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A randomised trial to assess whether the addition of a beta blocker infusion (landiolol) to standard treatment in patients with septic shock, requiring prolonged (>24 hours) support with high-dose vasopressor agents, improves organ failure (the STRESS-L trial)

Submission date
04/12/2017

Recruitment status
No longer recruiting

Registration date
18/12/2017

Overall study status
Completed

Last Edited
29/01/2025

Condition category
Infections and Infestations

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English Summary
Background and study aims
Septic shock (blood poisoning) is a life-threatening condition caused by severe infection. For reasons still poorly understood, in some patients, their immune system remains excessively activated. Instead of fighting the infection, an ongoing inflammatory state results in widespread injury and failure of normal functioning of the body's vital organs, such as the lungs, heart, brain and kidneys. A hallmark of septic shock is a very low blood pressure that does not improve with an intravenous fluid drip. Despite huge research efforts over the last 20-30 years the survival rate has remained stubbornly unchanged. Outcomes have improved for sepsis in general through earlier recognition and intervention with antibiotics, however once septic shock takes hold, the risk of dying remains very high. This research project wants to see if infusing a very short-acting beta-blocker in addition to standard treatment improves organ failure in patients with septic shock. Beta-blockers are widely used to counteract the stressful long-term actions of the hormones adrenaline and noradrenaline, for example in high blood pressure, chronic heart failure, abnormally fast heart rates and cardiac rhythms, and tremor. Recently, an Italian group gave a beta-blocker to reduce, and then maintain, heart rates of patients with septic shock at between 80-95 beats per minute. They found this treatment strategy to be safe and associated with improvements in survival and reduced time in intensive care. However, their study was relatively small and recruitment occurred at a single centre so did not provide enough information to make the use of beta-blockers a mainstream recommendation. This trial aims to repeat the Rome study in approximately 35 ICUs in the UK to see if the safety and benefits that were seen can be confirmed and will also investigate the way in which beta blockers act in septic shock patients.

Who can participate?
Adults aged 18 and older who are have septic shock.

What does the study involve?
Participants are randomly allocated to one of two groups. Those in the first group receive the usual care. Those in the second group receive the usual care with the addition of landiolol. For participants in the landiolol group, the rate of the drug is adjusted until their heart rate is controlled at 80-95 beats per minute and the infusion is stopped when they are able to control their heart rate themselves. Landiolol is given intravenously (IV) as an infusion whilst a participant's heart rate is too high. This drug may be used for up to 2 weeks within the ICU where the treating team are able to monitor the participant closely. After discharge from ICU, or if the heart rate remains high after 14 days, ongoing treatment will be the decision of the treating doctor. One of the aims of this study is to better understand the biological mechanisms that are altered by beta-blockade in septic shock. As part of standard clinical care blood will be taken from a cannula (a thin tube inserted into a vein or body cavity to administer medication). Additional blood samples will be taken at study entry, on days 0, 1, 2, 4 and 6 and at the end of noradrenaline treatment (if not a sampling day). Routinely collected clinical data will be recorded for the trial. However the progress of participants will be followed at day 28 and day 90 after trial entry, at these time points the local research team will call the participant and their GP to find out how they are. The trial will not follow participants beyond 90 days.

What are the possible benefits and risks of participating?
As landiolol is an exceptionally short-acting drug, switching off the infusion is expected to reverse any possible side effects. Beta blockers are not confirmed to be useful in septic shock and it is possible that landiolol has the potential for toxicity. Full information on the possible side effects are available on request from local treating teams. The main risks are the heart could go too slowly or blood pressure could lower if a participant is sensitive to the drug. Trial participants will be closely monitored within the ICU and should they experience any side effects from the study drug, the hospital staff will take measures to stop the infusion as with any other inpatient treatment.

Where is the study run from?
This study is being run by Warwick Clinical Trials Unit (University of Warwick) and takes place in hospitals in the UK.

When is the study starting and how long is it expected to run for?
June 2017 to October 2023.

