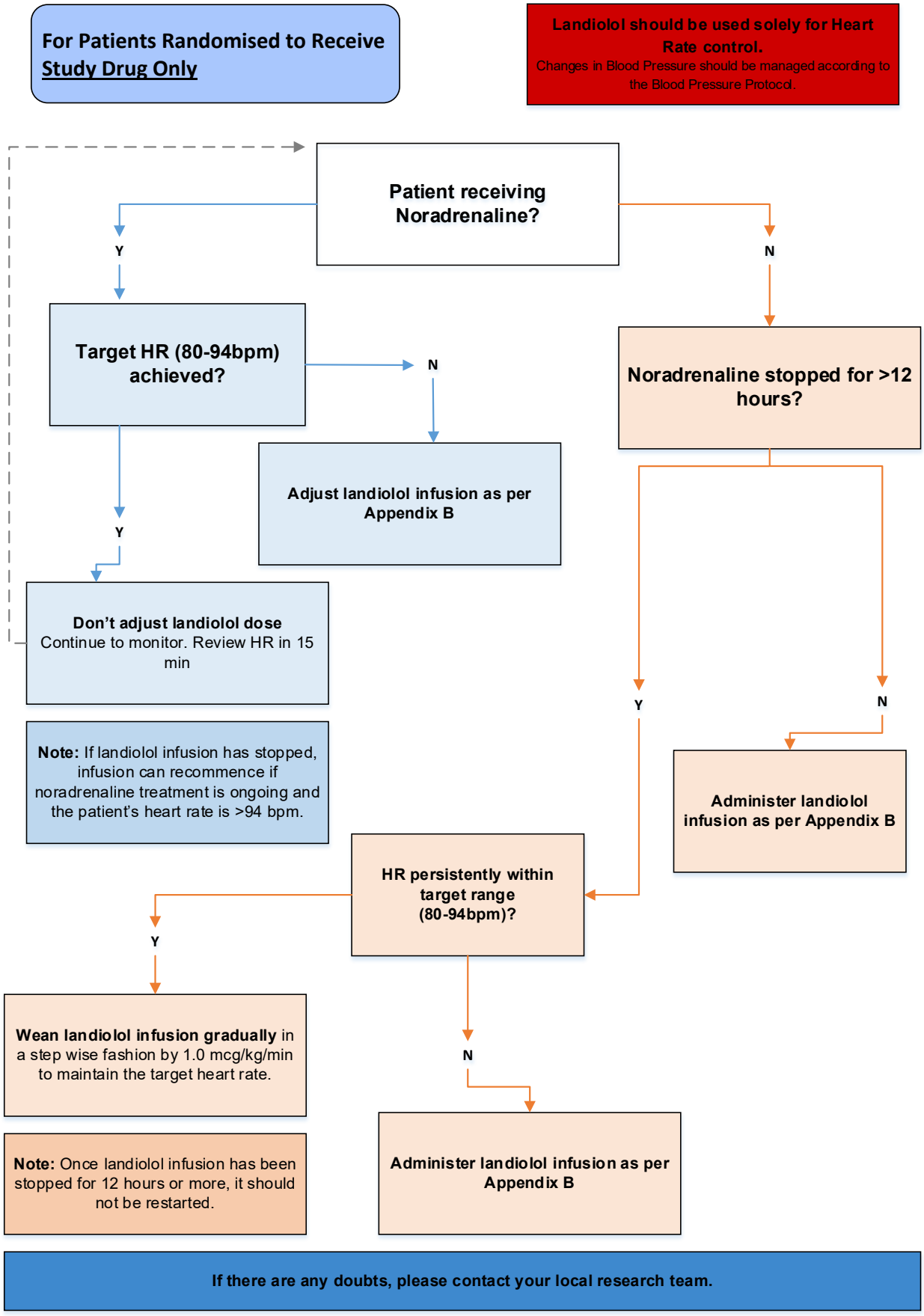


eFigure 2: STRESS-L vasopressor infusion protocol

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



eFigure 3: STRESS-L timing and weaning of the study drug



eTable 1: landiolol infusion rate

Concentration of landiolol:	300	mg per	50	ml	=	6	mg/ml

Body weight (kg)	1.0 mcg/kg/min	2.0 mcg/kg/min	3.0 mcg/kg/min	4.0 mcg/kg/min	5.0 mcg/kg/min	6.0 mcg/kg/min	7.0 mcg/kg/min	8.0 mcg/kg/min	9.0 mcg/kg/min	10.0 mcg/kg/min	
40	0.4	0.8	1.2	1.6	2.0	2.4	2.8	3.2	3.6	4.0	ml/hr
45	0.5	0.9	1.4	1.8	2.3	2.7	3.2	3.6	4.1	4.5	ml/hr
50	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	ml/hr
55	0.6	1.1	1.7	2.2	2.8	3.3	3.9	4.4	5.0	5.5	ml/hr
60	0.6	1.2	1.8	2.4	3.0	3.6	4.2	4.8	5.4	6.0	ml/hr
65	0.7	1.3	2.0	2.6	3.3	3.9	4.6	5.2	5.9	6.5	ml/hr
70	0.7	1.4	2.1	2.8	3.5	4.2	4.9	5.6	6.3	7.0	ml/hr
75	0.8	1.5	2.3	3.0	3.8	4.5	5.3	6.0	6.8	7.5	ml/hr
80	0.8	1.6	2.4	3.2	4.0	4.8	5.6	6.4	7.2	8.0	ml/hr
85	0.9	1.7	2.6	3.4	4.3	5.1	6.0	6.8	7.7	8.5	ml/hr
90	0.9	1.8	2.7	3.6	4.5	5.4	6.3	7.2	8.1	9.0	ml/hr
95	1.0	1.9	2.9	3.8	4.8	5.7	6.7	7.6	8.6	9.5	ml/hr
100	1.0	2.0	3.0	4.0	5.0	6.0	7.0	8.0	9.0	10.0	ml/hr

Body weight (kg)	11.0 mcg/kg/min	12.0 mcg/kg/min	13.0 mcg/kg/min	14.0 mcg/kg/min	15.0 mcg/kg/min	16.0 mcg/kg/min	17.0 mcg/kg/min	18.0 mcg/kg/min	19.0 mcg/kg/min	20.0 mcg/kg/min	
40	4.4	4.8	5.2	5.6	6.0	6.4	6.8	7.2	7.6	8.0	ml/hr
45	5.0	5.4	5.9	6.3	6.8	7.2	7.7	8.1	8.6	9.0	ml/hr
50	5.5	6.0	6.5	7.0	7.5	8.0	8.5	9.0	9.5	10.0	ml/hr
55	6.1	6.6	7.2	7.7	8.3	8.8	9.4	9.9	10.5	11.0	ml/hr

60	6.6	7.2	7.8	8.4	9.0	9.6	10.2	10.8	11.4	12.0	ml/hr
65	7.2	7.8	8.5	9.1	9.8	10.4	11.1	11.7	12.4	13.0	ml/hr
70	7.7	8.4	9.1	9.8	10.5	11.2	11.9	12.6	13.3	14.0	ml/hr
75	8.3	9.0	9.8	10.5	11.3	12.0	12.8	13.5	14.3	15.0	ml/hr
80	8.8	9.6	10.4	11.2	12.0	12.8	13.6	14.4	15.2	16.0	ml/hr
85	9.4	10.2	11.1	11.9	12.8	13.6	14.5	15.3	16.2	17.0	ml/hr
90	9.9	10.8	11.7	12.6	13.5	14.4	15.3	16.2	17.1	18.0	ml/hr
95	10.5	11.4	12.4	13.3	14.3	15.2	16.2	17.1	18.1	19.0	ml/hr
100	11.0	12.0	13.0	14.0	15.0	16.0	17.0	18.0	19.0	20.0	ml/hr

Body weight (kg)	**21.0** mcg/kg/min	**22.0** mcg/kg/min	**23.0** mcg/kg/min	**24.0** mcg/kg/min	**25.0** mcg/kg/min	**26.0** mcg/kg/min	**27.0** mcg/kg/min	**28.0** mcg/kg/min	**29.0** mcg/kg/min	**30.0** mcg/kg/min	
40	8.4	8.8	9.2	9.6	10.0	10.4	10.8	11.2	11.6	12.0	ml/hr
45	9.5	9.9	10.4	10.8	11.3	11.7	12.2	12.6	13.1	13.5	ml/hr
50	10.5	11.0	11.5	12.0	12.5	13.0	13.5	14.0	14.5	15.0	ml/hr
55	11.6	12.1	12.7	13.2	13.8	14.3	14.9	15.4	16.0	16.5	ml/hr
60	12.6	13.2	13.8	14.4	15.0	15.6	16.2	16.8	17.4	18.0	ml/hr
65	13.7	14.3	15.0	15.6	16.3	16.9	17.6	18.2	18.9	19.5	ml/hr
70	14.7	15.4	16.1	16.8	17.5	18.2	18.9	19.6	20.3	21.0	ml/hr
75	15.8	16.5	17.3	18.0	18.8	19.5	20.3	21.0	21.8	22.5	ml/hr
80	16.8	17.6	18.4	19.2	20.0	20.8	21.6	22.4	23.2	24.0	ml/hr
85	17.9	18.7	19.6	20.4	21.3	22.1	23.0	23.8	24.7	25.5	ml/hr
90	18.9	19.8	20.7	21.6	22.5	23.4	24.3	25.2	26.1	27.0	ml/hr
95	20.0	20.9	21.9	22.8	23.8	24.7	25.7	26.6	27.6	28.5	ml/hr
100	21.0	22.0	23.0	24.0	25.0	26.0	27.0	28.0	29.0	30.0	ml/hr

	31.0	**32.0**	**33.0**	**34.0**	**35.0**	**36.0**	**37.0**	**38.0**	**39.0**	**40.0**	

Body weight (kg)	mcg/kg/min	mcg/kg/min	mcg/kg/min	mcg/kg/min	mcg/kg/min	mcg/kg/min	mcg/kg/min	mcg/kg/min	mcg/kg/min	mcg/kg/min	
40	12.4	12.8	13.2	13.6	14.0	14.4	14.8	15.2	15.6	16.0	ml/hr
45	14.0	14.4	14.9	15.3	15.8	16.2	16.7	17.1	17.6	18.0	ml/hr
50	15.5	16.0	16.5	17.0	17.5	18.0	18.5	19.0	19.5	20.0	ml/hr
55	17.1	17.6	18.2	18.7	19.3	19.8	20.4	20.9	21.5	22.0	ml/hr
60	18.6	19.2	19.8	20.4	21.0	21.6	22.2	22.8	23.4	24.0	ml/hr
65	20.2	20.8	21.5	22.1	22.8	23.4	24.1	24.7	25.4	26.0	ml/hr
70	21.7	22.4	23.1	23.8	24.5	25.2	25.9	26.6	27.3	28.0	ml/hr
75	23.3	24.0	24.8	25.5	26.3	27.0	27.8	28.5	29.3	30.0	ml/hr
80	24.8	25.6	26.4	27.2	28.0	28.8	29.6	30.4	31.2	32.0	ml/hr
85	26.4	27.2	28.1	28.9	29.8	30.6	31.5	32.3	33.2	34.0	ml/hr
90	27.9	28.8	29.7	30.6	31.5	32.4	33.3	34.2	35.1	36.0	ml/hr
95	29.5	30.4	31.4	32.3	33.3	34.2	35.2	36.1	37.1	38.0	ml/hr
100	31.0	32.0	33.0	34.0	35.0	36.0	37.0	38.0	39.0	40.0	ml/hr

For participants below 40 kg or over 100 kg ideal body weight will be used (method as per local practice)

The maximum recommended daily dosage of landiolol for this patient population is **40 mcg/kg/min.** The trial team should be aware of the unit of measurement given to the patient when administering landiolol to adhere to the protocol.

eTable 2: Compliance on landiolol infusion

- For all patients, the heart rate was recorded hourly from randomization to day 2 and then 6 hours thereafter up to day 14.
- The landiolol dose was adjusted according to the study drug infusion protocol depending on the heart rate.

