STRESS-L TRIAL

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

CRF COMPLETION GUIDELINES
V3.0 06 July 2020
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1. General Instructions for CRF Completion

- All dates should be recorded in the format DD-MMM-YYYY format.
- Enter all times in the 24-hour format.
- Select ‘Yes’ or ‘No’ where applicable. Do not leave any Yes/No questions blank.
- When entering numerical values, ensure the correct unit is used. If decimal values are required but not known, enter 0 e.g. 92.0 kg.
- All CRFs must be completed, signed and dated by an appropriately trained member of staff who is listed on the Site Signature and Delegation Log with the relevant trial responsibilities.

General Remote Data Entry Instructions

- The Remote Data Entry (RDE) system is accessed by navigating to the STRESS-L database.
- To open the STRESS-L database, go to: https://ctu.warwick.ac.uk/StressL
- Sign in to the database by entering your user name and password (Figure 1.)
- eCRFs are accessed by clicking on the ‘Data Entry’ tab at the top left of the database and selecting either ‘Daily Data’, ‘Scheduled Events’ or ‘Unscheduled Events’ (Figure 2).
- To navigate to a participant, type in their participant trial number in the search bar and click enter (Figure 2). Please note – when switching between the ‘Daily Data’, ‘Scheduled Events’ or ‘Unscheduled Events’ pages, the participant trial number will reset. Participant trial number MUST be entered within the search tool each time you navigate to a new tab to ensure you are completing forms for the correct participant.
- When entering data in tables (Figure 3):
  - Click the plus symbol (+) to add a new record.
  - Click the delete symbol (−) to remove a record.
  - Use the arrow button to navigate between records.
- At the end of each form on the RDE system there is a Form Status field which can be used to categorise the information within the form (Figure 4). The default status is ‘Not Started’. Once data is entered into the form, one of three statuses must be selected:
  - If the form has been completed, all of the fields have been entered and there is no outstanding data, mark the form as ‘Clean’.
  - If the form has been completed but some data is unattainable, leave these fields blank and mark the form as ‘Clean with unattainable missing data’.
  - If the form is partially completed and you wish to save the form before exiting and returning to later, mark the form as ‘Incomplete’.

Paper CRF Instructions

- The Eligibility, Randomisation, End of Trial and Serious Adverse Event Forms should be completed using our paper CRFs. Please refer to the Data Transfer Working Instruction for guidance on how to send these to WCTU.
- If completing a paper CRF, participant initials and trial number should be recorded at the top of each page.
- Paper CRFs should be completed in black ball point pen.

Data Collection Time Point Guidelines

- Time 0 (or T0) = the time of randomisation
• Day 0 (or D0) is the baseline time period. This spans from 24 hours prior to the time of randomisation (T0) up until the time of randomisation. This is displayed on the Cardiovascular Form as -24hours to 0hours.
• Day 1 (or D1) spans from the time of randomisation up until 24hours post-randomisation.
• All subsequent days will commence in line with the time of randomisation and finish 24hours later.
• e.g. a patient is randomised at 15:00 on the 02nd January. This is T0.
  o Day 0 spans from 15:00 on the 1st January to 15:00 on the 2nd January.
  o Day 1 spans from T0, 15:00 on the 2nd January, to 15:00 on the 3rd January.
  o Day 2 spans from 15:00 on the 3rd January to 15:00 on the 4th January etc.
• Calendar days are **NOT** in use.

**Figure 1: Signing in to the STRESS-L Database**

![Sign in to STRESS-L Database](image-url)
Figure 2: Accessing the eCRFs (1.), navigating to a participant trial number (2.) and opening a form (3.)