Who is funding the study?
National Institute for Health Research (UK)

Who is the main contact?
STRESS-L@warwick.ac.uk

Study website
http://www2.warwick.ac.uk/fac/med/research/hscience/ctu/trials/stressl

Contact information

Type(s)
Scientific

Contact name
Dr Study Team

Contact details
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United Kingdom
CV4 7AL
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Additional identifiers

EudraCT/CTIS number
2017-001785-14

IRAS number
213669

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 35229

Study information

Scientific Title
STudy into the REversal of Septic Shock with Landiolol (Beta Blockade)

Acronym
STRESS-L

Study hypothesis
A reduction in heart rate using landiolol infusion in patients with septic shock and tachycardia improves organ failure during the 14 days after the patient is started in the trial. This study is investigate whether the changes are through a reduction in cardiac and immune dysfunction.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 09/11/2017, East of England – Essex Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, United Kingdom; +44 207 104 8107; NRESCommittee.EastofEngland-Essex@nhs.net), ref: 17/EE/0368

Study design

Randomised; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet STRESS-L@warwick.ac.uk

Condition
Septic shock

Interventions
Current interventions as of 28/02/2019:
Participants are randomised to receive standard treatment with the addition of a beta blocker infusion (landiolol) or standard treatment alone.

For those in the landiolol group, the rate of drug are adjusted until the heart rate is controlled between 80-94 beats per minute. Landiolol may be used for up to 14 days within the ICU. Follow up continues for up to 90 days following randomisation.

One of the aims of this study is to better understand the biological mechanisms that are altered by beta-blockade in septic shock. As part of standard clinical care blood will be taken from a cannula (a thin tube inserted into a vein or body cavity to administer medication). Additional blood samples will be taken at study entry, on days 0, 1, 2, 4 and 6 and at the end of noradrenaline treatment (if not a sampling day). These samples will be sent to University of Birmingham and University Hospitals Birmingham NHS Foundation Trust and will be used in laboratory research to help define the mechanisms involved in treating sepsis with beta blockade. These samples will be destroyed once analysis has been completed.

Routinely collected clinical data will be recorded for the trial. However the progress of participants will be followed at day 28 and day 90 after trial entry, at these time points the local research team will call the participant and their GP to find out how they are. The trial will not follow participants beyond 90 days.

Previous interventions:
Participants are randomised to receive standard treatment with the addition of a beta blocker infusion (landiolol) or standard treatment alone.

For those in the landiolol group, the rate of drug are adjusted until the heart rate is controlled between 80-94 beats per minute. Landiolol may be used for up to 14 days within the ICU. Follow up continues for up to 90 days following randomisation.

One of the aims of this study is to better understand the biological mechanisms that are altered by beta-blockade in septic shock. As part of standard clinical care blood will be taken from a cannula (a thin tube inserted into a vein or body cavity to administer medication). Additional blood samples will be taken at study entry, on days 1, 2, 4 and 6 and at the end of noradrenaline treatment (if not a sampling day). These samples will be sent to University Hospitals Birmingham NHS Foundation Trust and will be used in laboratory research to help define the mechanisms involved in treating sepsis with beta blockade. These samples will be destroyed once analysis has been completed.

Routinely collected clinical data will be recorded for the trial. However the progress of participants will be followed at day 28 and day 90 after trial entry, at these time points the local research team will call the participant and their GP to find out how they are. The trial will not follow participants beyond 90 days.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Landiolol

Primary outcome measure
Organ failure is measured using the mean SOFA score over the first 14 days from entry to the trial and whilst in ICU. Measurement of the SOFA score will cease if the patient dies or is discharged from the ICU.

Secondary outcome measures
Current secondary outcome measures as of 12/11/2019:
1. Mortality is measured using patient records and telephone visits at day 28 and day 90
2. Length of ICU and hospital stay are measured using patient notes up to 90 days
3. Reduction in dose and duration of vasopressor treatment is measured using patient notes for up to 14 days following randomisation

Exploratory Outcome Measures:
4. Myocardial dysfunction and inflammation are measured using assays on blood samples taken on days 0, 1, 2, 4, 6 and the End of Noradrenaline Treatment Visit

Previous secondary outcome measures:
1. Mortality is measured using patient records and telephone visits at day 28 and day 90
2. Length of ICU and hospital stay are measured using patient notes up to 90 days
3. Individual organ failure-days in 28 day survivors is measured using medical tests (recording SOFA score parameters - oxygenation, renal, hepatic and coagulation function) at day 28
4. Reduction in dose and duration of vasopressor treatment (total doses of adrenaline, dobutamine, phosphodiesterase inhibitors) is measured using patient notes for up to 14 days following randomisation
5. Cardiovascular safety outcomes are measured using hospital notes for the first 14 days

Exploratory Outcome Measures:
6. Myocardial dysfunction and inflammation are measured using assays on blood samples taken on days 0, 1, 2, 4, 6 and the End of Noradrenaline Treatment Visit

Overall study start date
01/06/2017

Overall study end date
05/10/2023

Eligibility

Participant inclusion criteria
Current inclusion criteria as of 14/08/2020:
1. Aged 18 years or above
2. Being treated on an ICU
3. Septic shock according to internationally accepted definitions*
4. Heart rate ≥95 bpm (at the time of randomisation)
5. Receiving vasopressor support to maintain a target blood pressure for ≥24 hours
6. Are being treated with noradrenaline at a rate ≥ 0.1 mcg/kg/min

*Sepsis -3 definitions:
1. Confirmed or suspected infection requiring antibiotic therapy
2. New organ dysfunction, as evidenced by an increase in SOFA score ≥2
3. A blood lactate >2 mmol/l at any point during shock resuscitation
4. 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.