A patient was said to not adhere to the drug infusion protocol if:

- if the patient was in the trial and the landiolol was not started within 6 hours of randomization;
- the starting landiolol infusion dose was not 1.0 mcg/kg/min;
- the heart rate was <80 bpm and the landiolol infusion was not reduced by at least 1.0 mcg/kg/min;
- the heart rate was >94 bpm and the landiolol infusion was not increased by 1.0 mcg/kg/min;
- if the landiolol dose was not an integer;
- landiolol dose was over 40mcg/kg/min (max trial dose);
- if the landiolol was restarted, 12 hours or more since last landiolol dose.

A rate of non-adherence (i.e., number of non-compliant intervals out of the total number of intervals) of over 10% for a patient triggered further investigation.

eTable 3: Trial assessments

Procedure	Screening (T0-12)	Baseline 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	FU Visit Day 28	Final visit Day 90
Eligibility assessment	●																		
Informed consent		●																	
Randomization		●																	
Demographics		●																	
Medical History		●																	
ECG		●	According to clinical need or if AE/SAE																
Pregnancy test		●																	
IMP		Dispense														End			
Blood sample		●	●	●		●		●									●		
Biobank blood sample (optional)		●	●														●		
Transport of stored serum																	Batch		
Local laboratory tests (normal clinical care):		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●		
C-Reactive Protein (CRP)		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●		
Glucose		●	●	●		●		●									●		
Lactate		●	●	●		●		●									●		
Worst PaO2/FiO2		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●		
Platelets		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●		
Creatinine		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●		
Bilirubin		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●		
White Cell Count		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●		
Liver Function Tests (ALT or AST)		●	●	●		●		●									●		
Central Venous Blood Gas / Arterial BG		●	●	●		●		●									●		
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 / inotropes		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●		
In/Out Fluids		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●		
SOFA score		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●		
Adverse Events (SAEs up to Day 90)		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Steroid use		●	●	●		●		●									●		
Compliance		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●		
Mortality status																		●	●
End of Trial																			●

End of all vasopressor infusions +12 hours (may occur at any point between day 1 and day 14). The maximum duration of landiolol treatment is 14 days. 2. Pregnancy test on women of childbearing potential at the discretion of local investigator

eTable 4: Other baseline characteristics for patients in the STRESS-L Study		
	Landiolol (n=63)	Standard Care (n=63)
Chest X-ray taken, No. (%)		
yes	60 (95.2)	57 (90.5)
no	3 (4.8)	6 (9.5)
Diffuse bilateral pulmonary infiltrates on chest-Xray, No. (%)	(n=60)	(n=57)
yes	25 (41.7)	14 (24.6)
no	35 (58.3)	43 (75.4)
Received beta-blockers on ICU admission	(n=36)	(n=36)
yes	1 (2.8)	3 (8.3)
no	35 (97.2)	33 (91.7)

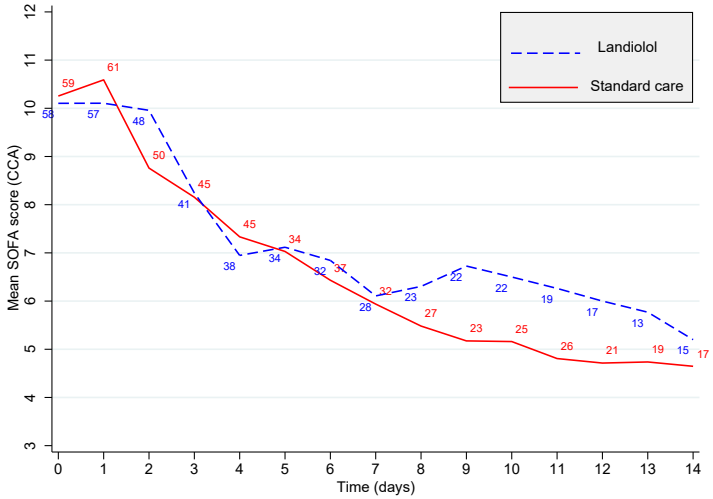
eTable 5: Sensitivity analysis of primary outcome analysis (landiolol vs standard care)

	Landiolol (n=63)	Standard care (n=63)	Unadjusted		Adjusted[a]	
			Effect estimate (95%)	P-value	Effect estimate (95%)	P-value
Primary outcome: Mean SOFA score, mean (sd)						
Imputation Method1[b]	8.6 (4.1)	7.6 (3.1)	MD, 0.95 (-0.31 to 2.20)	0.14	MD, 0.82 (-0.29 to 1.94)	0.15
Imputation Method 2[c]	8.6 (4.1)	7.6 (3.1)	MD, 0.93 (-0.33 to 2.18)	0.15	MD, 0.80 (-0.31 to 1.92)	0.16
Imputation Method [3d]	8.4 (4.2)	7.4 (3.1)	MD, 0.99 (-0.29 to 2.27)	0.13	MD, 0.86 (-0.26 to 1.99)	0.13
CACE Analysis			MD, 0.82 (-0.54, 2.17)	0.24	MD, 0.69 (-0.50, 1.87)	0.26
Mean SOFA score (8 days or more days up to 14 days)	5.9 (3.9)	4.7 (2.8)	MD, 1.13 (-0.76 to 3.01)	0.24	MD, 0.95 (-0.70 to 2.60)	0.26
Pocock's Win Ratio using composite of SOFA score and 28-days mortality status[f]	0.81, (0.54 to 1.21), P=.30					
Pocock's Win Ratio using composite of SOFA score and 90-days mortality status	0.80, (0.53,1.20), P=.28					

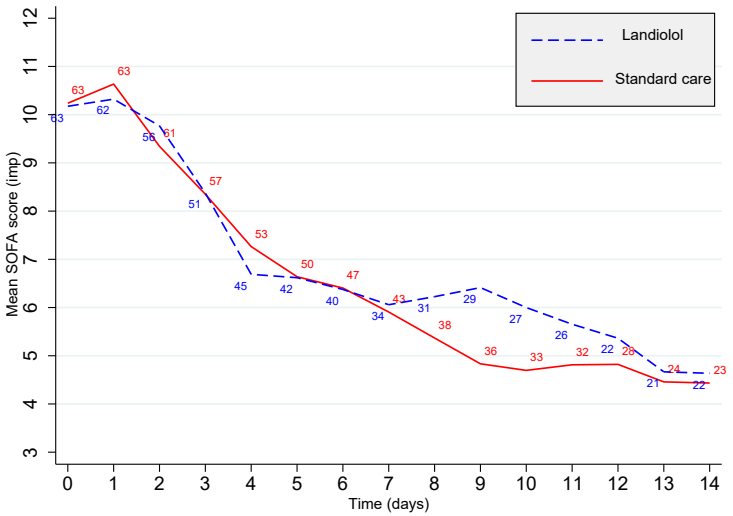
[a]Adjusted for age, gender, and baseline norepinephrine value
[b]Method 1: As explained in the method section of the statistical analysis plan
[c]Method 2: Last observation carried forward. If still there are missing values due to no observed values before the missing values, we impute the first observed values.
[d]Method 3: If the patient discharge alive from ICU, the minimum score zero is imputed for the missing values. If the patient is discharge died from ICU, the maximum score that the patient ever obtained for that item is imputed for the missing values.
[e]based on complete case analysis
[f]The Pocock's Win Ratio calculated using the composite of the SOFA score and survival status (both at 28 days and 90 days) illustrated no evidence of statistically significant difference in the treatment effect. In terms of interpretation: The win ratio at 28-days is 0.81 indicates that a patient in the landiolol arm is 19% less likely to survive longer or to have lower sofa score than a patient in standard care arm.

eFigure 4: Mean SOFA score over 14 days using (a) complete case analysis, (b) METHOD 1 imputation (as described in the manuscript methods section). Figures on the lines inside the plots represent the number of observations used to calculate the mean SOFA score

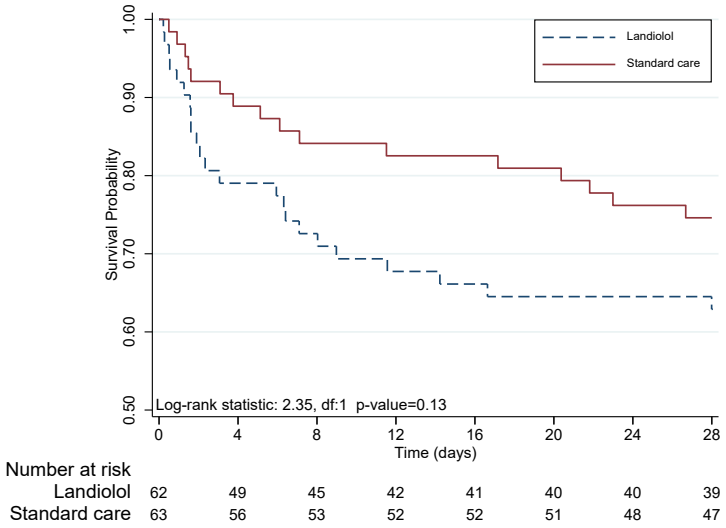
(a)



(b)

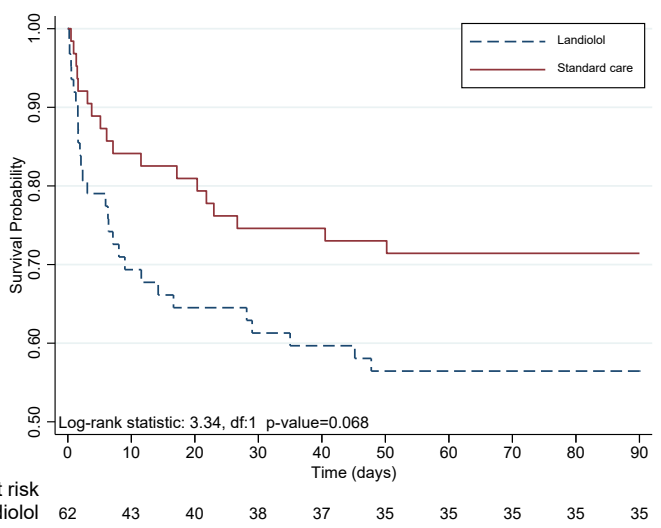


eFigure 5a: Kaplan-Meier curve over 28 days period by treatment arms



Cox Proportional Hazards model:
unadjusted HR:1.64 (95% CI: 0.87 to 3.10) P= .13; PH test: P= .19
adjusted HR:1.54 (95% CI: 0.81 to 2.91) P= .18; PH test: P= .18

eFigure 5b: Kaplan-Meier curve over 90 days period by treatment arms



Cox Proportional Hazards model:
unadjusted HR:1.73 (95% CI: 0.95 to 3.15) P=.07; PH test: P=0.63
adjusted HR:1.58 (95% CI: 0.87 to 2.87) P=.14; PH test: P=0.72

In both cases (for 28- and 90-days mortality), there were no evidence that the proportional hazard assumption has been violated and thus there was no evidence of a statistically significant treatment difference.