Figure 3: Entering data in tables
2. IVR Randomisation

- This form should be completed on paper prior to randomisation.
- Trial arm allocation and participant trial number will be provided once the participant has been randomised.
- Randomisations will be carried out using an Interactive Voice Response (IVR) system:
  - Dial 02476 932036, enter your personal PIN provided to you and follow the automated instructions.
  - Answers to all questions will be facilitated through keypad entry.
- In the event of a system outage affecting the IVR system or loss of personal PIN, follow the emergency randomisation procedure:
  - Dial 02476 150402 and you will connect with a randomisation officer.
  - This line is operational 9am – 5pm, Monday to Friday.
  - It will not be possible to perform an emergency randomisation out of this time period.
- You will be guided through the randomisation procedure and the randomisation officer will provide you with a trial number and trial arm allocation.
- Provide the unique site number allocated to your site. This should be a two digit number e.g. 01.
- Provide ‘Yes’ or ‘No’ for the eligibility and consent questions. In order for the patient to be eligible for randomisation, the answers to these questions **MUST** be ‘Yes’.
- Provide the noradrenaline dose at time of randomisation. If this is exactly 0.3 mcg/kg/min, this will fall into the ≤0.3 mcg/kg/min category.
- After randomisation, this information should be entered retrospectively into the Participant Form on the RDE system (Figure 2).

**Allocation Details**

- Participant trial number and trial arm allocation will be provided at the end of randomisation. Please record this information on the paper form once provided. This will be prepopulated on the RDE system.
- Participant trial number will be comprised of the two digit site number followed by a unique three digit participant identifier. The participant identifier is allocated sequentially to participants.
- The participant will be randomised to either ‘Landiolol Plus Standard Treatment’ OR ‘Standard Treatment Only’.
- A confirmation email will be sent following randomisation to confirm allocation and participant trial number.
3. Scheduled Events

- Click on ‘Scheduled Events’ under the ‘Data Entry’ Tab (Figure 2.)
- Select a form by clicking the open button on the right side of the page (Figure 2.)

1. Confirmation of Eligibility Form

- This form acts as a checklist to confirm eligibility and a paper copy should be completed and signed by an authorised investigator prior to randomisation.
- Following randomisation, the Confirmation of Eligibility Form should be completed on the RDE system.

Inclusion Criteria

- Select ‘Yes’ or ‘No’ for all questions.
- In order for a patient to be eligible for the trial, all answers to the inclusion criteria must be ‘Yes’. If any answers are ‘No’, the patient is ineligible and should not be entered into the trial.

Exclusion Criteria

- Select ‘Yes’ or ‘No’ for all questions.
- In order for a patient to be eligible for the trial, all answers to the exclusion criteria must be ‘No’. If any answers are ‘Yes’, the patient is ineligible and should not be entered into the trial.

2. Participant Form

- This form documents information provided at randomisation and also the informed consent process.
- Randomising site, caller name and the IVR questions will be prepopulated on the system (Figure 5). The remaining information must be added following randomisation.
- Click the ‘Edit’ button in the bottom left of the window.

Caller and Site Information

- Specify your role on the trial using free text entry. This should match your role documented in the site signatures and delegation log e.g. Research Nurse, Principle Investigator etc.
- Include your extension number with your telephone number.
- Specify your professional email address, not a personal email.

Participant Details

- This information will have to be entered onto the STRESS-L database after randomisation.
- Provide the initials of the patient’s first/given name, middle name and surname. If the patient does not provide a middle initial, separate the first and last initial with a dash e.g. ABC or A-C.
- Select either Female or Male for gender.
- Enter the participant’s full date of birth in the format DD/MMM/YYYY.

Informed Consent

- Written informed consent must be in place prior to randomisation. After randomisation, this information should be entered retrospectively into the Participant Form on the RDE system (Figure 2).
- ‘Yes’ or ‘No’ should be selected for each consent type.
- Date of informed consent MUST be before or equal to date of randomisation.
• The participant or legal representative **MUST** initial to consent for collection of research blood samples as this is mandatory for the trial. It is optional to consent to ‘Storage and Use in Possible Future Research’. Either ‘No’ or ‘Yes’ can be selected.

**Figure 5: Participant Form**

3. **Baseline**

• This CRF should be completed on Day 1, after the patient is randomised into the trial, using data collected in the baseline time period: This spans from 24 hours prior to the time of randomisation (T0) up until the time of randomisation.