Previous inclusion criteria from 28/02/2019 to 14/08/2020:
1. Male or female aged 18 years or above
2. Being treated on an ICU
3. Septic shock according to internationally accepted definitions*
4. Heart rate ≥95 bpm (24 hours after start of vasopressor therapy)
5. Receiving vasopressor support to maintain a target blood pressure for ≥24 hours
6. Are being treated with noradrenaline at a rate ≥ 0.1 mcg/kg/min

*Sepsis -3 definitions:
1. Confirmed or suspected infection requiring antibiotic therapy
2. New organ dysfunction, as evidenced by an increase in SOFA score ≥2
3. A blood lactate >2 mmol/l at any point during shock resuscitation
4. 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.

Previous inclusion criteria:
1. Male or female aged 18 years or above
2. Being treated on an ICU
3. Septic shock according to internationally accepted definitions*
4. Heart rate ≥95 bpm (24 hours after start of vasopressor therapy)

5. Receiving vasopressor support with noradrenaline to maintain a target blood pressure for ≥24 hours
6. Are being treated with noradrenaline at a rate ≥ 0.1 mcg/kg/min

*Sepsis -3 definitions:
1. Confirmed or suspected infection requiring antibiotic therapy
2. New organ dysfunction, as evidenced by an increase in SOFA score ≥2
3. A blood lactate >2 mmol/l at any point during shock resuscitation
4. 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

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 340; UK Sample Size: 340

Participant exclusion criteria
Current exclusion criteria as of 14/08/2020:
1. Tachycardia as a result of pain, discomfort from medical devices (including endotracheal tubes), during interventions or other patient distress
2. Any form of vasodilatory shock that is not caused by sepsis
3. Noradrenaline infusion <0.1mcg/kg/min
4. >72 hours after start of vasopressor therapy
5. <12 hours since noradrenaline to treat a medical condition after than septic shock stopped
6. Having pre-existing severe cardiac dysfunction (NYHA grade 4 or more)
7. Having pre-existing severe pulmonary hypertension (mean PA pressures > 55mmHg)
8. Acute severe bronchospasm (due to asthma or COPD)
9. Untreated second or third-degree heart block
10. Untreated phaeochromocytoma
11. Prinzmetal's angina
12. A past history of ischaemic stroke or transient ischaemic attack (TIA) or untreated severe carotid stenosis.
13. Advanced liver disease with Child-Pugh Score of ≥B.
14. Known sensitivity to beta-blockers
15. Patient/legal representative unwilling to provide written informed consent
16. Known to be pregnant
17. Terminal illness other than septic shock with a life expectancy < 28 days
18. Participants who have been administered an investigational medicinal product for another

research trial in the past 30 days
19. Patients in whom the clinical team feel are about to finish their noradrenaline therapy
20. Receiving extracorporeal membrane oxygenation (ECMO) treatment

Previous exclusion criteria from 12/11/2019 to 14/08/2020:
1. Any form of compensatory tachycardia
2. Any form of vasodilatory shock that is not caused by sepsis
3. Noradrenaline infusion <0.1mcg/kg/min
4. >72 hours in the current cause of septic shock after start of vasopressor therapy
5. Having pre-existing severe cardiac dysfunction (NYHA grade 4 or more)
6. Having pre-existing severe pulmonary hypertension (mean PA pressures > 55mmHg)
7. Acute severe bronchospasm (due to asthma or COPD)
8. Untreated second or third degree heart block
9. Untreated phaeochromocytoma
10. Prinzmetal's angina
11. A past history of ischaemic stroke or transient ischaemic attack (TIA) or untreated
12. Severe carotid stenosis.
13. Advanced liver disease with Child-Pugh Score of ≥B.
14. Known sensitivity to beta-blockers
15. Patient/legal representative unwilling to provide written informed consent
16. Known to be pregnant
17. Terminal illness other than septic shock with a life expectancy < 28 days
18. Participants who have been administered an investigational medicinal product for
19. Another research trial in the past 30 days
20. Patients in whom the clinical team feel are about to finish their noradrenaline
21. Therapy
22. Decision of withdrawal of care is in place or imminently anticipated