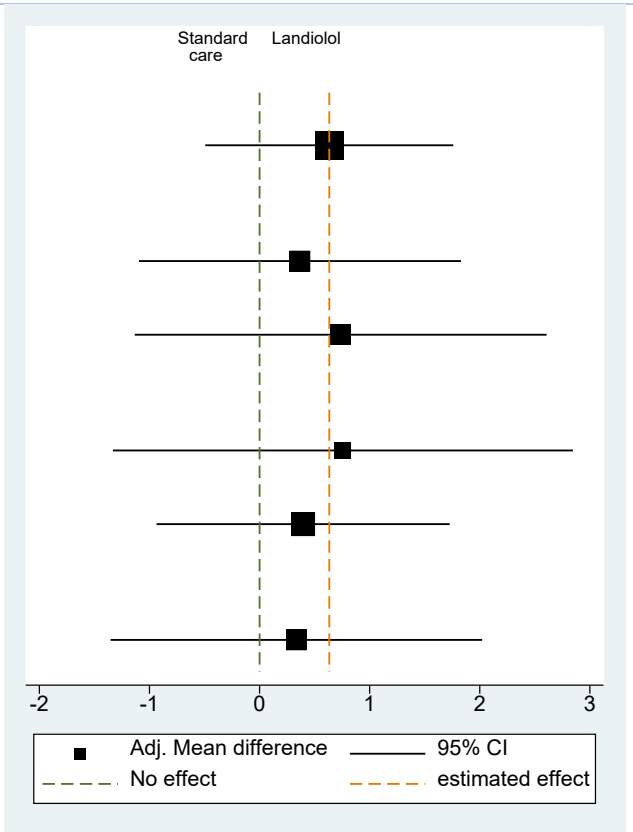
eTable 6: Routinely collected in-fluid and out-fluid data[a] (Landiolol vs Standard care)

In fluid and out fluid	Landiolol (n=63)	Standard Care (n=63)		**Unadjusted**			**Adjusted[b]**	
				Effect estimate (95%)	P-value		Effect estimate (95%)	P-value
Fluids In (mL)	2635.5 (1112.0)	2682.9 (1114.6)		MD, -74.43 (-391.61 to 242.76)	.65		MD, -62.36 (-381.27 to 256.55)	.70
Fluids Out (mL)	2287.8 (1573.7)	2318.2 (990.0)		MD, -20.48 (-342.16 to 301.20)	.90		MD, -13.63 (-307.80 to 280.55)	.93
Fluids Balance (mL)[c]	1504.0 (1543.9)	1520.8 (825.0)		MD, -97.25 (-413.28 to 218.78)	.55		MD, -78.49 (-388.33 to 231.35)	.62

[a]The value of unadjusted mean difference may not be the same to the difference in means presented between the arms (Standard care vs Landiolol). This is because the model was fitted to the observed values for each timepoint. Whereas the means are calculated by first calculating mean for each patient over time and then mean of the means over all patients in each arm.
[b]Adjusted for age, gender, and baseline norepinephrine value
[c]This is the absolute difference between in fluid and out fluid

eTable 7: Subgroup analysis for mean SOFA score over 14 days in the landiolol arm vs Standard arm

	landiolol (n=63)	Standard care (n=63)	Adjusted mean difference, 95% CI	p-values for interaction
Overall	8.8 (3.9)	8.1 (3.2)	0.63 (-0.49 to 1.76)	
Subgroup: Baseline severity (norepinephrine)				
<= 0.3 mcg/kg/min	(n=32); 7.5 (2.7)	(n=32); 7.1 (3.0)	0.37 (-1.10 to 1.83)	0.47
>0.3 mcg/kg/min	(n=31); 10.3 (4.5)	(n=31); 9.1 (3.2)	0.73 (-1.13 to 2.61)	
Subgroup: Having ARDS				
Yes	(n=21); 10.2 (4.5)	(n=16); 9.1 (3.0)	0.76 (-1.33 to 2.85)	0.56
No	(n=42); 8.2 (3.5)	(n=46); 7.8 (3.3)	0.40 (-0.94 to 1.73)	
Subgroup: Beta blockers prior to randomization				
No	(n=33); 8.8 (3.8)	(n=31); 8.8 (3.6)	0.33 (-1.35 to 2.02)	0.18
Yes[a]	(n=3); 12.2 (5.4)	(n=5); 8.4 (1.1)	-	



[a]No estimate was calculated as only 5 and 3 observations are in the standard care and landiolol arm, respectively

eTable 8: Adverse event and serious adverse events

	landiolol (n=63)	Standard care (n=63)	p-value[a]
No of patients with at least one adverse event, No. (%)			
No	53 (84.1)	55 (87.3)	0.80
Yes	10 (15.9)	8 (12.7)	
Total number of adverse events, N (%)	58 (55.2)	47 (44.8)	
Relationship of adverse event No. (%)			
	(n=57)	(n=47)	
Possibly	2 (3.5)	0 (0.0)	<0.001
Unlikely	22 (38.6)	0 (0.0)	
Unrelated	33 (57.9)	47 (100)	
No. of patients with at least one serious adverse event (SAE), No. (%)			
No	47 (74.6)	59 (93.6)	0.006
Yes	16 (25.4)	4 (6.4)	
Total number of SAE and SAR, No. (%)	30 (76.9)	9 (23.1)	
Classification of SAE and SAR, No. (%)			
	(n=30)	(n=9)	
SAE	21 (70.0)	9 (100.0)	0.09
SAR	9 (30)	0	
Causal relationship of SAE and SAR, No. (%)	(n=30)	(n=9)	
Definitely	3 (10)	0	0.003
Probably	1 (3.3)	0	
Possibly	4 (13.3)	0	
Unlikely	14 (46.7)	0	
Unrelated	8 (26.7)	9 (100)	
Cardiovascular Safety	(n=12)	(n=6)	
Bradycardia	3 (25.0)	3 (50.0)	0.73
Significant hypotension requiring intervention	1 (8.3)	0	
Other arrhythmia	8 (66.7)	3 (50.0)	

[a] Fisher's exact test

eTable 9: Details of non-complier patients

		Timepoints with one or more queries		By Query				
TNO	**Total no. Cardiovascular Data Timepoints Entered**	**No. Timepoints with query**	**Percentage of total number of timepoints**	**Query Name**	**No. Timepoints with query**	**Percentage of total number of timepoints**	**Compliant Y/N**	**Details**
01020	69	64	93%	On trial, Landiolol not started	64	93%	**N**	Response was chased, agreed by TMG to longer chase as trial had closed and no safety issue posed.
01022	57	18	32%	HR > 94 bpm, Landiolol not increased	16	28%	**N**	Response was chased, agreed by TMG to longer chase as trial had closed and no safety issue posed
				On trial, Landiolol not started	1	2%	Y	Query below 10% no action required.
				Starting Dose not 1 mcg/kg/min	1	2%	N	Response was chased, agreed by TMG to longer chase as trial had closed and no safety issue posed
02001	61	56	92%	On trial, Landiolol not started	56	92%	**N**	Landiolol not administered as initially the patient had no free central access. Once central access was achieved and confirmed safe to use, the patients' heart rate was consistently below 95 bpm and the clinical team took the decision not to administer the Landiolol.
07010	101	14	14%	HR > 94 bpm, Landiolol not increased	13	13%	**N**	Response was chased, agreed by TMG to longer chase as trial had closed and no safety issue posed
				Starting Dose not 1 mcg/kg/min	1	1%	Y	Query below 10% no action required.
				Starting Dose not 1 mcg/kg/min	1	1%	Y	Query below 10% no action required.

25003	69	64	93%	On trial, Landiolol not started	64	93%	**N**	Response was chased, agreed by TMG to longer chase as trial had closed and no safety issue posed.

eTable 10: Serious Adverse Events (SAEs) and Serious Adverse Reactions (SARs)

SAE ref. no	*Initial or Follow Up SAE form*	*Patient ID and treatment arm*	*Event types selected*	*Date event deemed serious*	*Date of reporting*	*Causal relationship: Could this event have been caused by the trial medication*	*Action taken*	*Event classification*	*Outcome of event*	*Severity /Toxicity assessment*		
										System Organ Class (SOC)	*Adverse term (CTCAE term v.4.0)*	*CTCAE grade*
028	Follow up	01022 (Landiolol)	• Life threatening • Hospitalization or prolongation of existing hospitalization	13 Oct 2021	23 Nov 2021	Unlikely	None	**SAE**	Resolved	12	Gastrointestinal anastomotic leak	2
	Initial				05 Oct 2021			**SAE**				
027	Follow up	01020 (Landiolol)	Life threatening	21 July 2021	24 Nov 2021	Unrelated/ Unlikely	None	**SAE**	Death	15	Soft tissue necrosis lower and upper limb	4
	Initial				13 July 2021				Ongoing			
026	Follow up	01020 (Landiolol)	Hospitalization or prolongation of existing hospitalization	07 July 2021	24 Nov 2021	Unrelated/ Unlikely	None	**SAE**	Resolved	17	Ischemia cerebrovascular	2
	Initial				07 July 2021				Ongoing			
025	Follow up	01020 (Landiolol)	Hospitalization or prolongation of existing hospitalization	07 July 2021	24 Nov 2021	Unrelated/ Unlikely	None	**SAE**	Death	1	Spleen disorder	1
	Initial				07 July 2021				Ongoing			
024	Initial	20005 (Landiolol)	Other reason: Hemodynamic compromise	05 May 2021	06 May 2021	Definitely	Dose adjusted/ interrupted	**SAR**	Resolved	2	Hypotension	4
023	Initial	42003 (Landiolol)	Other reason: Hypotension requiring Intervention.	09 Mar 2020	09 Mar 2020	Definitely	Other: Noradrenaline increased as directed by vasopressor infusion protocol	**SAR**	Death	26	Hypotension	4

022	Follow up	42002 (Standard Care)	Life-threatening	29 Feb 2020	04 Mar 2020	Unrelated	None	**SAE**	Death	17	Stroke	5
	Initial				02 Mar 2020				Ongoing	2	Cardiac arrest	4
021	Initial	12003 (Landiolol)	Life-threatening	03 Feb 2020	04 Feb 2020	Possibly	Trial treatment permanentl y discontinue d	**SAR**	Resolved	26	Hypotension	4
020	Follow up	39001 (Landiolol)	• Death • Life-threatening •Hospitalization or prolongation of existing hospitalization	28 Jan 2020	04 Feb 2020	Unrelated	None	**SAE**	Death	22	Pneumonia ARDS	5
	Initial				29 Jan 2020				Death		Severe Pneumonia	
019	Initial	07009 (Standard care)	Life-threatening	15 Jan 2020	16 Jan 2020	Unrelated	None	**SAE**	Resolved	2	Atrial fibrillation	4
018	Initial	20004 (Landiolol)	Life-threatening	12 Jan 2020	13 Jan 2020	Unlikely	None	**SAE**	Resolved	2	Ventricular tachycardia	2
017	Follow up	07009 (Standard care)	Other reason: Significant bleed requiring endoscopy	09 Jan 2020	20 Mar 2020	Unrelated	None	**SAE**	Death	7	Duodenal ulcer	3
	Initial				09 Jan 2020				Ongoing			
016	Follow up	01015 (Standard care)	• Life-threatening •Hospitalization or prolongation of existing hospitalization	25 Dec 2019	02 Jan 2020	Unrelated	Other: N/A Participant not randomized to treatment arm	**SAE**	*Patient exceeded 90-day Follow up, no further actions*	1	Blood and lymphatic system disorders - Other, specify	4
	Initial				29 Dec 2019							
015	Initial	25002 (Landiolol)	• Other reason: Significant hypotension requiring Intervention.	06 Nov 2019	10 Dec 2019	Definitely	Trial treatment permanentl y discontinue d	**SAR**	Resolved	26	Vascular disorders	3
014	Follow up	01016 (Landiolol)		13 Nov 2019	16 Dec 2019	Unrelated	None	**SAE**	Resolved	2		2

