STRESS-L TRIAL

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

CRF COMPLETION GUIDELINES

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University Hospitals Birmingham NHS
NHS Foundation Trust

WARWICK
CLINICAL TRIALS UNIT

NHS
National Institute for Health Research

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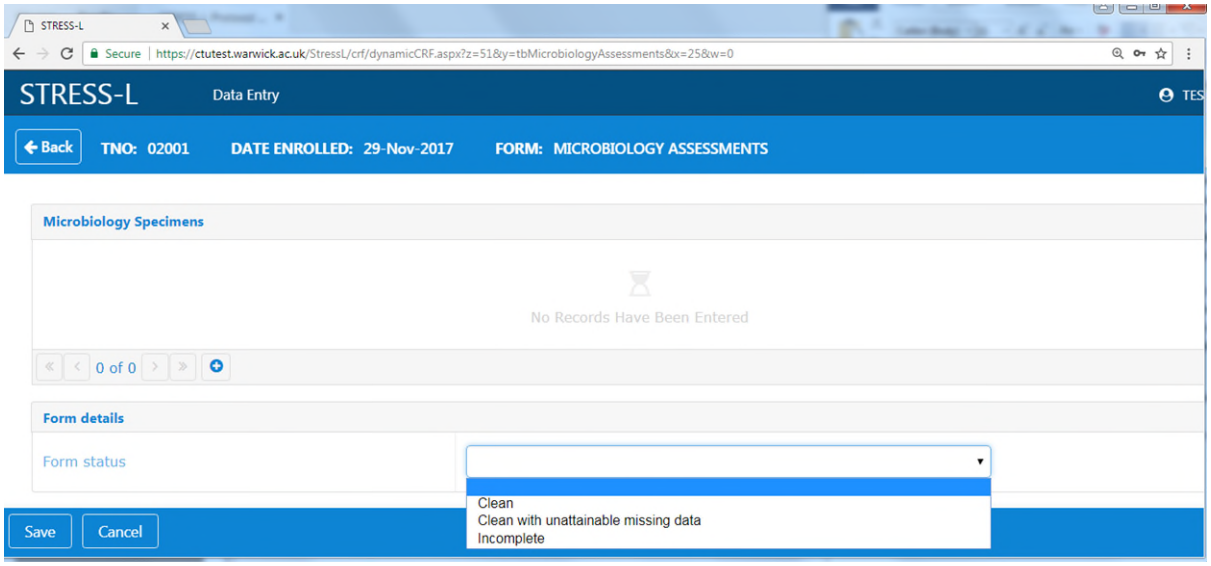
1. General Instructions for CRF Completion

- 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.
- When entering data in tables:
    - 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 database there is a Form Status field which can be used to categorise the information within the form (Figure 1). 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'.