Previous exclusion criteria as of 28/02/2019:
1. Noradrenaline infusion < 0.1mcg/kg/min
2. > 72 hours after start of vasopressor therapy
3. Having pre-existing severe cardiac dysfunction (NYHA grade 4 or more)
4. Having pre-existing severe pulmonary hypertension (mean PA pressures > 55mmHg)
5. Acute severe bronchospasm (due to asthma or COPD)
6. Untreated second or third degree heart block
7. Untreated phaeochromocytoma
8. Prinzmetal's angina
9. A past history of ischaemic stroke or transient ischaemic attack (TIA) or untreated severe carotid stenosis.
10. Advanced liver disease with Child-Pugh Score of ≥B
11. Having been treated with any beta-blocker drug in the seventy two hours prior to screening.
12. Known sensitivity to beta-blockers
13. Patient/legal representative unwilling to provide written informed consent
14. Known to be pregnant
15. Terminal illness other than septic shock with a life expectancy < 28 days
16. Participants who have been administered an investigational medicinal product for another research trial in the past 30 days.
17. Patients in whom the clinical team feel are about to finish their noradrenaline therapy

Previous exclusion criteria:
1. Noradrenaline infusion < 0.1mcg/kg/min
2. > 48 hours after start of vasopressor therapy

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

Recruitment start date
10/01/2018

Recruitment end date
25/09/2021

Locations

Countries of recruitment
England

Northern Ireland

Scotland

United Kingdom

Study participating centre
Queen Elizabeth Hospital
University Hospitals Birmingham NHS Foundation Trust
Trust HQ, PO Box 9551
Birmingham
United Kingdom
B15 2TH

Study participating centre
University College London Hospital
University College London Hospitals NHS Foundation Trust
250 Euston Road

London
United Kingdom
NW1 2PG

Study participating centre
Heartlands Hospital
UHB NHS Foundation Trust
Bordesley Green East
Birmingham
United Kingdom
B9 5SS

Study participating centre
Royal Victoria Hospital
Belfast Health & Social Care Trust
Grosvenor Road
Belfast
United Kingdom
BT12 6BA

Study participating centre
St. Mary's Hospital
Imperial College Healthcare NHS Trust
Praed Street
London
United Kingdom
W2 1NY

Study participating centre
Charing Cross Hospital
Imperial College Healthcare NHS Trust
Fulham Palace Rd
Hammersmith
London
United Kingdom
W6 8RF

Study participating centre
Hammersmith Hospital
Imperial College Healthcare NHS Trust
Du Cane Road

London
United Kingdom
W12 0HS

Study participating centre
Musgrove Park Hospital
Taunton & Somerset NHS Foundation Trust
Parkfield Drive
Taunton
United Kingdom
TA1 5DA

Study participating centre
King's Mill Hospital
Sherwood Forest Hospitals NHS Foundation Trust
Mansfield Road
Sutton in Ashfield
United Kingdom
NG17 4JL

Study participating centre
Bristol Royal Infirmary
University Hospitals Bristol NHS Foundation Trust
Upper Maudlin Street
Bristol
United Kingdom
BS2 8HW

Study participating centre
Queen's Medical Centre
Nottingham University Hospitals NHS Trust
Derby Road
Nottingham
United Kingdom
NG7 2UH

Study participating centre
Dorset County Hospital
Dorset County Hospital NHS Foundation Trust
Williams Ave
Dorchester

United Kingdom
DT1 2JY

Study participating centre
Royal Cornwall Hospital
Royal Cornwall Hospitals NHS Trust
Treliske
Truro
United Kingdom
TR1 3LJ

Study participating centre
Poole Hospital
Poole Hospital NHS Foundation Trust
Longfleet Road
Poole
United Kingdom
BH15 2JB

Study participating centre
Derriford Hospital
Derriford Road
Crownhill
Plymouth
United Kingdom
PL6 8DH

Study participating centre
Queen Alexandra Hospital
Portsmouth Hospitals NHS Trust
Cosham
Portsmouth
United Kingdom
PO6 3LY

Study participating centre
St Thomas' Hospital
Guy’s and St Thomas’ NHS Foundation Trust
Westminster Bridge Rd
Lambeth
London

United Kingdom
SE1 7EH

Study participating centre
Sunderland Royal Hospital
South Tyneside and Sunderland NHS Foundation Trust
Kayll Rd
Sunderland
United Kingdom
SR4 7TP