	Initial		Hospitalization or prolongation of existing hospitalization		13 Nov 2019				Ongoing		Cardiac disorders - Other, specify	
011	Initial	20003 (Landiolol)	Life-threatening	01 Sep 2019	01 Sep 2019	Probably	Dose adjusted / interrupted	**SAR**	Resolved	2	Sinus Bradycardia	2
010	Initial	19004 (Landiolol)	Life-threatening Hospitalization or prolongation of existing hospitalization	02 Jul 2019	15 August 2019	Unlikely	Other – temporary pacing wire fitted 03/07/2019	**SAE**	Resolved	2	Sinus Bradycardia	4
009	Follow Up	19004 (Landiolol)	Life-threatening	04 Jun 2019	18 Jul 2019	Unlikely	Trial treatment permanently discontinued	**SAE**	*Patient exceeded 90-day Follow up, no further actions*	26	Peripheral Ischemia	3
	Initial				04 Jun 2019					14	Acidosis	4
008	Initial	02007 (Landiolol)	Life-threatening	19 Mar 2019	20 Mar 2019	Unrelated	None	**SAE**	Resolved	Gastrointestinal disorders	Gastric hemorrhage	3
007	Initial	02005 (Landiolol)	Other reason: Significant increased ALT	02 Mar 2019	03 Mar 2019	Unlikely	Trial treatment permanently discontinued	**SAE**	*Patient exceeded 90-day Follow up, no further actions*	Hepatobiliary disorders	Elevated ALT	3
006	Follow Up	05001 (Landiolol)	Hospitalization or prolongation of existing hospitalization	11 Jan 2019	28 Mar 2019	Possibly	None	**SAR**	*Patient exceeded 90-day follow up, no further actions*	2	Myocardial Infarction	3
	Follow Up				26 Feb 2019				Ongoing			
	Initial				11 Jan 2019				Ongoing			
005	Initial	15001 (Landiolol)	Other reason: Transient and gradual reduction in blood pressure to a	10 Dec 2018	21 Dec 2018	Possibly	Trial treatment permanently	**SAR**	Resolved	2	Heart failure	2

			lower but not dangerous level				discontinued					
004	Initial	16001 (Landiolol)	Life-threatening	17 Dec 2018	20 Dec 2018	Unlikely	Other: Not on landiolol Infusion at time of event.	**SAE**	Other	7	Gastric hemorrhage	4
003	Follow up	16001 (Landiolol)	Hospitalization or prolongation of existing hospitalization	07 Dec 2018	21 Dec 2018	Unlikely	None	**SAE**	Resolved	7	Diarrhea	3
	Initial				14 Dec 2018				Ongoing			
002	Initial	04001 (Standard care)	Persistent or significant disability/ incapacity	05 Jul 2018	09 Jul 2018	Unrelated	None	**SAE**	Resolved with sequelae	12	Injury, poisoning and procedural complications - Other, specify	3
001	Initial	04001 (Standard care)	Other reason: MEDICALY SIGNIFICANT	03 Jul 2018	03 Jul 2018	Unrelated	None	**SAE**	Resolved with sequelae	2	Atrial fibrillation	2

eTable 11: Detailed summary of all reported adverse events

Patient ID	*Treatment arm*	Adverse event diagnosis	Adverse event onset date	Relationship to trial medication	Action taken IMP	Outcome	Adverse event end date
01020	Landiolol	Blistering to lips and nose. Reviewed by Dermatologist and diagnosed HSV.	02 Jul 2021	Unrelated	None	Recovered/Resolved	11 Jul 2021
		Blistering seen over body along with dusky necrosis. Either due to Noradrenaline or Sepsis effect.	02 Jul 2021	Unrelated	None	Recovered/Resolved with Sequelae	23 Jul 2021
20005	Landiolol	Sinus bradycardia	07 May 2021	Unlikely	None	Recovered/Resolved	07 May 2021
20005		Asystole	07 May 2021	Unlikely	None	Recovered/Resolved	07 May 2021
10006	Landiolol	Global severe impairment on echo.	02 Mar 2020	Possibly	None	Unknown	Unknown
07010	Landiolol	Transaminitis	31 Jan 2020	Unlikely	None	Unknown	12 Feb 2020
07010		GI Bleed	31 Jan 2020	Unlikely	None	Unknown	12 Feb 2020
38002	Landiolol	Constipation	11 Dec 2019	Unlikely	None	Recovered/Resolved	12 Dec 2019
38002		Diarrhoea	07 Dec 2019	Unlikely	None	Recovered/Resolved	11 Dec 2019
38002		Bilateral pleural effusion	27 Nov 2019	Unlikely	None	Unknown	19 Dec 2019
38002		Edema Trunk/general	26 Nov 2019	Unlikely	None	Unknown	19 Dec 2019
38002		Limbs Edema	23 Nov 2019	Unlikely	None	Unknown	19 Dec 2019
38002		Malabsorption	22 Nov 2019	Unlikely	None	Unknown	19 Dec 2019
38002		Abdominal Distension	21 Nov 2019	Unlikely	None	Recovered/Resolved	27 Nov 2019
38002		Ileus	21 Nov 2019	Unlikely	None	Recovered/Resolved	27 Nov 2019
38002		Acute Kidney Injury	21 Nov 2019	Unlikely	None	Recovered/Resolved with Sequelae	19 Dec 2019
38002		Pericardial effusion	20 Nov 2019	Unrelated	None	Recovered/Resolved with Sequelae	11 Dec 2019

01011	Landiolol	New case of MRSA	08 Aug 2019	Unlikely	None	Unknown	Unknown
01011		Patient developed nosebleed early morning requiring blood transfusion with Hb dropping to 63.	04 Aug 2019	Unrelated	None	Recovered/Resolved	07 Aug 2019
01011		Post-op continuous bleeding from arm requiring return to theatre.	15 Jul 2019	Unlikely	None	Recovered/Resolved with Sequelae	20 Jul 2019
01011		AKI with ongoing Sepsis. Septic picture with increasing noradrenaline requirements. Creatinine increase.	14 Jul 2019	Unlikely	None	Recovered/Resolved	16 Aug 2019
07006	Landiolol	Decreased Liver Function	31 May 2019	Possibly	None	Unknown	20 Jun 2019
07006		Paroxysmal SVT	31 May 2019	Unlikely	None	Recovered/Resolved	01 Jun 2019
07006		Diabetes Insipidus	29 May 2019	Unlikely	None	Unknown	20 Jun 2019
07006		Deranged Clotting; INR 4.2	29 May 2019	Unlikely	None	Recovered/Resolved	02 Jun 2019
07006		Splenoportal venous thrombosis	28 May 2019	Unlikely	None	Unknown	20 Jun 2019
07006		Right pneumothorax	26 May 2019	Unlikely	None	Recovered/Resolved	06 Jun 2019
02005	Landiolol	T Wave inversion on ECG	28 Feb 2019	Unlikely	None	Recovered/Resolved	01 Mar 2019
05001	Landiolol	Alkalosis	20 Jan 2019	Unrelated	None	Recovered/Resolved	23 Jan 2019
05001		Diarrhoea	18 Jan 2019	Unrelated	None	Recovered/Resolved	20 Jan 2019
05001		Hypocalcaemia	17 Jan 2019	Unrelated	None	Recovered/Resolved	17 Jan 2019
05001		Increase to Alkaline Phosphatase	17 Jan 2019	Unrelated	None	Recovered/Resolved	26 Jan 2019
05001		Hypermagnesemia	15 Jan 2019	Unrelated	None	Recovered/Resolved	16 Jan 2019
05001		Hypokalaemia	15 Jan 2019	Unrelated	None	Recovered/Resolved	15 Jan 2019
05001		Genital edema	14 Jan 2019	Unrelated	None	Recovered/Resolved	17 Jan 2019
05001		Hypernatremia	13 Jan 2019	Unrelated	None	Recovered/Resolved	21 Jan 2019
05001		Hypoglycaemia	12 Jan 2019	Unrelated	None	Recovered/Resolved	12 Jan 2019
05001		Hypoalbuminemia	11 Jan 2019	Unrelated	None	Recovered/Resolved	10 Feb 2019
05001		Vascular Access Complication	11 Jan 2019	Unrelated	None	Recovered/Resolved	12 Jan 2019

05001		Hypoglycaemia	11 Jan 2019	Unrelated	None	Recovered/Resolved	11 Jan 2019
05001		Rash	10 Jan 2019	Unrelated	None	Recovered/Resolved	16 Jan 2019
05001		Alkalosis	10 Jan 2019	Unrelated	None	Recovered/Resolved	18 Jan 2019
05001		Anaemia	09 Jan 2019	Unrelated	None	Recovered/Resolved	11 Jan 2019
05001		Dry Eye	08 Jan 2019	Unrelated	None	Recovered/Resolved	16 Jan 2019
05001		Hypercalcaemia	08 Jan 2019	Unrelated	None	Recovered/Resolved	12 Jan 2019
05001		Acidosis	08 Jan 2019	Unrelated	None	Recovered/Resolved	10 Jan 2019
05001		Alkalosis	07 Jan 2019	Unrelated	None	Recovered/Resolved	08 Jan 2019
05001		Hypothermia	07 Jan 2019	Unrelated	None	Recovered/Resolved	07 Jan 2019
05001		Hypokalaemia	07 Jan 2019	Unrelated	None	Recovered/Resolved	07 Jan 2019
05001		Extravasation (of CT Contrast)	06 Jan 2019	Unrelated	None	Recovered/Resolved	13 Jan 2019
05001		Anaemia	06 Jan 2019	Unrelated	None	Recovered/Resolved	07 Jan 2019
05001		Hypoglycaemia	06 Jan 2019	Unrelated	None	Recovered/Resolved	07 Jan 2019
05001		Acidosis	06 Jan 2019	Unrelated	None	Recovered/Resolved	06 Jan 2019
05001		Hypermagnesemia	06 Jan 2019	Unrelated	None	Recovered/Resolved	07 Jan 2019
05001		Fever	05 Jan 2019	Unrelated	None	Recovered/Resolved	08 Jan 2019
05001		Hyperglycaemia	05 Jan 2019	Unrelated	None	Recovered/Resolved	10 Jan 2019
02003	Landiolol	Pyrexia	05 Aug 2018	Unrelated	None	Recovered/Resolved	13 Aug 2018
14003	Standard care	Exploratory Laparotomy	11 Feb 2020	Unrelated	None	Unknown	11 Feb 2020
14003		2nd look Laparotomy	09 Feb 2020	Unrelated	None	Unknown	09 Feb 2020
14003	Standard care	Purulent fluid in pelvis - abdomen washout.	30 Jan 2020	Unrelated	None	Unknown	30 Jan 2020
14003		Turbid fluid in abdomen, Infarcted omentum.	28 Jan 2020	Unrelated	None	Unknown	Unknown
07009	Standard care	Deep vein thrombus right internal jugular vein.	17 Jan 2020	Unrelated	None	Unknown	26 Jan 2020

07009		Atrial fibrillation	15 Jan 2020	Unrelated	None	Recovered/Resolved	15 Jan 2020
07009		Sinus bradycardia	13 Jan 2020	Unrelated	None	Recovered/Resolved	17 Jan 2020
07009		Clostridium difficile PCR positive	13 Jan 2020	Unrelated	None	Unknown	26 Jan 2020
07009		Left Pneumothorax	09 Jan 2020	Unrelated	None	Recovered/Resolved	09 Jan 2020
07009		Duodenal ulcer	09 Jan 2020	Unrelated	None	Fatal	26 Jan 2020
07009		Proximal right leg deep vein thrombus	07 Jan 2020	Unrelated	None	Unknown	26 Jan 2020
38001	Standard care	Bradycardia	26 Sep 2019	Unrelated	None	Recovered/Resolved	26 Sep 2019
38001		Anaemia	25 Sep 2019	Unrelated	None	Unknown	28 Sep 2019
38001		Bradycardia	23 Sep 2019	Unrelated	None	Recovered/Resolved	23 Sep 2019
38001		Bradycardia	22 Sep 2019	Unrelated	None	Recovered/Resolved	22 Sep 2019
38001		Anaemia	22 Sep 2019	Unrelated	None	Unknown	25 Sep 2019
38001		Bradycardia	20 Sep 2019	Unrelated	None	Recovered/Resolved	20 Sep 2019
38001		Anaemia	20 Sep 2019	Unrelated	None	Unknown	21 Sep 2019
38001		Anaemia	19 Sep 2019	Unrelated	None	Unknown	20 Sep 2019
38001		Anaemia	18 Sep 2019	Unrelated	None	Unknown	18 Sep 2019
38001		Anaemia	17 Sep 2019	Unrelated	None	Unknown	17 Sep 2019
38001		Anaemia	15 Sep 2019	Unrelated	None	Unknown	16 Sep 2019
38001		ECG changes TWI leads II, III, aVF, V2-3 Trop sent, cardiology review.	13 Sep 2019	Unrelated	None	Recovered/Resolved	13 Sep 2019
38001		Anaemia	11 Sep 2019	Unrelated	None	Unknown	15 Sep 2019
14002	Standard care	Seizure	12 Jul 2019	Unrelated	None	Recovered/Resolved	12 Jul 2019
01010	Standard care	Following discharge to ward, patient got out of bed during night and fell. Reported as confused.	30 Apr 2019	Unrelated	None	Recovered/Resolved	30 Apr 2019
19001	Standard care	Cardiac arrest	11 Mar 2019	Unrelated	Treatment adjustment	Recovered/Resolved with Sequelae	11 Mar 2019