**Baseline Characteristics**

• Date and time of hospital admission refers to when the patient first arrived in hospital, e.g. A&E admission, not the time they arrived at a hospital ward.
• Date and time of ICU admission should correspond to the time that ICU charts began.
• Specify the main site of infection only. If the applicable infection site is not listed, select ‘Other’ and specify using free text entry.
• Specify where the infection was acquired by entering ‘In the Community’ OR ‘Hospital’. Infections are considered to be hospital acquired if they were acquired at least 48 hours since hospital admission. Otherwise, infection will be classified as community acquired.
• Please enter date and time vasopressor support was started. This question should **ONLY** be completed if another vasopressor was administered prior to starting noradrenaline. If noradrenaline was the only administered vasopressor, this question can be left blank.
• Please enter date and time noradrenaline was started.
Please enter date and time of lactate >2mmol/l used to confirm eligibility prior to randomisation.

Select 'Yes' or 'No' to confirm whether a chest x-ray has been taken. If 'Yes', complete date & time and specify whether diffuse bilateral pulmonary infiltrates were present by selecting 'Yes' or 'No'.

Select 'Yes' or 'No' to confirm whether the patient could have ARDS. If 'No', provide a reason using free text entry.

**Pregnancy Test**

Pregnancy testing is not mandated for this trial as this would not be carried out in standard care. However, a pregnancy test may be carried out on women of childbearing potential at the discretion of the local investigator (See Protocol section 4.1).

Select 'Yes' or 'No' to confirm whether a pregnancy test was performed.
  - If 'No', skip to Baseline Medical History.
  - If 'Yes', specify assessment date and result.

**Baseline Medical History**

- If the patient has no concomitant illnesses, select 'No' and skip to the Baseline Assessments section.
- If the patient has any concomitant illnesses, select 'Yes' and complete the details in the table.
- If an actual onset date is not known, provide an estimated date containing as much information as possible. If day is not known, enter the 15th (the middle of the month) as the start date e.g. September 1999 would be entered as 15/SEP/1999. If month is not known, enter June (the middle of the year) e.g. if only the year 1999 is known, enter 15/JUN/1999.

**4. Follow Up Day 28**

- This follow up form should be completed 28 days from randomisation.
- Firstly, the participant’s GP will be contacted to ascertain whether the patient is alive.
- The Patient may then be contacted via telephone.

**Follow Up Information**

- Specify date the follow up assessment was made
- Select mortality status. If 'Deceased' ensure a Death Notification Form has been completed and, where applicable, a Serious Adverse Event Report.

**SOFA Score and Inflammatory Indicators**

- Complete details using the most recent results prior to Day 28. If participant has been discharged before Day 28, complete using results as close to discharge date as possible.
- Enter the result NOT the score.
- Complete either Lowest PaO2 / FiO2 Ratio OR Saturation percentage.
- Highest inotrope includes ALL inotropes taken.

**5. Follow Up Day 90**

- This follow up form should be completed 90 days from randomisation and will be the final study visit.
- Firstly, the participant’s GP will be contacted to ascertain whether the patient is alive.
• The Patient may then be contacted via telephone.
• Specify date the follow up assessment was made
• Select mortality status. If ‘Deceased’ ensure a Death Notification Form has been completed and, where applicable, a Serious Adverse Event Report.

6. End of Noradrenaline Treatment (EONT)
• This form should be completed once noradrenaline has been discontinued for >12 hours.
• If noradrenaline has been discontinued for >12 hours but is restarted before you can complete the EONT Form, the form should still be completed.

End of Noradrenaline Treatment
• Enter date and time that Noradrenaline was discontinued for >12 hours

7. Landiolol Treatment Form
• This form should ONLY be completed for participants on the Landiolol Plus Standard Treatment arm.
• Complete date and time landiolol started once landiolol treatment has commenced.
• Once landiolol is discontinued, return to this form, click the ‘Edit’ button and enter date and time discontinued.

8. ICU Discharge Form
• This form should be completed once a patient is discharged from ICU.
• Briefly specify diagnosis at end of ICU admission using free text entry.
• Enter summary of ICU admission using free text entry.
• Select discharge location following ICU stay (HDU, ward or other hospital/care facility).