Figure 1: STRESS-L database form status



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

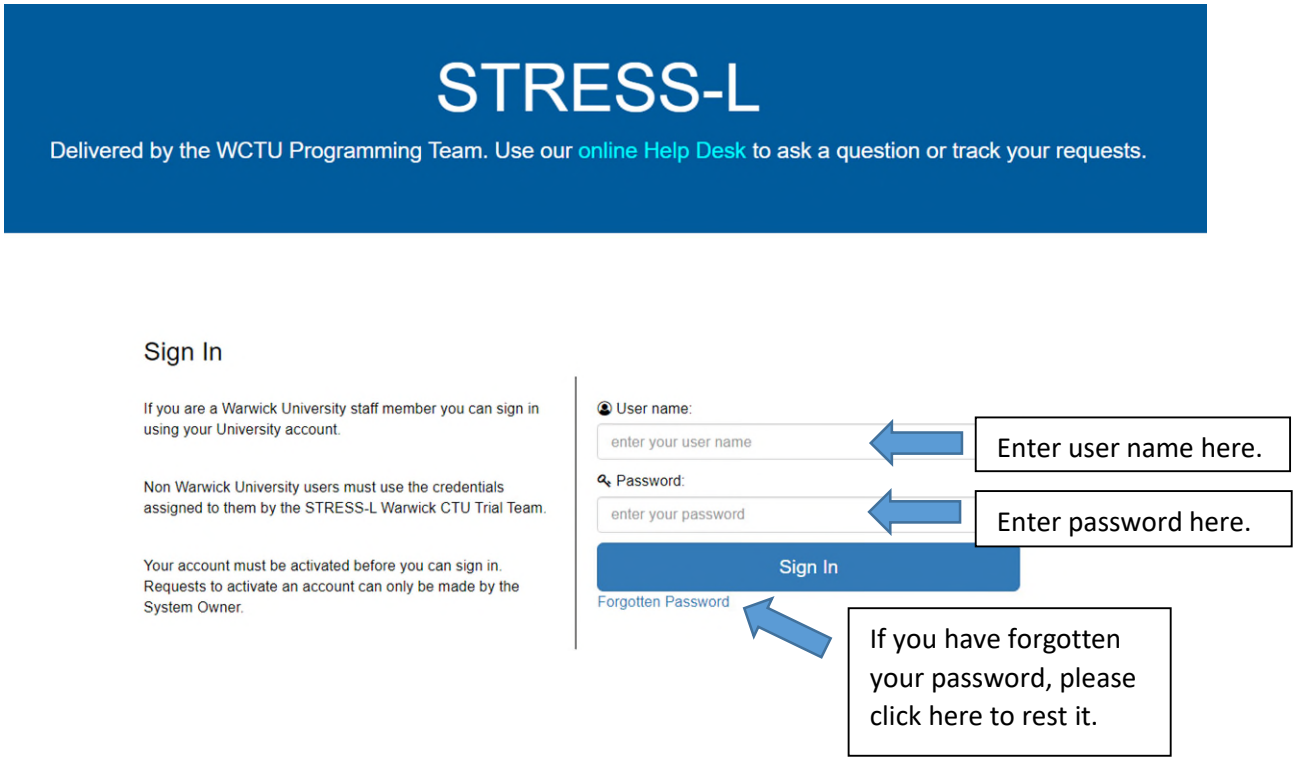
- Time 0 (or T0) = the time of randomisation

- 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.
    - Day 0 spans from 15:00 on the 1st January to 15:00 on the 2nd January.
    - Day 1 spans from T0, 15:00 on the 2nd January, to 15:00 on the 3rd January.
    - Day 2 spans from 15:00 on the 3rd January to 15:00 on the 4th January etc.
- Calendar days are **NOT** in use.

2. How to gain access and log in to the STRESS-L database

- 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 into the database by entering your individual user name and password (Figure 2.). These details are issued to you by the Warwick CTU trial team once the following have been emailed to **stress-l@warwick.ac.uk**: signed delegation log with responsibility code 'G' allocated, signed investigator training log, signed copy of CV and copy of GCP certificate to confirm you are appropriately trained to collect and input data for the trial.
- If you have forgotten your password, you can click 'Forgotten Password' underneath the Sign In blue button. To reset, you need your user name and registered email account. Upon verification of your username and email, the system will send an email containing a temporary password.
- Please be aware the system will lock a user's account after 5 attempts have been made to authenticate their current password.

