STRESS-L

Frequently Asked Questions

V4.0 06 July 2020

WARWICK

CLINICAL TRIALS UNIT

Contents

1. Data Collection

Daily Data

Q: Should data for all daily data forms be collected until day 14?
A: **SOFA score** – always continue until day 14 unless the patient is discharged from ICU or the patients dies

Cardiovascular data – always continue until day 14, even after patient has finished Landiolol treatment, unless the patient is discharged from ICU or the patient dies.

IN | OUT Fluids – always continue until day 14 unless the patient is discharge from ICU or the patient dies.

Additional assessments – only required on days 0, 1, 2, 4, 6 and EONT. Data is not required if the patient stops Landiolol and Noradrenaline.

Q: When does Day 0 and Day 1 begin?
A: **Day 0** – 24 hours prior to randomisation up until the point of randomisation. This is written on the Cardiovascular Form as T-24hours.
Day 1 – time of randomisation up until 24 hours after randomisation. All subsequent days will commence in line with the time of randomisation and finish 24 hours later. Please do **not** use calendar days.

SOFA score
Q: Should the worst or closest value to the time point be collected?
A: The worse score over the 24 hour period will be recorded. An exception to this is for the Other Outcome Data i.e. WCC, Delirium & CRP where the value will be as close as possible to the 24 hour mark at the end of the data collection day. Therefore, it a patient is randomised at 15:00 and assessment data is available at 11:00 and 14:00, the 14:00 data will be used.

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 and save the form as 'Clean with unattainable missing data' on the e-CRF.

Q: Highest inotrope: are inotropes limited to Vasopressin, Dobutamin and Noradrenaline as general SOFA score parameters? Or you are referring to all inotropes including Adrenaline and others?
A: All inotropes.

Q: If the patient is anuric but receiving CVVHF do we put the amount of fluid removed by the filter in the Urine Output column?
A: Yes it will be the cumulative balance for that day.

Q: Is Day 28 SOFA Score still collected?
A: Day 28 SOFA Score is no longer being collected. Please leave the SOFA Score section of the Day 28 Follow Up eCRF blank until this can be removed on the database.

Cardiovascular data
Q: How often is data collected?
A: Data on this form is collected hourly until day 2 and then 6 hourly up until day 14. Values should be entered as close as possible to the exact N hours. -24hr time point refers to 24 hours prior to randomisation. Data will continue to be collected beyond day 5 even if the patient stops Landiolol.

IN | OUT Fluids

Q: Do total fluids by the NG feed and medication via NG feed need to be included into the oral in?
A: Yes. Fluids in refers to all fluids that a patient intakes.

Q: Where should TPN be recorded?
A: Currently there isn't a field on the eCRF appropriate to save this information – this change will be made during the next database amendment. In the meantime, please record the TPN separately until the database change can be made.

Additional Assessments

Q: Cardiovascular measurement: for multiple values available, which value do you collect?
A: Measurements collected should always be the value as close as possible to the end of each time point, so the most current value.

End of Noradrenaline Treatment Visit

Q: When should this form be completed?
A: Once the patient has been off Noradrenaline for 12 hours the EONT is completed on the e-CRF and a blood sample is taken. If EONT falls on a blood sample day i.e. day 0, 1, 2, 4 or 6, an additional sample is NOT required.

Q: What happens if the patient recommences noradrenaline after EONT has been completed?
A: You will not need to do anything and will not be required to commence additional assessments or complete EONT again.

Q: What happens if the patient reaches the EONT but is still tachycardic?
A: The Landiolol should be continued until the heart rate is consistently within the target heart rate of 80-94 bpm.

Q: Should we complete the EONT form if the patient dies whilst still on Noradrenaline?
A: No, this form should be left blank if the participant passes away prior to end of noradrenaline treatment.

Missing data

Q: If there is no data to collect or it is not possible to obtain the data what do I do?
A: Ultimately, if an assessment hasn't been done, and therefore the result is unobtainable, the answer should be left blank or marked as not done if permitted. If a patient is not receiving a dose of a particular drug, such as vasopressin for example, please enter the value '0' in the cardiovascular form as this will aid in the trial team in the data cleaning process.