9. Hospital Discharge Form
• This form should be completed once a patient is discharged from hospital to another location.
• Select discharge location. If the applicable discharge location is not listed, select ‘Other’ and briefly specify using free text entry.

10. End of Trial Form
• This form should be completed following the final follow up visit at Day 90.

End of Trial
• Select ‘Yes’ or ‘No’ to specify whether the participant has completed the trial.
• Specify the primary reason for discontinuation.
  o If the participant withdrew consent, ensure the Withdrawal Form has been completed prior to signing off this form.
  o If death is the primary reason, ensure the Notification of Death Form and/or Serious Adverse Event Report Form have been completed as appropriate prior to signing off this form.
  o If the applicable primary reason is not listed, select ‘Other’ and specify using free text entry.
Sign-off Statement

- The PI should only sign-off and date the paper form once they have confirmed that reasonable effort has been made to ensure **ALL** of the data in the CRF is a true, accurate and complete report and that all log pages have been reviewed for completeness ensuring all records have end dates or are marked as ongoing.
- This form should **ONLY** be completed after confirmation has been received from WCTU following discussion.
- Confirm that the PI has signed the paper form by selecting 'Yes' on the RDE system.
4. Daily Data

- Click on ‘Daily Data’ under the ‘Data Entry’ Tab (Figure 2.)
- Daily data collection is organised into a grid system to display which eCRFs need to be completed on each day.
- Please refer to section 1. Data Collection Time Point Guidelines for further instruction.
- The progress of each day can be viewed under ‘Tracked Day’. For instance, Figure 6 shows that 2 of 5 forms have been completed for Day 0.
- The form status is listed underneath each form at each time point. For instance, Figure 6 shows that ‘SOFA’ and ‘Assessments’ have been completed for Day 0 whilst the other forms have not been started.
- Select a form by clicking the open button for each form (Figure 6).
- To begin entering data for a new day, click the ‘Start Day X’ button in the bottom left of the window (Figure 6). You will then be asked to confirm the action before the next day is added onto the Daily Data grid.
- Once noradrenaline treatment has finished, click the ‘End of Treatment’ button in the bottom left of the window (Figure 6). You will then be asked to confirm the action before the end of noradrenaline time point is added onto the Daily Data grid.

Figure 6: Daily Data Grid

11. Cardiovascular Data

- This section should be completed daily from Day 0 to Day 14 or up until ICU discharge, whichever comes first.
- Enter data for each time point specified at the top of the cardiovascular data table (Figure 7) e.g. -24h is 24 hours prior to time of randomisation and T+1h is 1 hour after the time of randomisation.
- Specify rate of inotrope administration for each inotrope administered. If an inotrope other than noradrenaline, landiolol or vasopressin is administered, specify the name of the drug using free text entry in addition to rate.
- Day 0 (pre-randomisation) – data for Day 0 should be entered using data collected prior to and including the time of randomisation (T0).
- Days 1-14 (post-randomisation) – data should be entered using data collected after the patient is randomised.
12. SOFA Score
- This form should be completed daily from D0 up to Day 14 or ICU discharge, whichever comes first.
- This form should also be completed at end of noradrenaline treatment.
- Enter SOFA Score component results daily using data collected over the 24 hour time period.
- If blood tests are not routinely taken every day on ICU and therefore, lowest platelets, highest bilirubin, highest creatinine, WCC and CRP cannot be obtained for that day, please leave this field blank.
- Highest or lowest values over the 24 hour period will be collected as indicated by the CRF and trial database e.g. at Day 0, the lowest PaO2/FiO2 ratio collected from 24 hours prior to randomisation up until time of randomisation will be recorded on the CRF.
- Enter the result NOT the score.
- Highest inotrope includes ALL inotropes taken.

Other Outcome Data
- If multiple assessments are available for Other Outcome Data, this should be completed using assessments closest to the end of the time point e.g. if a patient is randomised at 15:00 on Day 0 and assessment data is available at 11:00 and 14:00, the 14:00 data will be recorded as this is closer to the point of randomisation which is the end of Day 0 data collection.