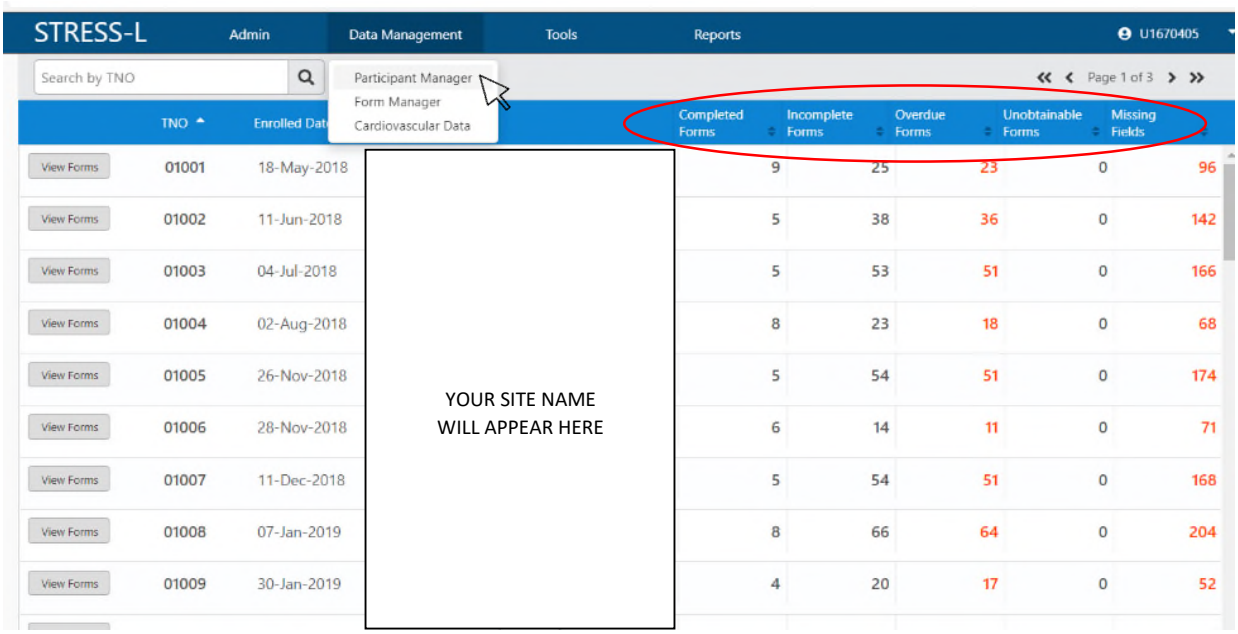
Figure 2: STRESS-L database login page



3. How to find a participant on the database

- eCRFs are accessed by clicking on the 'Data Management' tab at the top of the database and selecting either 'Participant Manager' or 'Cardiovascular Data' (Figure 3).
- Following randomisation of a patient using the IVR telephone system, the participant will automatically appear in the STRESS-L database.
- To navigate to a participant, click on 'Participant Manager' and a list of participant trial numbers (TNO) recruited from your sites will be displayed. Please select the relevant TNO you wish to enter data for by clicking 'View Forms'. To filter the participant list based on the full or partial TNO enter the TNO into the search box on the top left-hand corner and either press the return key or click the search button. The list of participants can be ordered by clicking one of the header columns. The sort order icon indicates if the column is sorted ascending or descending. The list displays the participants TNO, Enrolled Date and Enrolled Site. The following aggregated totals are also displayed (circled below in Figure 3):
  - Completed Forms – the total number of forms with no missing fields.
  - Incomplete Forms – the total number of forms with missing fields.
  - Overdue Forms – the total number of scheduled forms with missing fields with an elapsed expected date.
  - Unobtainable Forms – the total number of forms that have been flagged unobtainable.
  - Missing Fields – the total number of missing fields (incomplete responses across all forms