Scheduled Events

Baseline

Q: ECG/CXR would be obtained on admission to ICU but unless clinically indicated are not performed on a regular basis. Would it be acceptable to use these results as the patient may not have had any others performed after this and prior to enrolment in STRESS L, or do we need to perform new ones at the baseline visit?

A: There isn't a need to perform new ECG/CXR for randomisation to STRESS-L as long as the clinician doesn't feel that they will have changed from baseline or if not clinically indicated. The ECG at baseline is so that if the patient goes onto develop atrial fibrillation or some other dysrhythmia, we have a baseline record to demonstrate that it wasn't there before. Similarly, if Landiolol is being used, that any change in the ECG can be documented for safety reporting.

ICU Discharge Form

Q: There is no option for outcome as death in Discharge destination drop-down menu.
A: For the purpose of this trial, death is not considered a cause for discharge. The ICU discharge form should only be completed if the participant is discharged alive to another location. If a participant dies whilst on ICU, a death notification form should be completed but not an ICU discharge form.

End of Trial Form

Q: When should the PI sign off the End of Trial Form?
A: In order to streamline our processes, we will now request that the PI sign off form is completed at the end of the study, not after each participant. Therefore, please wait until we request for these to be completed before sending to WCTU.

2. IMP Management

Q: If the patient's heart rate fall bellows 80 bpm but the patient is receiving noradrenaline, should the Landiolol Infusion continue?
A: **NO.** If the patient's heart rate falls below 80 bpm, the Landiolol Infusion should be reduced in a step wise fashion by 1.0 mcg/kg/min to achieve the target heart rate or weaned off if the target heart rate cannot be achieved regardless of if the patient's noadrenaline treatment is ongoing.

Q: When should the Landiolol be weaned and stopped?
A: Once all vasopressor agents have been stopped for 12 hours, and the patient is consistently within the target heart rate range, the Landiolol should be weaned.

Q: What happens to the Landiolol if the noadrenaline has been discontinued for <12 hours?
A: The Landiolol dose should be adjusted accordingly to maintain the target heart rate of 80-94bpm as per the Landiolol Infusion Protocol.

Q: What happens to the Landiolol if the noradrenaline has been discontinued for >12 hours?
A: Once Noradrenaline treatment has ceased for over 12 hours, the EONT visit is triggered. If heart rate is persistently within the target range of 80-94 bpm, landiolol should begin to be weaned by gradually reducing the infusion in a step wise fashion by 1.0 mcg/kg/min to maintain the target heart rate. If heart rate falls below 80 bpm, landiolol infused should be reduced in a step wise fashion by 1.0 mcg/kg/min to achieve the target heart rate. If heart rate increases above 94 bpm, the landiolol infusion should be increased as per the protocol. Once the end of noradrenaline treatment visit has passed and landiolol has been stopped for 12 hours or more, it should not be restarted.

Q: Can the Landiolol be restarted at any point whilst the patient remains on ICU?
A: The Landiolol may be started according to the infusion protocol at any point before the EONT regardless of if the Landiolol has been stopped for more than 12 hours. The Landiolol can also be restarted within 12 hours of EONT, **however,** it should **NOT** be restarted once the EONT has passed and the Landiolol has been stopped for 12 hours or more.

Q: If the patient reaches 14 Days whilst still on Landiolol, when should Landiolol be stopped?
A: The Landiolol should be begin to be weaned at the end of Day 14 and eventually stopped.

Q: Is a dedicated lumen on a multi-lumen central line considered adequate for administering Landiolol?
A: Each lumen will be considered as its own separate line as there is no mixing until the IMP enters the bloodstream. The IMP can be administered via its own dedicated lumen on a multi-lumen line.

Q: Do the research nurses have to titrate the drug for 6 hours or is this something that can be delegated to the bedside nurse?
A: This may be delegated to the bedside nurse. The bedside nurses can be involved in reconstituting IMP and preparing infusion for participants randomised to receive Landiolol, and the research nurses will not be required to provide oversight in person over the weekend. However, **the research nurses must conduct a handover on Friday** with the bedside nurses to communicate study requirements and how to access the vials and manage the infusion, which should be then **clearly documented in the patient's notes**. It is the research nurses responsibility to ensure there is oversight and we encourage you to provide training to non-research colleagues to relay the requirements of the study; this could perhaps be done through coffee mornings. We have collated training slides for ICU clinical staff which you may find a useful tool to provide training. We have also provided dosing chart laminates and A5 laminates of the Landiolol and Vasopressor protocols in your site file which can be kept at the patient's bedside.