19001	Standard care	Thrombocytosis	24 Feb 2019	Unrelated	Treatment adjustment	Recovered/Resolved	10 Mar 2019
19001		Pleural effusions	19 Feb 2019	Unrelated	Treatment adjustment	Recovered/Resolved with Sequelae	19 Feb 2019
19001		Atrial Fibrillation	18 Feb 2019	Unrelated	None	Recovered/Resolved	20 Feb 2019
19001		Moderate Left ventricular failure	18 Feb 2019	Unrelated	None	Unknown	18 Feb 2019
19001		Sepsis induced cardiomyopathy	18 Feb 2019	Unrelated	Treatment adjustment	Recovered/Resolved	22 Feb 2019
19001		Atrial Flutter	16 Feb 2019	Unrelated	None	Recovered/Resolved	17 Feb 2019
19001		Supraventricular Tachycardia	16 Feb 2019	Unrelated	None	Recovered/Resolved	16 Feb 2019
05002	Standard care	Diarrhoea	07 Feb 2019	Unrelated	None	Recovered/Resolved	06 Mar 2019
05002		Vomiting	07 Feb 2019	Unrelated	None	Recovered/Resolved	07 Feb 2019
05002		Platelet count decreased	06 Feb 2019	Unrelated	None	Recovered/Resolved	14 Feb 2019
05002		Alk phos increase	06 Feb 2019	Unrelated	None	Recovered/Resolved	24 Feb 2019
05002		Alanine aminotransferase increased.	06 Feb 2019	Unrelated	None	Recovered/Resolved	18 Feb 2019
05002		Blood bilirubin increased	06 Feb 2019	Unrelated	None	Recovered/Resolved	09 Feb 2019
05002		Activated partial thromboplastin time prolonged.	06 Feb 2019	Unrelated	None	Recovered/Resolved	07 Feb 2019
05002		Hypophosphatemia	06 Feb 2019	Unrelated	None	Recovered/Resolved	07 Feb 2019
05002		Acidosis	05 Feb 2019	Unrelated	None	Recovered/Resolved	05 Feb 2019
05002		Hypocalcaemia	05 Feb 2019	Unrelated	None	Recovered/Resolved	05 Feb 2019
05002		Fever	05 Feb 2019	Unrelated	None	Recovered/Resolved	05 Feb 2019
07003	Standard care	Atrial fibrillation	12 Aug 2018	Unrelated	None	Recovered/Resolved	12 Aug 2018
07003		Left pneumothorax	10 Aug 2018	Unrelated	None	Recovered/Resolved	12 Aug 2018

eTable 12: Protocol deviations

There have been 58 protocol deviations.

Number of protocol deviations occurring at sites	Number of protocol deviations occurring at Warwick/other
55	3

Deviation	Number of protocol deviations
Inclusion/Exclusion Criteria Deviation	0
Trial procedure not performed per protocol	29
Visit not performed within window	4
Informed Consent Deviation	0
Non-Compliance	20
Treatment Randomization Error	0
Other	5
TOTAL	**58**

eTable 13: Details of protocol deviations

Patient ID (Treatment arm)	**Date of deviation**	Comments
01020 (Landiolol)	27-Jun-21 and 28-Jun-2021	Patient randomised 26/06/2021 at 19:17. Blood samples were not taken for this patient on Day 1 (27/06/2021) and Day 2 (28/06/2021) due to uncertainty amongst the team regarding the eligibility of the patient and whether they should remain in the study or be withdrawn. Due to COVID deployment it was one of the first patients enrolled after a long break from the trial this contributed to a lack of familiarity.
01020 (Landiolol)	26-Jun-21	The patient's medical records were updated to confirm the eligibility criteria was met. After 24 hours passed since start of vasopressor therapy treatment, the research nurse reviewed the patient's medical records remotely via PICS away from bed space to confirm the patient met all of the eligibility criteria including receiving >24 - <72 hours vasopressor therapy (noradrenaline) treatment at 0.63 mcg/kg/min based on weight of 101 kg with a heart rate of 96bpm. The research nurse proceeded to randomise the patient at 19:17 after reviewing the patient's medical record details as stated above with the latest available heart rate recorded at 18:01 – 96 bpm. When the research nurse attended critical care at approximately 19:30 to start Landiolol administration it was noted the patient's heart rate was below 80bpm therefore, Landiolol could not be administered as per protocol. It was discovered when entering the baseline data on the trial database on 27/06/2021 the patient's heart rate was 82 bpm at 19:10. The observations have been backfilled meaning the research nurse did not see this reported on the patients' electronic records prior to randomisation. ICU nursing staff were informed to start Landiolol if heart rate increases to greater than 95bpm. 29/06/2021 patients heart rate <95 bpm therefore, Landiolol treatment was not given. Heart rate did increase Days 5-7 and 13-14 however the team has deemed this due to failed sedation hold and ventilation weaning. Landiolol was not administered. The research nurse team were also slightly delayed in randomising the patient due to difficulties in locating their IVR pin number for randomisation and dialling the correct IVR randomisation telephone line due to an additional incorrect number stated in the randomisation line on the Trial Participant Checklist.
25003 (Landiolol)	29-May-21 and 01-Jun-2021	Patient randomised on 26/05/2021. Blood samples were not obtained for Days 2, 4 (30/05/2021), 6 (01/06/2021) and EONT (29/05/2021). The trial team experienced great difficulty with obtaining Days 0 and 1 samples and the patient subsequently lost vascular access resulting in being unable to take Day 2 samples. The subsequent samples were not taken as no research nurse staff were available to take bloods over the bank holiday weekend. The reason for this is due to staff capacity as the team are operating at 50% reduced capacity and back-up staff have been involved in COVID vaccine trials over the weekend.
25003 (Landiolol)	26-May-2021	Baseline bloods were obtained (with some difficulty after trying several lines) at approximately 14:05. It was decided then to attempt and insert new vascular access in order to monitor vital signs and administer medication including the Landiolol. However, despite prolonged efforts, this was not achieved and to avoid causing further distress to the patient it was decided to stop and try again the following day (27/05/2021) when eventually a line was established at approximately 10:00.

		This only last for about 24 hours and following a delay of about 10 hours a 3rd line was inserted later on 28/05/2021. This also meant it was not possible to obtain Day 2 blood samples. Several peripheral cannulas had been inserted over this period and all were short-lived. The patient was not sedated but was confused, which is why the decision was made to not persist with access attempts. Her noradrenaline requirements decreased, and she was discharged to the hospital ward.
20005 (Landiolol)	05-May-21	The patient had experienced a prolonged period of haemodynamic instability, probably related to a new episode of sepsis. The patient was already receiving maximum dose of inotropes (vasopressin and noradrenaline). A decision was made to stop Landiolol to assess its impact on haemodynamics. After stopping Landiolol the blood pressure increased and so did the heart rate. A decision was made to restart Landiolol, albeit with caution at lower to avoid further episodes of haemodynamic instability.
32001 (Landiolol)	20-May-19	Identified through blood sampling checks following shipment to Birmingham lab. Day 1 bloods taken 3 hours early on 21/05/2019 and Day 2 bloods taken 3 hours early at 09:30 when Day 1 starts 12:20. Duplicate plasmas samples were taken on Day 2 and incorrectly labelled EONT as EONT refers to when noradrenaline has been stopped for more than 12 hours, not when noradrenaline has been initially stopped which the site misunderstood. A Pax Gene RNA sample was also not taken.
26002 (Landiolol)	18-Dec-20	Heart Rate at the time of randomisation was 87bpm. For the patient to be eligible the heart rate must be >95bpm. However, the site have confirmed this discrepancy is due to the time taken to ring the IVR randomisation line. The site confirmed the patient had a persistent sepsis driven tachycardia before the IVR was dialled and it was greater than 95bpm.
26003 (Landiolol)	02-Mar-20	The doctor who signed off the eligibility form was not signed off by the PI on the delegation log prior to completing the eligibility assessment. The site has confirmed the doctor was trained on the trial and the PI will countersign the eligibility form to confirm they are happy they were adequately trained. Root cause is due to time constraint to randomise the patient and PI availability.
26003 (Landiolol)	19-Jan-21	The doctor who signed off the eligibility form was not signed off by the PI on the delegation log prior to completing the eligibility assessment. The site has confirmed the doctor was trained on the trial and the PI will countersign the eligibility form to confirm they are happy they were adequately trained. Root cause is due to time constraint to randomise the patient and PI availability.
26002 (Landiolol)	18-Dec-20	The incorrect version of the eligibility form was used for patient. The site has subsequently confirmed the patient meets all of the eligibility criteria for the current updated version of the eligibility form. Further to this the doctor who signed off the eligibility form was not signed off by the PI on the delegation log prior to completing the eligibility assessment. The site has confirmed the doctor was trained on the trial and the PI will countersign the eligibility form to confirm they are happy they were adequately trained. Root cause is due to time constraint to randomise the patient and PI availability.

03001 (Landiolol)	20-May-2019	Incorrect Pax gene collected for EONT, should have been Pax gene RNA but Pax gene DNA collected in error. Error realised when arranging for blood sample collection. CTU informed. Staff retrained on blood collection and protocol deviation completed.
12003 (Landiolol)	03-Feb-20	Patient received Landiolol at rate of 1mcg/kg/min. After 15 mins infusion was titrated and patient remained tachycardic. Then required line insertion and positional change. He became unstable and dropped his blood pressure significantly following these interventions. BP around 50 at lowest. Landiolol stopped whilst unstable. BP improved and Landiolol restarted. BP then dropped again and Landiolol was stopped after 5 minutes. Clinical team did not restart a thought it was comprising the patient's blood pressure too much.
03004 (Landiolol)	01-Nov-19	The Landiolol infusion was stopped prematurely as the patient deteriorated (severe infection / multi organ failure). The patient was taken for a CT scan of their abdomen to identify an area to treat. But no surgical interventions were required. The patient required maximum cardiac and respiratory support and the family were informed that the patient was showing no signs of improvement and was not expected to survive. At this point a DNACPR was placed on the patient and comfort care started
38002 (Landiolol)	25-Nov-19	Metoprolol administered 25/11/2019 – 28/11/2019 Research nurse confirmed via email to STRESS-L trial team, Metoprolol was administered as the patient's Heart Rate was increased to 117bpm as the patient experienced a sinus tachycardia. Metoprolol settled the patient's heart rate to a sinus rhythm.
38002 (Landiolol)	21-Nov-19	The Landiolol infusion has been stopped prematurely as the patient was deteriorating. CI and PI agreed this event does not need to be reported as a SAE or AE.
25002 (Landiolol)	06-Nov-19	Infusion started and up-titrated as per protocol. Patient's MAP subsequently started to fall & noradrenaline requirements increased considerably. Reviewed throughout by PI and given bolus doses of fluid and changes made to sedatives to try and maintain MAP with no success. Decision made to trial temporary stop of Landiolol infusion after approx. 3 hours. Noradrenaline requirements more than halved in the minutes after stopping infusion and decision made to not restart.
21001 (Landiolol)	11-Sep-19	EONT bloods not taken as noradrenaline discontinued out of hours at the weekend so no staff available to take and process the samples.
09001 (Landiolol)	23-Aug-19	Site did not take EONT bloods on morning of 24/08/2019 as research nurse staff off sick. Site took bloods on 27/08/2019 (Day 6) as instructed by the CI.
05001 (Landiolol)	14-Jun-19	Site sent completed SAE follow up form following initial SAE event Myocardial Infarction for TNO 05001 on 14th June 2019. It was identified by the Trial Manager that patient had exceeded their 90 day follow up date (05 April 2019) therefore, data collection for this patient after this date should cease. This was not initially identified due to an oversight by the WCTU Trial team. All copies of the SAE follow up form have been deleted and CAPA is pending.