Figure 3: STRESS-L database – Participant Manager Form

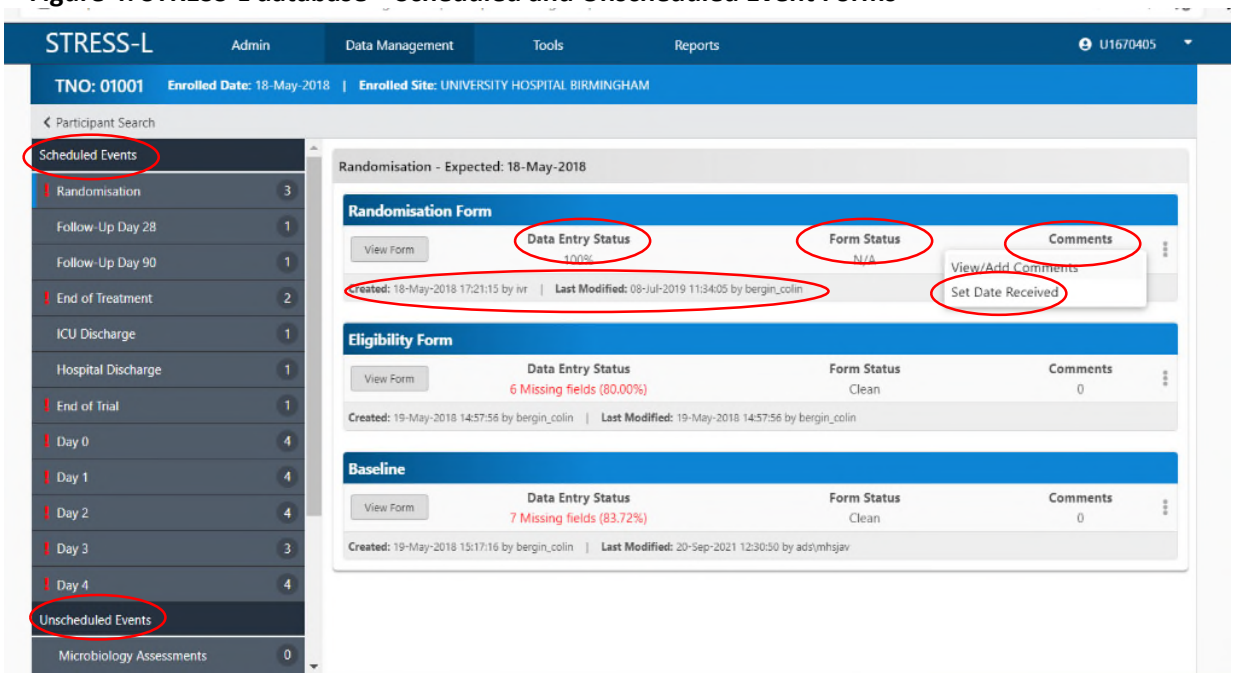


4. How to enter data for a participant on the database

- The side navigation bar displays a list of the participant's Schedule and Unscheduled events (Figure 4). Selecting an event displays all the forms associated with an event. The number of forms that have been entered for any given event is displayed next to the event's name.
- Each form displays the name of the form, data entry status, form status and the number of user added comments.

- If data entry has started, audit data i.e., 'created and last modified' is displayed in the form's footer.
- The data entry status is set to pending for scheduled forms if no data has been entered.
- When data entry is in progress or is completed, the number of missing fields is displayed together with the percentage of completeness.
- The data entry status is changed to 'Form is unobtainable' if the form level unobtainable flag has been set. The form status if copied over from the form's form status field. If the form does not have a form status field, then 'N/A' is displayed.
- The comments are the total number of submitted forms and field level comments. If the date received has been set, this is displayed in the form's footer. Clicking the 'View Form' button will navigate to the data entry screen for the selected form. This button **cannot be clicked if the unobtainable flag has been set.**
- The 'Set Date Received' option displays a dialogue to set a value for the date the form was received. This date can be used for paper-based forms that are received in the office before being entered. Forms that have been received but have no data entered can then be tracked via the Form Tracking Tool.
- All forms have an Edit button on the top right hand corner which must be selected to enter data for the participant.

Figure 4: STRESS-L database – Scheduled and Unscheduled Event Forms

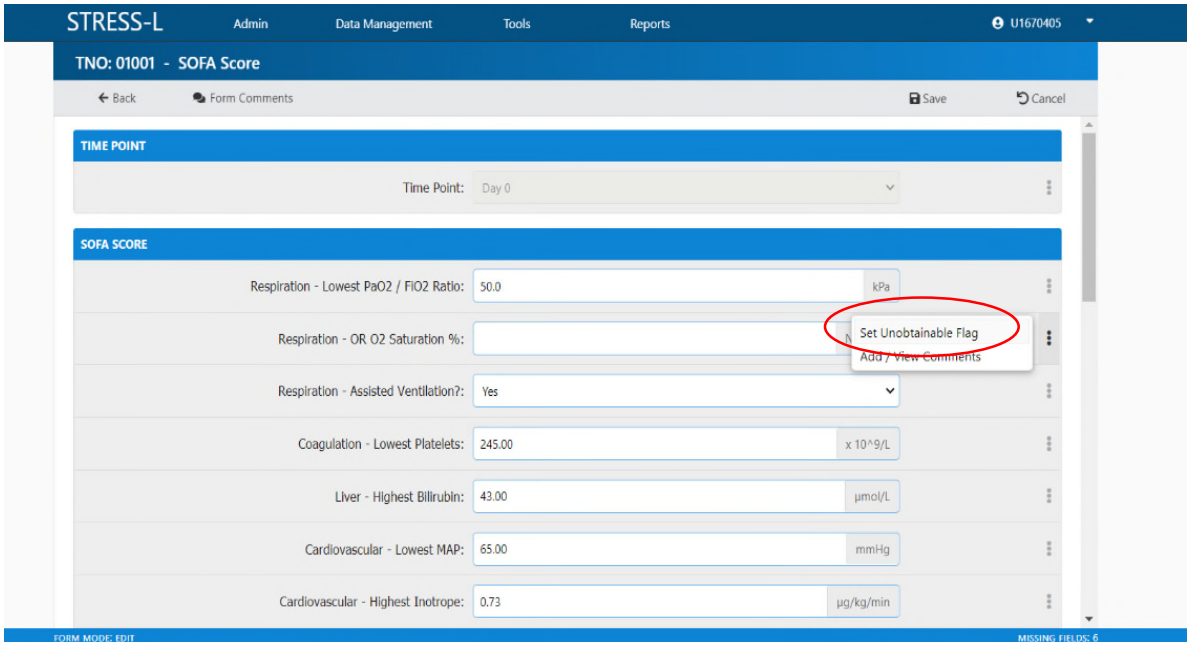


How to set the unobtainable data flag

- The unobtainable flag can only be set if no data has been entered for an individual field, therefore it is only possible to use this flag on scheduled forms (unscheduled forms will only exist if data has been saved). Please see figure 5.
- Setting the unobtainable flag disables the 'View Form' button and changes the data entry status.
- Any forms set as unobtainable will not be counted in the overdue forms total as displayed on the participants search list.