Q: Can we hold a supply of the study drug on ITU and maintain our own accountability log so that the research nurses would be able to issue the drug to the randomised patient or is this something that only the pharmacist can do?
A: Yes a box of vials will be kept on ITU with 2 back up boxes in pharmacy. There is an ICU IMP inventory log and a pharmacy IMP inventory log.

Q: Who is responsible for informing the trial team at WCTU further supply is required?
A: Pharmacy will be responsible for letting us know when you require re-supply, as they will be holding the 2 back up boxes. Each time a box is released, please keep us updated by emailing: stress-l@warwick.ac.uk . The research nurses will also take responsibility for this by informing us if a patient is on max dose as they are a heavy patient however, pharmacy will also be responsible for informing us if your stock levels are running low.

Q: Is one box of vials used for one patient?
A: No. 20 vials supplied in one box can be used on more than one patient. Unused vials at the end of the trial or expiry of the batch will be destroyed locally and it will not be returned to the manufacturer AOP.

Q: Can ambient IMP be stored in the fridge as this is a convenient storage space?
A: Yes. Ambient IMP can be stored in the fridge for ease of storage, as no special storage conditions are required for this stock. If a fridge is not available the drug should be stored in a secure location with restricted access to the research team.

Q: Is it ok to alternate between ambient and refrigerated temperature conditions for the ambient IMP stock?
A: Yes this is fine as it will not affect the stability of the drug.

Q: Can beta-blockers be administered in the control group?

A: As per the protocol, the control group will receive usual care and not be supplied additional beta-blockade whilst on ICU. If a clinical decision is made to administer a beta-blocker to a control group patient, a protocol deviation form must be completed on the e-CRF under unscheduled events.

Pharmacy

Q: Do the ICU research nurses need to submit any specific paperwork to request further supply of IMP from pharmacy?
A: There is no specific request form the ICU research nurses need to complete when asking for a box to be released by pharmacy. The trust will follow their own internal policy when doing this. The transfer should be clearly and adequately documented on both the ICU and Pharmacy Inventory logs

Q: Do used vials need to be returned to pharmacy for destruction?
A: The ICU research team will destroy these and they do not need to be returned to pharmacy. The same goes for damaged vials (a note will be made next to the entry on the inventory log). If a vial is used to make up an infusion that isn't issued to the participant (for example the patient dies) they should also make a note of this on the inventory log or they could do a file note.

Q: If any reconstituted drug is left over in a syringe can the ICU research team dispose of this?
A: Yes this is fine but it must be documented on the ICU IMP destruction log.

3. Laboratory

Blood samples

Q: Can bloods be taken by staff nurses at weekend and left for processing on Monday?
A: No - these blood samples are mandatory and it is expected that a member of the research team or a co-investigator will have to come in on the weekend to process the samples. Only minimal weekend work will be required over the duration of the trial. Paxgene tubes (biobank samples) can be kept at room temperature for 72 hrs max. Green lithium heparin tubes need to be kept at room temperature on a rotator (i.e. in continuous motion) until processed and not placed in the fridge. They must be processed straight away.

Q: Will you be providing blood kits for the trial bloods, gases and serums?
A: The following consumables will be provided:
Lithium Heparin Blood Tubes (green top)
PaxGene RNA Blood Tubes
PaxGene DNA Blood Tubes
Cryovials (for storage of plasma)
Plastic or cardboard storage boxes with internal racks for cryovial storage
Racking/boxes for Paxgene blood tubes
Pens for writing on labels

Q: What are the timelines for the bloods – how long plus or minus the infusion time do we have to take the bloods?
A: We require Day 0 bloods to be taken as close as possible to the time of randomisation and prior to the administration of Landiolol. Day 1 starts as soon as you randomise. We haven't specified when the bloods have to be taken on each sampling day, as long as they are taken on days 0, 1, 2, 4, 6 and end of noradrenaline treatment. If a patient is randomised in the evening or the middle of the night for example it would be fine for you to take the bloods for day 1 and process them when you

are in the following morning. You must record in the medical notes when a blood sample has been taken.