13. In/Out Fluids
- This form should be completed daily from D0 up to Day 14 or ICU discharge, whichever comes first.
- Calculate the total balance taking into account the fluids in and fluids out.
- The following guidance provides instruction and guidance for each of the headings. The STRESS-L database is pending an update to expand the headings therefore, in the meantime a liberal approach has been adopted to ensure everything is captured accurately.

**Total Fluids IN**

- ORAL (ml): Includes anything the patient receives via the mouth and/or has a calorific value. This includes enteral feeding, NG feed, water etc.
- CRYSTALLOID: Includes all IV drugs whether or not diluted with crystalloid, TPN etc.
- COLLOID: Includes all colloids and blood products

**Total Fluids OUT**

- URINE: Includes urine, drains, NG aspirates, blood loss during surgery etc.
- CVVHF Balance: Balances from the 24 hour CVVH

**14. Additional Assessments**

- This form should be completed at days 0, 1, 2, 3, 4 and 6 or up to ICU discharge, whichever comes first.
- This form should also be completed at end of noradrenaline treatment.

**Other Treatment**

- If the patient is receiving steroid treatment, specify name and dose. If not, leave this question blank and skip to cardiovascular section.

**Optional cardiovascular assessments**

- Venous PaO2, Venous PaCO2, Cardiac Output (CO) and Stroke Volume (SV) are optional assessments. If these assessments were carried out, enter the numerical result. If these assessments were not performed, leave the question blank.

**Biochemistry**

- If multiple glucose measurements were taken, specify the most recent value.
- Day 0 ONLY – specify the highest lactate value over the previous 48 hours.
  - Days 1, 2, 4, 6 and EONT: If multiple lactate measurements were taken, specify the most recent value.
- One of either AST or ALT should be entered for Liver Function Tests. Please enter the result for the completed test and leave the other blank.

**Central Laboratory Specimens**

- Select ‘Yes’ or ‘No’ to confirm whether the mandatory Research Blood Sample was collected.
- Please complete date and time of assessment. If ‘No’ provide a reason why the sample could not be taken.
- Biobank sampling is an optional part of the trial and a participant’s involvement in this aspect will be documented on the Informed Consent Form.
  - If the participant is not taking part in this part of the trial, tick ‘No’ and provide a reason e.g. not participating.
  - If the participant is taking part, complete this section.
15. Landiolol Infusion
- This form should be completed daily from D0 up to Day 14 or ICU discharge, whichever comes first.
- Once Landiolol has stopped this form will not need to be completed.
- This form should also be completed at the end of noradrenaline treatment.
- Enter date and time of landiolol infusion preparation.
- Specify the number of vials used to make an infusion and the corresponding batch number.
- Add a new entry each time a new landiolol infusion is prepared.

5. Unscheduled Events
- Click on ‘Scheduled Events’ under the ‘Data Entry’ Tab (Figure 2).
- Select a form by clicking the open button on the left side of the page (Figure 8).

Figure 8: Unscheduled Event Forms

16. Microbiology Assessments
- This form should record all microbiology assessments from Day 0 up to End of Noradrenaline Treatment Visit.
- Baseline microbiology results should be recorded here followed by subsequent specimens.

Microbiology Specimens
- Add a new entry for each specimen.
- Document all relevant assessments including positive COVID-19 infections, nosocomial (hospital acquired) infections such as catheter-related blood stream infections and bacteraemias.
- For specimen, specify type of sample (e.g. swab) and location of sample using free text entry.
- Specify date of assessment (the date specimen sample was taken).
- Paper CRF completion only: if over 10 microbiology assessments are made, tick to confirm that the form continues onto an additional page and begin completing a new page. Repeat each time a page is fully completed.
17. Adverse Events

- This form should record all adverse events from Day 0 up to Day 14 or end of landiolol treatment, whichever comes first.
- All Serious Adverse Events (SAEs) / Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring from time of randomisation to final follow up visit at Day 90 must be recorded on the paper STRESS-L SAE Report Form and faxed to Warwick Clinical Trials Unit within 24 hours of the research staff becoming aware of the event. Please refer to the protocol and paper forms for further guidance.