19004 (Landiolol)	04-Jun-19	Clinical team made a decision to stop the Landiolol infusion at 05:30am due to worsening metabolic status, worsening urine output and increasing vasopressor requirements. Landiolol weaned over 30 mins, vasopressors titrated down and off by 6.30am. Peripheral perfusion reported to improve and urine output improving in the hour.
11002 (Landiolol)	13-Mar-19	Routine central monitoring checks revealed between the hours of T+3h – T+37h (Days 1-2) for patient, the patient's HR was >94bpm but the Landiolol was no increased and stopped completely at T+16h whilst the patient remained tachycardic. PI emailed the trial team to confirm the patient was very unstable on significant doses of vasopressors (including noradrenaline and vasopressin) and blood pressure appeared to be even more liable when the nursing team tried to increase the dose of Landiolol. On Day 2, the treating clinician and team decided to stop Landiolol as continuing the treatment would have been futile as the patient was deteriorating despite maximal organ support (email correspondence attached).
01006 (Landiolol)	28-Nov-18	Upon routine central monitoring, it was discovered the eligibility form was signed by a research nurse at site who has not been delegated the responsibility of eligibility on the delegation log. Furthermore, as per MHRA guidance for CTIMP's, the decision whether a subject is eligible for entry into the clinical trial is considered to be a medical decision and therefore, must be made by a delegated medically qualified doctor. Site confirmed doctor has reviewed and signed off eligibility in patient notes.
01008 (Landiolol)	07-Jan-19	Upon routine central monitoring, it was discovered the eligibility form was signed by a research nurse at site who has not been delegated the responsibility of eligibility on the delegation log. Furthermore, as per MHRA guidance for CTIMP's, the decision whether a subject is eligible for entry into the clinical trial is considered to be a medical decision and therefore, must be made by a delegated medically qualified doctor. Site confirmed doctor has reviewed and signed off eligibility in patient notes.
15001 (Landiolol)	10-Dec-18	Upon routine central monitoring, it was discovered eligibility form for patient was signed by a research nurse at site who has not been delegated the responsibility of eligibility on the delegation log. Furthermore, as per MHRA guidance for CTIMP's, the decision whether a subject is eligible for entry into the clinical trial is considered to be a medical decision and therefore, must be made by a delegated medically qualified doctor. Site confirmed doctor has reviewed and signed off eligibility in patient notes.
11002 (Landiolol)	13-Mar-19	Research site did not take Day 0 bloods at baseline timepoint. Misinformed by Trial Manager in February regarding when Day 0 bloods should be taken. Site has retained bloods and they have been allocated as Day 1 bloods.
12001 (Landiolol)	02-Dec-18	Site: Lab lead - unable to process blood samples for Day 2 and EONT

07004 (Landiolol)	07-Oct-18	Site: - EONT occurred out of office hours. A study protocol seems unclear to me if EONT visit performs at 12hrs and/or onwards following day. No clinical trial management team over the weekend to enquire. So, EONT blood samples was taken on 07/10/18 and processed. - 09/10/18 at 15.00pm, Trial manager confirmed EONT falls in Day2, so blood sample is not required. The sample was discarded as per local policy today.
13001 (Landiolol)	02-Oct-18	Site: Day 1 study bloods taken outside of protocol time point (taken on 04/10/2018)
01004 (Landiolol)	03-Aug-18	Site: Patient randomised into intervention arm. On assessing the next day the patient had deteriorated and required increase in the trial medication. However, we were unable to follow protocol in changing the rate every 15 mins due to the need for the treating medics working on the patient. Later that day it was decided to reduce the trial infusion with a view to stopping the infusion as the patient was now moribund and treatment was failing. P.I. and C.I. informed
02001 (Landiolol)	20-Apr-18	Site: Landiolol not administered as initially the patient had no free central access. Once central access was achieved and confirmed safe to use the patients' heart rate was consistently below 95 bpm and the clinical team took the decision not to administer the Landiolol.
15001 (Landiolol)	10-Dec-18	Site: Landiolol stopped due to Adverse Event
07001 02001 01001 02003 01004 13001 07004 01006 12001 16001 (Landiolol)	04-Dec-18	Dec 2018 TMG report contained data regarding patient's Landiolol treatment for listed TNO's. This may have caused potential bias during the discussion with the TMG as TNO's are also included in the protocol deviation and serious adverse events section. The two SAE's reported to date are related to patients randomised to the control arm therefore, this eliminates the bias regarding safety reporting.
23005 (Standard care)	28-Jan-21	Patient received Bisoprolol 2.5mg at 11am, restart of regular medication. Bisoprolol was given as an IV infusion of amiodarone was due to be stopped and Bisoprolol was given. This was given following a medical decision.
01018 (Standard care)	03-Jan-21	The STRESS-L Protocol states patients enrolled in the trial should not receive any beta blockade other than Landiolol (intervention arm only) for the duration of their ICU stay. However, if the treating clinician deems beta blockade necessary, this will be reported as a protocol deviation to the trial team. The patient was randomised to the Standard Arm of the STRESS-L study on the 30th December 2020. However, on the 3rd January 2021 (Day 5) he was commenced on Bisoprolol (1.25mg STAT dose, and 2.5mg OD moving forward). The

		prescription was stopped on the 4th January 2021, resulting in one stat dose of 1.25mg, and one regular prescription dose of 2.5mg being administered. The PI and CI were made aware of the deviation.
17003 (Standard care)	29-Oct-20	The doctor who signed off the eligibility form was not listed on the trial delegation log. PI has countersigned the eligibility form to confirm the doctor was adequately trained to perform the eligibility assessment. Site to confirm root cause. Predicted this is due to capacity strain on site.
26001 (Standard care)	02-Mar-20	Heart Rate at the time of randomisation was 89bpm. For the patient to be eligible the heart rate must be >95bpm. However, the site have confirmed this discrepancy is due to the time taken to ring the IVR randomisation line. The site confirmed the patient had a persistent sepsis driven tachycardia before the IVR was dialled and it was greater than 95bpm.
01018 (Standard care)	03-Jan-2021	The patient was randomised to the Standard Arm of the STRESS-L study on the 30th December 2020 and treating clinician made aware of need to refrain from beta-blockade in line with study protocol. However, on the 3rd January 2021(Day 5) the patient was commenced on Bisoprolol (1.25mg STAT dose, and 2.5mg OD moving forward). The prescription was stopped on the 4th January 2021, resulting in one stat dose of 1.25mg, and one regular prescription dose of 2.5mg being administered. CI and PI made aware
17003 (Standard care)	22-Oct-20	Patient given metoprolol at 22:00 22-oct-2020 and 06:00 23-oct-2020. Stopped by PI as soon as it was seen. Prescribing consultant reminded by PI of the need not to give beta blockers in the 14 days and to use amiodarone instead.
42002 (Standard care)	27-Feb-20	PI omitted to take a baseline 12 lead ECG. Patient randomised on to standard treatment only. Informed sponsor the next day, advised to take and ECG - done.
09002 (Standard care)	08-Feb-20 10-Feb-20	Patient was randomised Friday 07/02/2020 at 17:11 - Baseline samples taken on 07/02/20 at 18:30 - Day 1 samples taken on 08/02/20 at 17:30 - Day 2 samples/ EONT samples taken today 10/02/20 at 10:45 We understood day 0 as up to 24h after randomisation and day 1 the following day. That means day 1 samples have been taken 19min out of window time and day 2 15h out of window time.
14003 (Standard care)	27-Jan-20	Baseline bloods were not taken due to the time of randomisation
14003 (Standard care)	02-Feb-20	Noradrenaline stopped at 14:00 on 31 Jan 2020. EONT samples obtained on the morning of 02.02.2020. This was because we were not expecting patient to stop noradrenaline as soon as she did and ICU did not inform us that this had happened.
16002 (Standard care)	12-Jan-20	Sunday 12 Jan 2020 Day 0 bloods missed/not taken. No research cover at the time. Apologies for this oversight.

23003 (Standard care)	10-Dec-19	Noradrenaline stopped on 10/12/19 at 12 noon, EONT bloods taken at 14:30hrs. Stress L trial team informed that these bloods were taken sooner than the protocol demands. Stress L team advised site to retake EONT bloods again. Bloods were retaken on 11/12/19 at 15:13 hrs
38001 (Standard care)	11-Sep-19	Day 0 research bloods performed post randomisation. Patient randomised 09:24 and bloods taken 10:05 Day 0 Central Venous ECG not performed at requested time prior to randomisation. Completed by research team at 15:50 and 16:04 on 11/09/2019
23001 (Standard care)	20-May-19	Patient, end of Noradrenaline treatment bloods not taken as per protocol. P.I spoke to CI, advised by CI to carry on outside of protocol and take the missed end of Noradrenaline bloods.
19001 (Standard care)	17-Feb-19	Bisoprolol given to treat AF, prescribed by a SHO who was unaware of the trial procedures.
01007 (Standard care)	11-Dec-218	Upon routine central monitoring, it was discovered the eligibility form was signed by a research nurse at site who has not been delegated the responsibility of eligibility on the delegation log. Furthermore, as per MHRA guidance for CTIMP's, the decision whether a subject is eligible for entry into the clinical trial is considered to be a medical decision and therefore, must be made by a delegated medically qualified doctor. Site confirmed doctor has reviewed and signed off eligibility in patient notes.
11001 (Standard care)	27-Oct-18	Upon routine central monitoring, it was discovered the randomisation form for patient was signed off by a member of staff who is not listed on the delegation log to perform this task.
01007 (Standard care)	11-Dec-18	Patient was randomised into the STRESS-L study on the 11th December 2018. They were randomised to the Standard Treatment Arm. The patient was admitted to hospital following poly trauma from RTC. However, Bisoprolol was prescribed, and one dose was given. The drug was then subsequently paused. Patient data continues to be collected. Spoke to ITU consultant later who advised that the drug was given for agitation.
07003 (Standard care)	06-Dec-18	Baseline ECG not done on the 06th of December 2018 prior to IMP infusion. Informed Sponsor. Reminded research team members regarding trial procedures as per protocol.
01005 (Standard care)	28-Nov-18	Site: The patient was admitted to the hospital for an AVR, MV and TV annuloplasty operation. Following surgery he was admitted to ITU. He has had a 12-month history of cardiac problems including being prescribed Beta Blockers. However, up to randomisation he had not had these for 6 days, in line with protocol. Since recruitment, as the patient improved, he developed AF again. The decision was made by treating team to restart his Bisoprolol.
04001 (Standard care)	03-Jul-18	Site: Patient heart rate increased to 169 and then 180 b/min and patient went to AF. Bolus of metoprolol given to control the rate at 07:17 and subsequently amiodarone infusion started at 09:00.