PAXgene tubes are only for biobank samples (Whole Blood) to be taken on Day 0, Day 1 and at EONT (RNA PAXgene only), and are optional. Two 2.5ml samples are taken on day 0, one 2.5ml sample is taken on day 1 and one 2.5ml sample is taken at EONT, if this is not already a sampling day.
Green lithium heparin tubes are mandatory blood samples. These need to be spun and plasma extracted. 12 ml samples are taken on days 0, 1, 2, 4, 6 and at the EONT Visit;

Time points	**0**	**1**	**2**	**4**	**6**	**EONT**
PaxGene RNA Blood Tube (2.5mL)	1	1				1
PaxGene DNA Blood Tube (2.5mL)	1					
Green Lithium Heparin Blood Tube (4mL)	3	3	3	3	3	3
Total volume (mLs)	17	15	12	12	12	12

Q: Why doesn't the database capture the PAXgene sample taken at EONT?
A: The database requires a further update to the system to capture the additional EONT biobank sample now required. We will therefore be requesting blood sample storage logs to ensure this additional sample is being collected, and once the database has been updated this can be added on retrospectively

4. Contracts

Payments to sites are as follows;

- £500 per patient recruitment and follow up fee
- £7.53 per participant – drug accountability per patient (advised to move to critical care team)
- £12.54 per participant – drug dispensing per patient (advised to move to critical care team as the researchers will reconstitute IMP)
- £800 pharmacy set up, maintenance and close down fee

Q: Is a Material Transfer Agreement (MTA) required?
A: No, this is embedded into Schedule 4 of the site agreement.

Q: How long is your internal process for issuing green light once SIV has taken place and R&D Capacity and Capability is issued?
A: Once all documents have been received and the contract has been signed, the green light will usually be issued within 2 weeks (to allow sponsor authorisation of site and IMP despatch).

5. Inclusion Criteria and Screening

Q: On the inclusion criteria it states a patient becomes eligible following 24 hours on vasopressors, if they have a heart rate of ≥95. It also states the patient has to be receiving noradrenaline >0.1mcg/kg/min as their vasopressor support at this time point. For patients to be eligible, can we include time on metaraminol as part of the 24 hour, or is it from the start of noradrenaline infusion?
A: The 24 hour clock starts when you start any vasopressor therapy (including metaraminol).

Q: If the patient starts and restarts noradrenaline or another vasopressor therapy, when does the 24 hour window clock begin?
A: If a patient is receiving vasopressor support e.g. noradrenaline or metaraminol for their septic shock and this stops for less than 12 hours before recommencing again this is counted as the same vasopressor episode. The 24-72 hour window will apply from when they first started receiving vasopressor support.
E.g. if a patient receives noradrenaline on 14/08/2018 at 09:00, this stops at 15:00, then restarts at 20:00 (5 hour gap in between; less than 12 hours) the patient will become eligible on 15/08/2018 at 09:00 (24 hours since start of first episode). Remember, they will additionally have to be on a dose of noradrenaline >0.1 mcg/kg/min.

If the patient has a gap of more than 72 hours between the two episodes of vasopressor support because a new bout of septic shock has occurred, the 24-72 hour window will start at the beginning of the second episode.
E.g. if a patient receives noradrenaline on 14/08/2018 at 09:00 and this stops at 15:00 and then isn't restarted until 19/08/2018 at 09:00 as the patient has developed a new round of sepsis, the patient will become eligible on 20/08/2018 at 09:00 (24 hours since start of second episode).

If the scenario arises where the gap between the two episodes of vasopressor support is more than 12 hours but less than 72 hours, the trial team will need to be informed of this as these patients will be assessed on a case by case basis. This is because it will need to be assessed whether the vasopressor support has been recommenced to treat the same bout of sepsis or whether this is for a new round of sepsis the patient has developed. 12 hours is commonly defined as the end of noradrenaline treatment and we predict this particular scenario is unlikely to occur. Please contact the team to discuss these patients further.

If the patient is on metaraminol for longer than 72 hours and then start noradrenaline on the 73rd hour for instance with metaraminol continuing they would be excluded from the trial and should not be randomised.