- Clicking the 'View/Add Comments' option displays the comments screen and displays all the form level comments. When marking data as unobtainable please click the 'View/Add Comments' button next to the unobtainable flag to capture the **reason why this data in unobtainable.**

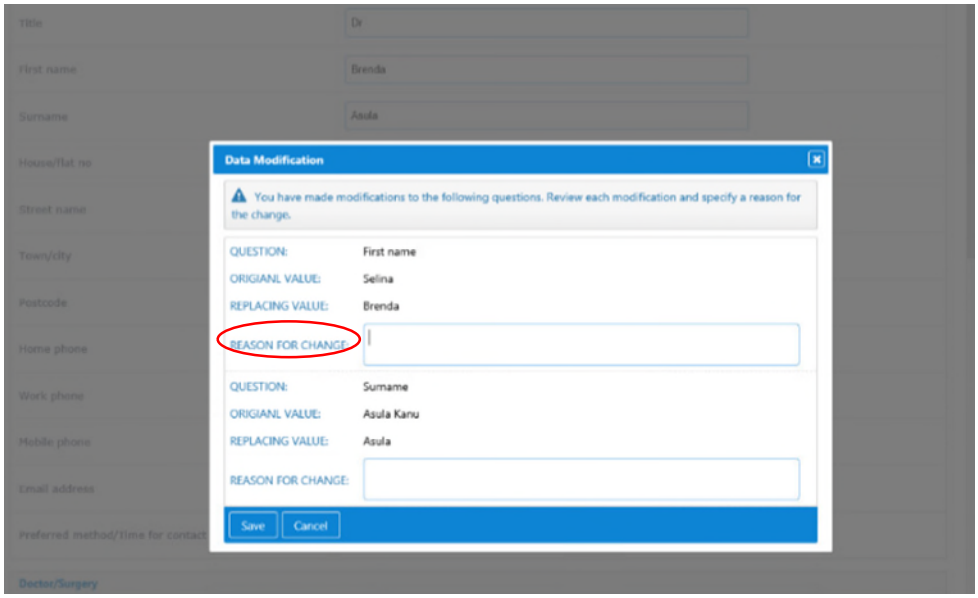
Figure 5: STRESS-L database – setting an unobtainable flag



Modifying data entered on the database

- When modifications are made to an initial saved form, a reason is required to be logged for each data item that is altered using the pop up box as shown in Figure 6.

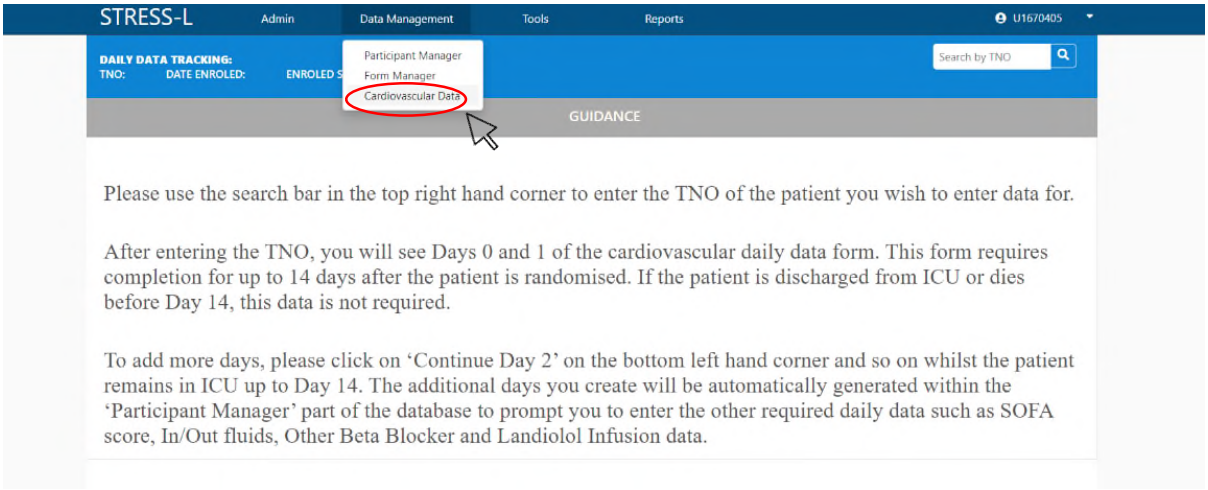
Figure 6: STRESS-L database – reason for change annotation pop-up