Adverse Events

- If the participant has not experienced any adverse events by day 14 or end of landiolol treatment, select ‘No’ to this first question and skip the remainder of the form. If a participant subsequently experiences a SAE (after end of landiolol treatment), ensure a corresponding adverse event entry is added to the Adverse Events Form.
- If a participant experiences their first adverse event during the trial, select ‘Yes’ to the first question and proceed to document the details of this event in the table.
- Add a separate entry for:
  - Each new adverse event.
  - All adverse events which have increased in severity.
  - All adverse events with changed treatment relationship
  - All medical conditions present at baseline which have worsened.
- Death is an Outcome, and should NOT be entered as an adverse event. Instead, enter the underlying condition that led to death.
- Specify Adverse Event Diagnosis using free text entry. This should match to a corresponding entry in the CTCAE booklet
- Select ‘Yes’ or ‘No’ to specify whether this event is considered a Serious Adverse Event (SAE). If ‘Yes’, ensure an SAE Report Form is completed and forwarded to Warwick Clinical Trials Unit. An SAE is an adverse event which fulfils one of the following criteria:
  - Results in death.
  - Is immediately life-threatening.
  - Requires hospitalisation or prolongation of existing hospitalisation.
  - Results in persistent or significant disability or incapacity.
  - Is a congenital abnormality or birth defect.
  - Is an important medical condition.
- Refer to the CTCAE booklet to assess CTCAE grade.
- Action taken (IMP) refers to any changes made to landiolol treatment.
- Specify adverse event end date. Every possible attempt will be made to document adverse event end date. If this is not possible, amend the outcome column to option 3 = ongoing at end of trial. If this is entered, the adverse event end date should be left blank.
- Paper CRF completion only: if over 10 adverse events are experienced, tick to confirm that the form continues onto an additional page and begin completing a new page. Repeat each time a page is fully completed.

18. Protocol Deviations

- This form should document all protocol deviations.
- If there are no protocol deviations to report by Day 90, select ‘No’ for the first question and skip the remainder of the form.
• If a first protocol deviation occurs, select ‘Yes’ to the first question and proceed to document the details of this protocol deviation in the table.

Protocol deviation details
• Add a separate entry for each protocol deviation. If there are multiple reasons, specify each reason using a separate entry.
• Specify any comments using free text entry, for instance, explaining why a protocol deviation occurred and what steps will be taken to ensure this is avoided in future.
• Paper CRF completion only: if over 10 protocol deviations occur, tick to confirm that the form continues onto an additional page and begin completing a new page. Repeat each time a page is fully completed.

19. Withdrawal Form
• This form should be completed if a participant withdrawal is necessitated.
• All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.
• Participants may also be discontinued from the trial treatment and/or the trial at any time.

Withdrawal Form
• Specify the applicable withdrawal status.
  o If the participant has withdrawn from trial treatment but remains on follow up, all trial intervention treatment must cease but data collection will continue as per the protocol. CRFs should continue to be completed as applicable.
  o If the participant has withdrawn from the trial entirely/withdrawn consent, any further trial involvement and follow up must cease. No further data will be collected.
• Specify the main reason for withdrawal using free text entry.

20. Death Notification Form
• Complete this form if a participant dies prior to final contact point at 90 days following randomisation.
• Complete form using information obtained from the death certificate.
• If applicable, ensure a Serious Adverse Event Report has also been completed.

Death Information
• Specify the main cause of death using free text entry.
• Briefly provide any additional details using free text entry.

21. Cardiovascular Safety Outcomes
• Enter cardiovascular safety outcomes daily from D0 (point of randomisation) up to Day 14 or end of landiolol treatment, whichever comes first.
• Add a new event for each type of event and each applicable intervention.
• If a new event has occurred add a new entry by pressing the ‘New’ button in the bottom right of the window (Figure 9).
Figure 9: Cardiovascular Safety Outcomes