Q: If a patient has received continuous vasopressor therapy for more than 72 hours for a medical condition other than septic shock and go on to develop septic shock which is treatment by vasopressor therapy, are they eligible for the trial?
A: **NO.** If a patient has received **continuous** vasopressor therapy for more than 72 hours they should not be recruited to the trial, even if the vasopressor therapy was initially started to treat a medical condition other than septic shock.

Q: Does the patient need to be tachycardic for the whole of the 24 hours or is it only necessary that the heart rate is >95 at the time of randomisation?
A: It is only necessary that the patient is tachycardic at the time of randomisation. They do not have to be consistently tachycardic for the whole 24 hours prior to randomisation.

Q: What do you mean by compensatory tachycardia?
A: Any tachycardia which is not sepsis driven, but is instead caused by another condition. Only patients with sepsis-driven tachycardia will be eligible for STRESS-L.

Q: Can patients be recruited if they're already on a beta blocker?
A: Yes, if a patient is on a beta blocker for a pre-existing condition they can still be eligible for the trial, and the beta blocker can be continued (as per clinician discretion), unless the beta blocker has been prescribed for Atrial Fibrillation, in which case the beta blocker would need to be switched to

Amiodarone, Magnesium or potassium as per the protocol. Any beta blocker (apart from Landiolol) the patient has administered during the trial up to Day 14 will be captured on a temporary beta blocker CRF until the database can be updated.

Q: Can we recruit patients from level 2 and level 3 care?
A: Yes ITU and HDU patients can be recruited. A medically qualified physician named on the delegation log will be required to assess and sign off eligibility. You have 24 hours once a patient becomes eligible to randomise them to the trial.

Q: Does the eligibility form need to be filed in the medical notes?
A: This is not an essential requirement but yes it can be filed. It must be clearly documented in the notes how the patient fits ALL of the eligibility criteria points as this will be evaluated during the monitoring visits.

Q: Who can sign the eligibility form?
A: The eligibility form **must** be signed by a medically qualified physician listed on the delegation log as per MHRA guidance for CTIMPs. This should be clearly documented in the patient's note as well. A research nurse should not sign the eligibility form.

Q: Do septic shock patients need to be added onto the screening log?
A: Yes. All septic shock patients should be included on the screening log and not just septic patients.

SEPSIS Diagnosis: Infection (known or suspected) + antibiotics + SOFA score change >=2 = **SEPSIS**
SEPSIS + Noradr (for Mean BP=65) + Lactate >=2 = **SEPTIC SHOCK**

Q: Are patients already in AF excluded?
A: No. Although we believe Landiolol therapy may prevent Atrial Fibrillation (AF), there is nothing in the protocol to exclude patients already in AF. This also includes AF from all sources whether Acute (as a result of the present Septic Shock episode) or chronically (as a result of old age, ischaemic heart disease or any other co-morbidity).

Q: Is there a specific reference that should be used when assessing Child-Pugh Score ≥B regarding the exclusion criteria of Advanced Liver Disease?
A: The following calculator located here can be used to calculate Child-Pugh scores - www.mdcalc.com/child-pugh-score-cirrhosis-mortality#evidence
It is only necessary to calculate the score where there is history, ultrasound or CT evidence of cirrhosis and the score should only be applied to blood test results that reflect the patient's chronic health. That is usually the admission bloods if no previous one exist.

Q: How should the SOFA score change of >2 for the Septic Shock diagnosis be assessed? Which two points should be compared?
A: The SOFA score change is from the patient's baseline upon admission. You can assume this to be 0 if there is no data available. Thereafter, once the patient has been diagnosed with septic shock which requires SOFA greater than 2 and starting noradrenaline the other eligibility criteria should be assessed.

Q: Should a patient withdrawing care be included in the trial?
A: **NO.** Patients should not be recruited if a withdrawal of care decision is in place or imminent. **HOWEVER**, as the target population under study are very sick (don't forget Morelli's [JAMA, 2013] population had a mortality of 80%!), patients should be considered for a trial where a withdrawal of care decision is not in place.

Q: Will the eligibility and randomisation forms be updated following the protocol amendment v3.0 18 October 2018 and v4.0 02 April 2019?
A: The inclusion and exclusion criteria have been updated on both the eligibility and randomisation paper forms following the protocol amendment. Due to resourcing issues at Warwick CTU, the trial database is awaiting an update by the programming team therefore, the eligibility form located on the database has not been changed as of yet. Until the database has been updated, **please leave the e-CRF eligibility form blank**. The trial team will update you when the database has been changed.