5. How to generate daily data forms for a participant on the database

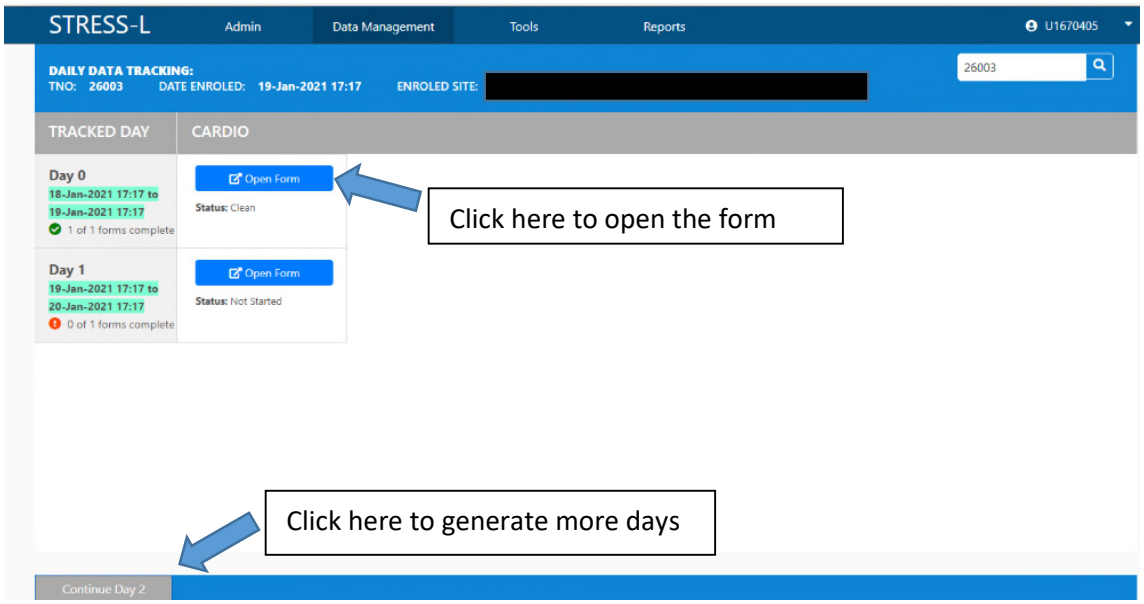
- To generate the required number of daily data forms for a participant please select **'Cardiovascular Data'** found under 'Data Management' at the top of the database.
- The below guidance will appear on the screen as illustrated in Figure 7.
- Please use the search bar in the top right-hand corner to enter the TNO of the patient you wish to enter data for.

Figure 7: STRESS-L database – Cardiovascular Data form



- After entering the TNO, you will see Days 0 and 1 of the cardiovascular daily data forms as displayed in Figure 8. This form requires completion for up to 14 days after the patient is randomisation. If the patient is discharged from ICU or dies before Day 14, this data is not required.
- To add more days, please click on 'Continue Day 2' on the bottom left-hand corner and so on whilst the patient remains in ICU up to Day 14. The additional days you create will be automatically generated within the 'Participant Manager' part of the database to prompt you to enter the other required daily data such as SOFA score, IN/OUT fluids, Other Beta Blocker and Landiolol Infusion data.
- Clicking 'Open Form' will display the required cardiovascular data.

Figure 8: STRESS-L database – Cardiovascular data form and generating more days



6. 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 key pad 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.

7. Data Forms

7.1 Scheduled Events

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 *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.

Randomisation 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 The remaining information must be added following randomisation.
- Click the 'Edit' button in the top right 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.

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

- Patient postcode should be entered in full if known.
- 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.
- Please enter COVID status if 'Suspected', 'Confirmed' or 'No. If COVID is suspected or confirmed **do not take blood samples for this participant.** If the patient is initially suspected to have COVID which is later confirmed with a positive test result, please update the database accordingly adding a comment to explain the reason for the change.
- Baseline ECG's should be taken prior to the patient starting Landiolol and as close as possible to the time of 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.
-

Other Beta-Blocker

- Select 'Yes' or 'No' to confirm if the patient was taking beta blockers 2 weeks prior to admission to the ICU, if the patient has received beta blockers on admission to ICU and if the patient has received beta blockers during ICU admission prior to randomisation.
- Please note patients who receive beta blockers prior to randomisation are eligibile for the trial.