Study participating centre
Royal Devon & Exeter Hospital
Royal Devon & Exeter NHS Foundation Trust
Barrack Rd
Exeter
United Kingdom
EX2 5DW

Study participating centre
King's College Hospital
King's College Hospital NHS Foundation Trust
Denmark Hill
Brixton
London
United Kingdom
SE5 9RS

Study participating centre
Royal Free Hospital
Royal Free London NHS Foundation Trust
Pond St
Hampstead
London
United Kingdom
NW3 2QG

Study participating centre
Royal Liverpool Hospital
Royal Liverpool and Broadgreen University Hospitals NHS Trust
Prescot St

Liverpool
United Kingdom
L7 8XP

Study participating centre
Craigavon Area Hospital
Southern Health and Social Care Trust
68 Lurgan Rd
Portadown
Craigavon
United Kingdom
BT63 5QQ

Study participating centre
Leeds General Infirmary
Leeds Teaching Hospitals NHS Trust
Great George St
Leeds
United Kingdom
LS1 3EX

Study participating centre
Russells Hall Hospital
The Dudley Group NHS Foundation Trust
Russells Hall
Pensnett Rd
Dudley
United Kingdom
DY1 2HQ

Study participating centre
University Hospitals Coventry and Warwickshire
University Hospitals Coventry and Warwickshire NHS Trust
Clifford Bridge Rd
Coventry
United Kingdom
CV2 2DX

Study participating centre
Warwick Hospital
South Warwickshire NHS Foundation Trust

Lakin Rd
Warwick
United Kingdom
CV34 5BW

Study participating centre
Rotherham General Hospital
The Rotherham NHS Foundation Trust
Moorgate Rd
Rotherham
United Kingdom
S60 2UD

Study participating centre
York Teaching Hospital
York Teaching Hospital NHS Foundation Trust
Freeman Rd
High Heaton
Newcastle upon Tyne
United Kingdom
NE7 7DN

Study participating centre
Stoke Mandeville Hospital
Buckinghamshire Healthcare NHS Trust
Mandeville Rd
Aylesbury
United Kingdom
HP21 8AL

Study participating centre
Addenbrooke's Hospital
Cambridge University Hospitals NHS Foundation Trust
Hills Rd
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
Aberdeen Royal Infirmary
NHS Grampian

Foresterhill Health Campus
Aberdeen
United Kingdom
AB25 2ZN

Study participating centre
Lister Hospital
East and North Hertfordshire NHS Trust
Coreys Mill Ln
Stevenage
United Kingdom
SG1 4AB

Study participating centre
Northampton General Hospital
Northampton General Hospital NHS Trust
Northampton General Hospital
Cliftonville
Northampton
United Kingdom
NN1 5BD

Study participating centre
Hull Royal Infirmary
Hull University Teaching Hosptials NHS Trust
Anlaby Rd
Hull
United Kingdom
HU3 2JZ

Study participating centre
Royal Sussex County Hospital
Brighton and Sussex University Hospitals NHS Trust
Barry Building
Eastern Rd
Brighton
United Kingdom
BN2 5BE

Study participating centre

St George's Hospital
St George’s University Hospitals NHS Foundation Trust
Cranmer Terrace
Tooting
London
United Kingdom
SW17 0RE

Study participating centre
Queen Elizabeth University Hospital Glasgow
NHS Greater Glasgow and Clyde
1345 Govan Rd
Glasgow
United Kingdom
G51 4TF

Study participating centre
Royal Victoria Infirmary
The Newcastle upon Tyne Hospitals NHS Foundation Trust
Queen Victoria Rd
Newcastle upon Tyne
United Kingdom
NE1 4LP

Sponsor information

Organisation
University Hospitals Birmingham NHS Foundation Trust

Sponsor details
Trust Headquaters
Po Box 9551
Queen Elizabeth Medical Centre
Edgbaston
Birmingham
England
United Kingdom
B15 2TH

Sponsor type
Hospital/treatment centre

ROR

https://ror.org/014ja3n03

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal. The Warwick Clinical Trials Unit will publish the results of the trial on their website when these are available.
https://warwick.ac.uk/fac/sci/med/research/ctu/trials/stressl/publications/ (added 14/09/2023)

Intention to publish date
31/10/2023

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from stress-l@warwick.ac.uk

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		16/02/2021	12/05/2021	Yes	No
HRA research			28/06		

summary			/2023	No	No
Results article		25/10 /2023	26/10 /2023	Yes	No
Other publications	Pre-planned sub-study of the effect of landiolol on inflammatory and metabolomic markers	22/01 /2025	29/01 /2025	Yes	No