N/A[a]	08-Oct-20	STRESS-L database access was accidentally granted by the CTU trial team for 2 members of staff at an investigator site prior them being signed off by the PI on the trial delegation log.
N/A[a]	01-Feb-21	Unable to perform daily IMP temperature monitoring checks on ICU due to COVID-19. Instead will perform weekly checks by downloading the temperature logger data which records the temperature every 10 minutes. Pharmacy unwilling to take back ICU IMP currently due to risk of infection. IMP fridge also found unlocked while research nurse was on annual leave. Research nurse has now moved the key to the IMP fridge to her research office for safe keeping whilst the site is paused to screening due to COVID-19.
N/A[a]	21-Apr-19	Research Nurse found the IMP fridge stored on ICU to be unlocked for an unconfirmed amount of time resulting in an internal breach to the security of storing the study drug. The IMP storage box was opened on receipt in ICU and checked to ensure 20 vials were present, then it was locked in the fridge by the research nurses. However, it was discovered the fridge has been unlocked with the door leading to the room where the fridge is stored being unlocked too. Therefore, visitors to the department could have potentially entered the room and access the IMP fridge. This could have potentially impacted on patient safety if the IMP was tampered with or IMP stock was to go missing resulting in no accountable trace for the stock.
N/A[a]	29-Jun-18	Thermometer from inside of ICU research drug fridge was removed by someone outside of research team resulting in continuous temperature recordings being missing for 24 hours.
N/A[a]	23-May-18	Mawdsleys (UK Drug Distributor) removed the labelled secondary packaging from batch of 120 vials and placed them inside of another unlabelled brown box inside of a validated shipping box to ship to three sites. This a deviation from Annex 13 of EU Guidelines to Good Manufacturing Practice. The secondary packaging was removed inside of a fridge; thus, no temperature deviation occurred. Mawdsleys will send original secondary packaging to sites to repack vials inside of alongside process of adjustment form for sites to sign to confirm this has been completed. QP to release batch once they have received the signed documentation. Mawdsleys carried out internal investigation and retrained staff on procedures. Reig Jofre and AOP aware of incident.
[a] they were not directly patient related, i.e., some of the deviations/violations were in relation to IMP issues		

eTable 14: Protocol violations

There have been 14 protocol violations.

Number of Protocol Deviations occurring at sites	Number of Protocol Deviations occurring at Warwick/Other
14	0

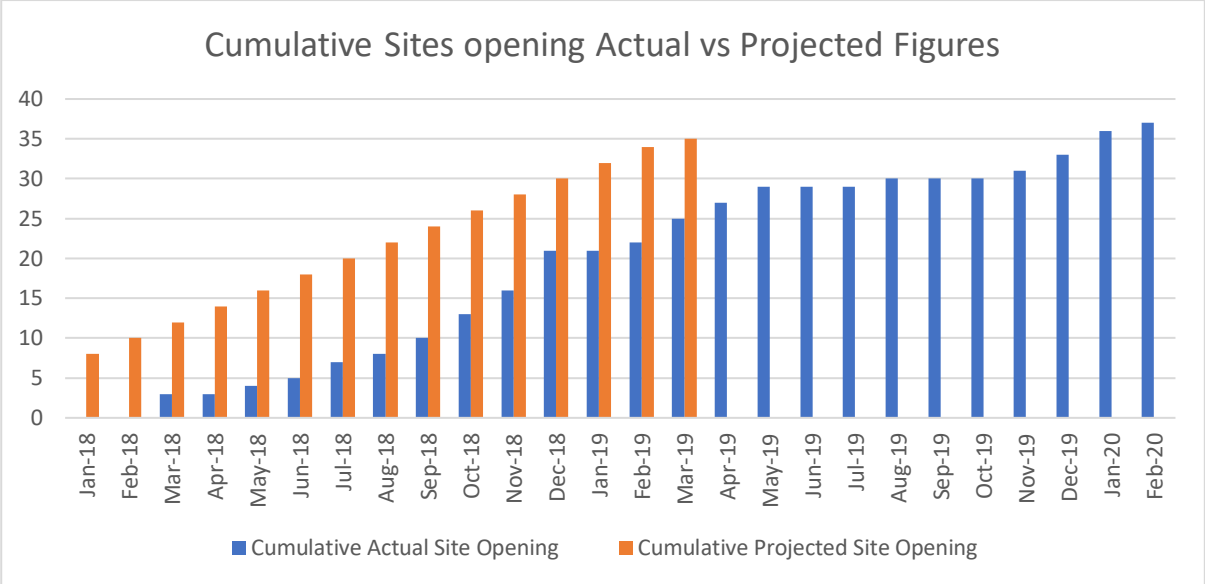
eTable 15: Details of Protocol Violations

Patient ID and Treatment arm	Date of violation	Comments
23006 (Landiolol)	21-Feb-20	Principal Investigator sent through a series of documents for patient in an email attachment to the STRESS-L team containing the consent form which included the patient's first name and surname. Warwick CTU do not have ethical permission to hold any patient identifiable data. All data received should be anonymised.
20003 (Landiolol)	31-Aug-19	Heart-rate < 80 bpm from 18:00 on 31/08/19 until SAE on 01/09/2019 at 06:45. Landiolol continued at 1mcg/kg/min during this time and not stopped as per bedside guidelines. Lowest heart-rate during this period (prior to SAE) 72 bpm. Bedside nurses failed to turn off Landiolol during 12 hour period.
09001 (Landiolol)	21-Aug-19	Site incorrectly stepped up Landiolol dose for TNO 09001 from 10 to 20 mcg/kg/min resulted in a higher dose than required being administered. CI and PI confirmed there are no patient safety concerns. Site also abruptly stopped Landiolol treatment on 24/08/2019 as they did not retrieve more stock from pharmacy on Friday (23/08/2019) and research nurse off sick; therefore, bedside nurses turned off Landiolol at 14:00. Site incorrectly adjusted weight from 90kg to 70 kg resulted in a period of time where Landiolol was given for the wrong weight; thus incorrect dosing.
05001 (Landiolol)	08-Jan-19	Patient randomised to the trial on 05/01/2019 had their eligibility form and Professional Legal Representative consent form signed off by the same ICU Consultant. Training slides have been revised by WCTU to clarify the responsibilities of ICU staff who are not on the delegation log and staff who are listed with responsibilities E, F, or K.
12001 (Landiolol)	30-Nov-18	Upon routine central monitoring, it was discovered an eligibility form was signed by a research nurse at site who has not been delegated the responsibility of eligibility on the delegation log. Furthermore, as per MHRA guidance for CTIMP's, the decision whether a subject is eligible for entry into the clinical trial is considered to be a medical decision and therefore, must be made by a delegated medically qualified doctor. Site were unaware a medic must assess eligibility and follow up actions have been put in place to rectify this incident.
12001 (Landiolol)	01-Dec-18	Randomised patient had a heart rate of less than 80 all night. Bedside nursing staff only reduced the infusion rate once. Protocol states HR should be monitored every 15 minutes to achieve a target HR of 80-94bpm and should be reduced once HR is below 80bpm. Event deemed safe and research nurse will ensure further training is provided to ICU nurses.
02007 (Landiolol)	09-Mar-19	Patient was randomised to receive Landiolol + Standard Care on 08/03/2019. At T+28h the heart rate fell to 79 bpm, however Landiolol dose was not reduced. For the next 14 hours the heart rate consistently dropped below 80 bpm, but the Landiolol dose was kept at 1 mcg/kg/min. This was due to a misunderstanding by the bedside nurses overnight, who believed that the Landiolol couldn't be switched off until vasopressors and noradrenaline treatment had finished. The wording of the current protocol contributed to this misunderstanding as it states: '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'.

15003 (Landiolol)	16-Feb-19	Patient dose of Landiolol exceeded the maximum 40 mcg/kg/min as per protocol at the following times: - T+17h = 44 mcg/kg/min - T+18-44h = 47 mcg/kg/min - T+45-48h = 46 mcg/kg/min These doses were received through the night. The dosing error was made largely due to confusion about the units of the running rate, which the bedside care team had mistakenly identified as mcg/kg/min, when in fact it was in ml/h. The confusion was also caused as the paper CRF requests for the Landiolol infusion in ml/hr as this was not changed to mcg/kg/min due to an oversight by the trial team.
39002 (Standard care)	06-Feb-20	Patient randomised to the trial with a Heart Rate of 84bpm. Patient not eligible.
38001 (Standard care)	22-Sep-19	EONT blood samples collected by PP at 09:15 am on the 20/09/2019- documented in participant notes and sample log as participant was off Noradrenaline since 15h 19/09/2019.However, the Nor-adrenaline was subsequently restarted at 15:30h 20/09/2019 and the weekend team collected further (2nd set) EONT samples on the 22/09/2019.
08001	15-May-19	Overnight the bedside nurse titrated the Landiolol infusion by one Millilitre increments instead of by Micrograms/kg/min. It should have gone up from 11.2ml/hr, 12.0ml/hr 12.8ml, 13.6ml/hr, 14.4ml/hr. Instead in ran as follows: 11.2ml/hr, 12.2ml/hr, 13.2ml/hr 14.4ml/hr. The bedside nurse had misread the Landiolol Infusion Flowchart instead of reading Increase Landiolol infusion by 1.0 mcg/kg/min. They had read it as Increase Landiolol by 1.0 ml/min
01008	07-Jan-19	Patient randomised using new eligibility criteria (extension of vasopressor window to 72 hours) prior to local R&D approval being in place. Research nurses aware of error and all future amendments will be sent directly to R&D and research nurses will not be copied in until amendment has been locally approved.
N/A[a]	07-Feb-20	Research Nurse accidentally sent through an excel spreadsheet containing a list of patients randomised which included the patient's first and surname. Warwick CTU do not have ethical permission to hold any patient identifiable data. All data should be anonymised.
N/A[a]	18-May-19	Upon quarantine of ambient IMP batch 1804_1 in pharmacy for destruction and transition to refrigerated IMP, it was discovered that two vials of 1804_1 were unaccountable.

[a]Not related to a single patient.

eFigure 6: Cumulative site opening over the course of the study



eTable 16: Site recruitment

Sites	Date opened to recruitment	Number of recruits
Queen Elizabeth University Hospital Birmingham	28/03/18	22
Heartlands Hospital	29/03/18	8
Royal Victoria Hospital, Belfast	04/05/18	4
Charing Cross Hospital	14/06/18	2
St Marys Hospital	14/06/18	2
Hammersmith Hospital	14/06/18	0
University College London Hospital	28/03/18	12
Nottingham University Hospitals NHS Trust	04/09/18	2
Guys and St Thomas' NHS Foundation Trust	27/12/18	2
Musgrove Park Hospital	10/07/18	7
Sunderland Royal Hospital	27/11/18	3
Bristol Royal Infirmary	13/08/18	3
Dorset Country Hospital NHS Foundation Trust	06/09/18	6
Royal Cornwall Hospital NHS Trust	05/10/18	2
University Hospitals Plymouth NHS Trust	12/10/18	3
QAH, Portsmouth Hospital NHS Trust	19/11/18	6
Royal Liverpool University Hospital	20/12/18	7
Kings College London Hospital	19/12/18	2
Russells Hall Hospital	13/03/19	6
Royal Free Hospital	19/12/18	1
UHCW NHS Trust	12/03/19	3
Brighton and Sussex University Hospital	20/01/20	3
Royal Victoria Infirmary, Newcastle	28/02/20	0
Leeds Teaching Hospital NHS Foundation Trust	01/03/19	1
York Teaching Hospital NHS Foundation Trust	02/05/19	1
Rotherham NHS Foundation Trust	15/04/19	1
Cambridge University Hospitals NHS Foundation Trust, Addenbrookes	29/08/19	2
Northampton General Hospital	04/12/19	2
Aberdeen Royal Infirmary Hospital	15/11/19	4
Hull University Teaching Hospital	05/12/2019	0
St George's University Hospital	20/01/2020	0
Craigavon Hospital	11/02/19	0
Queen Elizabeth Hospital, Glasgow	29/01/2020	0

eTable 17: Sites closed to recruitment during the course of STRESS-L

Sites	Date opened to recruitment	Date closed to recruitment	Number of recruits
Peterborough Hospital	21/12/18	07/10/2019	0
Poole Hospital	05/10/2018	26/08/2020	0
Kings Mill Hospital	10/07/18	16/06/2021	5
Royal Devon & Exeter NHS Foundation Trust	13/12/18	07/06/2021	3
Buckinghamshire Hospital	01/05/19	26/08/2020	0
Lister Hospital	26/11/2019	07/05/2021	0
Warwick Hospital	01/04/21	12/10/2020	1

eTable 18: Screening (pre-randomization)