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.

Follow Up Day 90

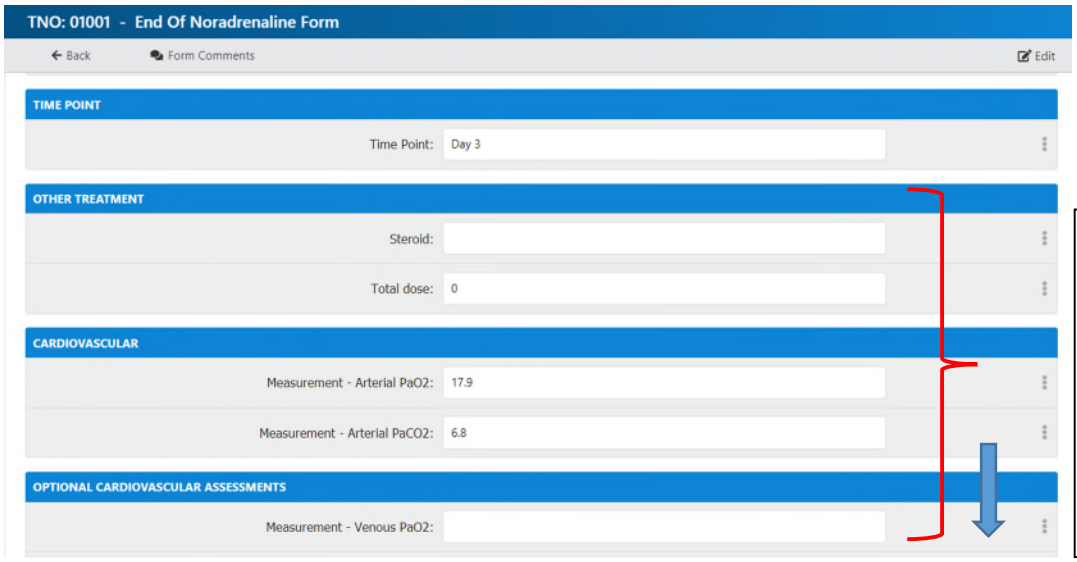
- This follow up form should be completed 90 days from randomisation and will be the final study visit.
- Firstly, the participant's GP will be contacted to ascertain whether the patient is alive.
- The Patient may then be contacted via telephone.
- Specify date the follow up assessment was made
- Select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

End of Treatment

End of Noradrenaline Form

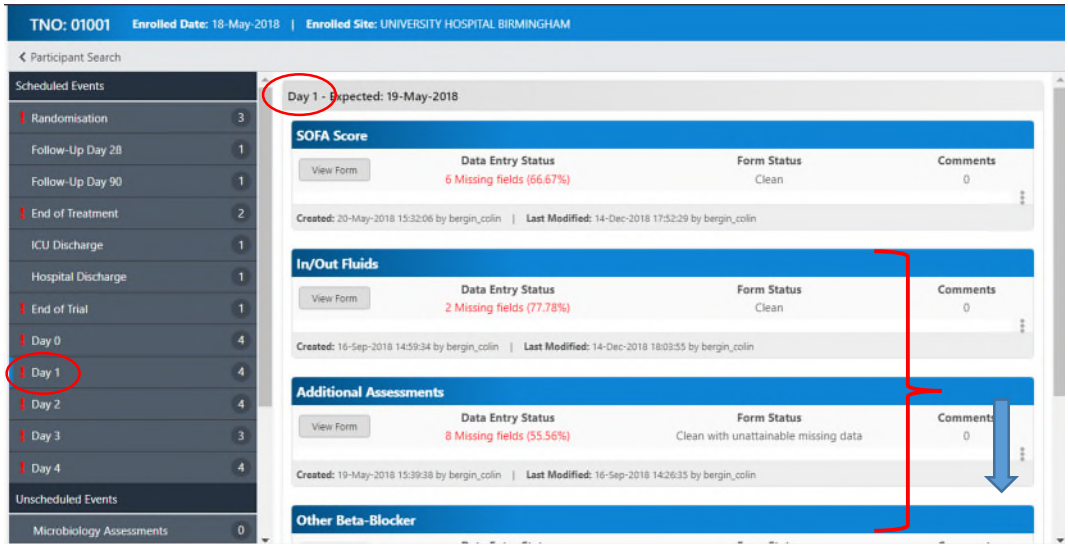
- This form should be completed once noradrenaline has been discontinued for >12 hours.
- If noradrenaline has been discontinued for >12 hours but is restarted before you can complete the *EONT Form*, the form should still be completed.
- Enter date and time that Noradrenaline was discontinued for **>12 hours.**(referred to as EONT timepoint).
- Select time point (between Day 0-14 or post Day 14) when EONT occurred.
- If days 3, 5, 7, 8, 9, 10, 11, 12, 13, 14 or EONT (if post Day 14) are selected, additional assessments, total fluids IN and OUT, SOFA score and inotrope data questions will appear below the Time Point field for completion (Figure 9).
- If days 0, 1, 2, 4 or 6 (blood sampling days) are selected, additional assessments, total fluids IN and OUT, SOFA score and inotrope data questions will be greyed out as these questions will appear within the relevant daily data form when EONT occurred for completion. You will not be required to duplicate the data or assessments required on blood sampling days which is why these questions appear greyed out here (Figure 10).