Flow of patients from screening to randomization summarized by site

Site	Total Screened	Eligible patients of those screened		Eligible but not randomized of those eligible		Informed Consent obtained and Randomized Patients of those eligible	
		Number	%	Number	%	Number	%
01 - UHB	446	44	10	22	50	22	50
02 - Heartlands Hospital	188	26	14	18	69	8	31
03 - Belfast	289	18	6	14	78	4	22
04 - St Mary's	303	10	3	8	80	2	20
05 - Charing Cross	130	9	7	7	78	2	22
06 - Hammersmith Hospital	168	2	1	2	100	0	0
7 - UCL	292	26	9	14	54	12	46
08 - Nottingham	203	13	6	11	85	2	15
09 - Guy's & St Thomas'	194	4	2	2	50	2	50
10 - Musgrove Park	114	34	30	27	79	7	21
11 - King's Mill	37	10	27	5	50	5	50
12 - Sunderland Royal	23	6	26	3	50	3	50
13 -Bristol Royal Infirmary	281	12	4	9	75	3	25
14 - Royal Devon & Exeter	13	5	38	2	40	3	60
15 - Dorset County Hospital	61	6	10	0	0	6	100
16 - Royal Cornwall	38	6	16	4	67	2	33
17 - Plymouth	58	5	9	2	40	3	60
18 - Poole	142	8	6	8	100	0	0
19 - Portsmouth	198	25	13	19	76	6	24
20 - Royal Liverpool	239	18	8	11	61	7	39
21 - King's College London	36	5	14	3	60	2	40
22 - Lister Hospital	0	0	0	0	0	0	0
23- Russells Hall	71	13	18	7	54	6	46
24 - Royal Free	129	1	1	0	0	1	100
25 - UHCW	22	3	14	0	0	3	100
26 – Brighton	46	4	9	1	25	3	75
28 - Warwick Hospital	27	4	15	3	75	1	25

29 - Peterborough Hospital	24	0	0	0	0	0	0
30 - Craigavon	31	0	0	0	0	0	0
32 - Leeds	205	10	5	9	90	1	10
33 - Royal Victoria Infirmary	0	0	0	0	0	0	0
35- York	16	5	31	4	80	1	20
36 - Buckinghamshire	9	0	0	0	0	0	0
37 - Rotherham	4	3	75	2	67	1	33
38 - Addenbrookes	39	2	5	0	0	2	100
39 - Northampton	2	2	100	0	0	2	100
42 - Aberdeen	35	7	20	3	43	4	57
43 - QE, Glasgow	3	0	0	0	0	0	0
44 - Hull Royal Infirmary	15	1	7	1	100	0	0
45 - St George's	6	1	17	1	100	0	0
TOTALS:	**4137**	**348**		**222**		**126**	

*Eligible patients of those screened – includes patients recruited, screening failure reasons 18, 21, 23, 24, 25, 26, 27, 29 (code below) and OTHER reasons where patient would have been clinically eligible but not randomized e.g. missed/staff cover, IMP issue, withdrawal of care/futile treatment, issues with consent etc.

Screening failure reason code
18 = Patient / legal representative unwilling to provide written informed consent
19 = Known to be pregnant
20 = Terminal illness other than septic shock with a life expectancy < 28 days
21 = Participants who have participated in another research trial involving an investigational medicinal product in the past 30 days
22 = Patients in whom the clinical team feel are about to finish their noradrenaline therapy
23 = Unable to contact Personal Legal Representative
24 = Unable to identify Professional Legal Representative
25 = Patient Declined (specify reason above, if provided)
26 = Personal Legal Representative Declined (specify reason above, if provided)
27 = Professional Legal Representative Declined (specify reason)
28 = Other (specify reason above)
29 = Excluded due to co-enrolment issue (specify trial name(s))

eTable 19: Top 10 reasons for non-enrolment (by site) into STRESS-L

Site No	Yes	No	Screened	1	2	3	4	5	6	7	8	9	10
01 - UHB	22	424	446	31 (7)	21 (5)	34 (8)	36 (8)	21 (5)	62 (15)	0 (0)	14 (3)	16 (4)	9 (2)
02 - Heartlands Hospital	8	180	188	17 (9)	22 (12)	23 (13)	21 (12)	8 (4)	14 (8)	3 (2)	6 (3)	0 (0)	3 (2)
03 - Belfast	4	285	289	12 (4)	20 (7)	26 (9)	11 (4)	12 (4)	4 (1)	17 (6)	11 (4)	1 (0)	4 (1)
04 - St Mary's	2	301	303	12 (4)	21 (7)	6 (2)	12 (4)	7 (2)	9 (3)	0 (0)	2 (1)	3 (1)	2 (1)
05 - Charing Cross	2	128	130	9 (7)	6 (5)	10 (8)	3 (2)	1 (1)	6 (5)	1 (1)	0 (0)	3 (2)	0 (0)
06 - Hammersmith Hospital	0	168	168	6 (4)	18 (11)	4 (2)	11 (7)	8 (5)	4 (2)	2 (1)	2 (1)	4 (2)	1 (1)
7 - UCL	12	280	292	36 (13)	3 (1)	16 (6)	6 (2)	25 (9)	4 (1)	6 (2)	5 (2)	30 (11)	8 (3)
08 - Nottingham	2	201	203	15 (7)	42 (21)	11 (5)	22 (11)	5 (2)	2 (1)	1 (0)	7 (3)	4 (2)	3 (1)
09 - Guy's & St Thomas'	2	192	194	48 (25)	24 (13)	14 (7)	27 (14)	15 (8)	3 (2)	1 (1)	5 (3)	4 (2)	4 (2)
10 - Musgrove Park	7	107	114	14 (13)	5 (5)	11 (10)	0 (0)	2 (2)	3 (3)	1 (1)	3 (3)	2 (2)	2 (2)
11 - King's Mill	5	32	37	3 (9)	3 (9)	5 (16)	1 (3)	0 (0)	0 (0)	1 (3)	1 (3)	3 (9)	0 (0)
12 - Sunderland Royal	3	20	23	8 (40)	0 (0)	0 (0)	2 (10)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (10)
13 -Bristol Royal Infirmary	3	278	281	35 (13)	31 (11)	9 (3)	13 (5)	23 (8)	10 (4)	4 (1)	17 (6)	4 (1)	6 (2)
14 - Royal Devon & Exeter	3	10	13	0 (0)	1 (10)	2 (20)	1 (10)	1 (10)	0 (0)	1 (10)	0 (0)	0 (0)	0 (0)
15 - Dorset County Hospital	6	55	61	6 (11)	8 (15)	9 (16)	0 (0)	0 (0)	4 (7)	5 (9)	5 (9)	3 (5)	1 (2)
16 - Royal Cornwall	2	36	38	6 (17)	0 (0)	4 (11)	3 (8)	1 (3)	1 (3)	4 (11)	1 (3)	0 (0)	4 (11)
17 - Plymouth	3	55	58	7 (13)	1 (2)	2 (4)	0 (0)	5 (9)	1 (2)	6 (11)	4 (7)	0 (0)	2 (4)
18 - Poole	0	142	142	14 (10)	21 (15)	7 (5)	2 (1)	12 (8)	4 (3)	7 (5)	4 (3)	1 (1)	2 (1)
19 - Portsmouth	6	192	198	53 (28)	5 (3)	33 (17)	2 (1)	9 (5)	5 (3)	12 (6)	1 (1)	12 (6)	7 (4)
20 - Royal Liverpool	7	232	239	79 (34)	24 (10)	40 (17)	3 (1)	6 (3)	5 (2)	6 (3)	14 (6)	0 (0)	9 (4)
21 - King's College London	2	34	36	4 (12)	0 (0)	2 (6)	14 (41)	2 (6)	3 (9)	0 (0)	0 (0)	0 (0)	0 (0)
22 - Lister Hospital	0	0	0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
23- Russells Hall	6	65	71	5 (8)	6 (9)	4 (6)	2 (3)	8 (12)	1 (2)	5 (8)	7 (11)	1 (2)	3 (5)
24 - Royal Free	1	128	129	33 (26)	13 (10)	3 (2)	2 (2)	12 (9)	25 (20)	2 (2)	13 (10)	7 (5)	0 (0)
25 - UHCW	3	19	22	1 (5)	1 (5)	4 (21)	2 (11)	2 (11)	2 (11)	1 (5)	0 (0)	0 (0)	1 (5)
26 – Brighton	3	43	46	8 (19)	13 (30)	3 (7)	2 (5)	2 (5)	0 (0)	5 (12)	2 (5)	0 (0)	1 (2)

28 - Warwick Hospital	1	26	27	3 (12)	6 (23)	8 (31)	3 (12)	3 (12)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
29 - Peterborough Hospital	0	24	24	2 (8)	2 (8)	1 (4)	1 (4)	0 (0)	0 (0)	1 (4)	0 (0)	1 (4)	0 (0)
30 - Craigavon	0	31	31	10 (32)	1 (3)	0 (0)	4 (13)	1 (3)	2 (6)	4 (13)	1 (3)	0 (0)	1 (3)
32 - Leeds	1	204	205	99 (49)	3 (1)	13 (6)	3 (1)	6 (3)	9 (4)	9 (4)	3 (1)	8 (4)	11 (5)
33 - Royal Victoria Infirmary	0	0	0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
35- York	1	15	16	6 (40)	4 (27)	4 (27)	2 (13)	2 (13)	3 (20)	0 (0)	2 (13)	0 (0)	0 (0)
36 - Buckinghamshire	0	9	9	3 (33)	0 (0)	1 (11)	0 (0)	3 (33)	1 (11)	0 (0)	1 (11)	0 (0)	0 (0)
37 - Rotherham	1	3	4	0 (0)	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (33)
38 - Addenbrookes	2	37	39	6 (16)	9 (24)	0 (0)	2 (5)	3 (8)	0 (0)	9 (24)	1 (3)	0 (0)	0 (0)
39 - Northampton	2	0	2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
42 - Aberdeen	4	31	35	7 (23)	0 (0)	1 (3)	0 (0)	3 (10)	2 (6)	1 (3)	3 (10)	1 (3)	3 (10)
43 - QE, Glasgow	0	3	3	1 (0)	0 (0)	0 (0)	1 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)
44 - Hull Royal Infirmary	0	15	15	3 (20)	2 (13)	4 (27)	1 (7)	0 (0)	0 (0)	0 (0)	1 (7)	0 (0)	3 (20)
45 - St George's	0	6	6	0 (0)	0 (0)	1 (17)	1 (17)	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	0 (0)
TOTALS	**126**	**4011**	**4137**	**602**	**336**	**316**	**216**	**208**	**191**	**115**	**136**	**108**	**93**

Non-enrolment reason code
1- Heart rate <95 bpm 24 to 72 hours after start of vasopressor therapy
2 - Heart rate never >95bpm
3 – Other
4 - >72 hours in the current cause of septic shock after start of vasopressor therapy
5 - Are being treated with noradrenaline at a rate 0.05 - 0.09mcg/kg/min
6 - Advanced liver disease with Child-Pugh Score of ≥B
7 - Heart rate <95 bpm 18 to 24 hours after start of vasopressor therapy
8 - Are being treated with noradrenaline at a rate <0.05mcg/kg/min
9 - Terminal illness other than septic shock with a life expectancy < 28 days
10 - Decision of withdrawal of care is in place or imminently anticipated