Figure 9: STRESS-L database – End of Noradrenaline Form – non-blood sampling days



Please complete additional assessments, total fluids IN and OUT, SOFA score and inotrope data questions here within the End of Noradrenaline Form.

Figure 10: STRESS-L database – End of noradrenaline Form – blood sampling days



Please complete additional assessments, total fluids IN and OUT, SOFA score and inotrope data questions here within the Daily Data form.

- Landiolol Treatment Form This form will **ONLY** appear 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.

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).

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.

End of Trial Form

- This form should be completed following the final follow up visit at Day 90. Select 'Yes' or 'No' to specify whether the participant has completed the trial.
- Specify the **primary** reason for discontinuation.
    - If the participant withdrew consent, ensure the Withdrawal Form has been completed **prior** to signing off this form.
    - 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.
    - 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.

7.2 Daily Data

- Daily data is displayed in the right-hand bar under 'Scheduled Events'.
- After a patient is randomised, Days 0 and 1 will automatically appear. To add more days please go to 'Cardiovascular Data' by clicking 'Data Management' at the top of the database.
- Please refer to Data Collection Time Point (pg 3) guidelines for further instruction.

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.
- Additional inotrope dose questions will also require completion towards the end of the CRF. **Please note:** the international name for Adrenaline is Epinephrine. The international name for Noadrenaline is Norepinephrine.

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.

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
- OTHER: Record additional data not listed in the above examples.

Total Fluids OUT

- URINE: Includes urine, drains, NG aspirates, blood loss during surgery etc.
- CVVHF Balance: Balances from the 24 hour CVVH
- OTHER: Record additional data not listed in the above examples.

Additional Assessments

- This form should be completed at days 0, 1, 2, 3, 4,6 and end of noadrenaline treatment timepoint (EONT). Please note if EONT falls on a blood sample day (i.e. days 0, 1, 2, 4 or 6, duplicate assessments are not required).

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.
- Please record number of plasma cryovials extracted and if a PaxGene RNA or DNA samples was taken alongside the date and time of the PaxGene assessment.
- 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.

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.
- 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.

7.2 Unscheduled Events

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 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.

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 emailed to Warwick Clinical Trials Unit (wctuqa@warwick.ac.uk) 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 in 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
- 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.

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.Add a separate entry for each protocol deviation.
- 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.
- Record all corrective and preventative actions.
- 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.

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.Specify the applicable withdrawal status.
    - 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.
    - 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.

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.

Cardiovascular Safety Outcomes

The following events must be reported:

- The episodes of Bradycardia (HR <50 bpm)

- Bradycardia with haemodynamic compromise requiring **significant** intervention
- Hypotension requiring **significant** intervention (not including temporarily stopping the infusion)
- Heart block
- Arrhythmia
- Arrhythmia with haemodynamic compromise requiring intervention

These events must be reported as a **Serious Adverse Event** if the delegated treating clinician deems this event fulfils the serious criteria or is **related to the drug.** If the event is **not** deemed to fulfil the serious criteria or is unrelated to the drug this should be reported on the Cardiovascular Safety Outcomes CRF.

- 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.

7.3 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.
- See Figures 7 and 8 which display cardiovascular data database screenshots.