In the meantime as already done, please ensure the eligibility form is being completed and signed on **paper** and a copy is sent to stress-l@warwick.ac.uk via the NHS encryption service.

Q: What studies can we co-enrol with?
A: A list of trials STRESS-L can co-enrol with can be found on the trial website: https://warwick.ac.uk/fac/sci/med/research/ctu/trials/stressl/health/coenrolment/. This page is regularly updated by the trial team. WCTU will inform all sites of any updates to co-enrolment via the website. Please let the team know if there are any studies you wish to be considered for co-enrolment.

Q: Can COVID-19 positive patients be enrolled in the trial?
A: Yes, patients with confirmed COVID-19 can be enrolled in to STRESS-L however, blood samples **SHOULD NOT** be obtained for these patients to protect staff safety and reduce the risk of viral transmission.

6. Consent

Q: Can consent be taken before the patient becomes eligible?
A: Yes. Consent can be taken in the pre-24 hour period if it is suspected the patient will remain on vasopressor treatment and likely to fulfil the other eligibility criteria. If the patient then becomes ineligible at the 24 hour mark the consent will be discarded. It must be made clear to the relatives that if the patient is no longer eligible at the 24 hour mark they will not be randomised in to the trial.

Q: Are research nurses able to consent or does it have to be a doctor?
A: As long as your NHS trust allows research nurses to take consent for CTIMPs we have no objection.

Q: Can the professional legal representative consent over the phone or does it have to be face to face?
A: Face-to-face. A physician who is not named on the delegation log and independent from the trial can provide professional legal representative consent. Any clinician who provides the professional legal representative consent cannot therefore be involved in the patient's trial participation, for example, would not be able to sign off eligibility forms.

Q: Can the personal legal representative consent be over the phone?
A: Significant limitations have been placed on the visitation of patients in hospital and therefore a personal legal representative is unlikely to be available to sign the consent form in person. The personal legal representative will be contacted by telephone or videoconference facilities and provided with information about the trial by the Investigator or their nominee. If the PerLR decides that the patient would have no objection to participating in the trial, verbal consent will be obtained

only and the investigator obtaining consent alongside a witness will sign the consent form. A copy of the information sheet and consent form will be sent to the personal legal representative after the patient has been enrolled in the trial and this process will be documented in the patient's medical notes. A second copy of the consent form will be placed in the patients' medical records whilst the original will be retained in the Investigator Site File.

7. Training

Q: What training is available for this study? Would it just be SIV training or would there be specific eCRF and randomisation training?
A: On-site SIVs are undertaken at each site, where protocol procedural training and database (EDC system) training is provided.

Q: Do all clinicians have to have GCP training?
A: Clinicians who **do not** have GCP training can be delegated the following three responsibilities: **E**: review eligibility and sign form, **F**: medical care and supervision of trial participants and **K**: prescribe medication and treatment. They **must** sign the delegation log and training log if they carry out one of these responsibilities.

Q: Are there any further training materials for the trial?
A: We have created two sets of training slides for STRESS-L, as detailed below;
Slides for non-GCP delegated clinical staff: these incorporate elements of GCP and key points about the trial. This presentation is suitable for those clinicians who have been listed on the delegation log as carrying out the three tasks which do not require GCP; roles E, F and K (see above).
Slides for ICU clinical staff: these incorporate some basic information about the trial, and are ideal for staff not directly involved in the trial (i.e. not on the delegation log).

8. Safety Reporting

Q: What events should be reported?
A: The following events are exempt from adverse event reporting AND serious adverse events as well as SUSAR's and SAR's UNLESS the investigator deems the event to be related to the administration of the study drug:

- Death Related to sepsis
- Cardiovascular failure, including the need for vasopressors / inotropes
- Respiratory failure, including mechanical ventilation and acute lung injury
- Hepatic impairment as measured by Transaminases <1000 IU/L
- Renal failure, including the need for renal replacement therapy
- Haematological / Coagulation failure, including thrombocytopaenia and disseminated intravascular coagulopathy
- Delirium / confusion

If an event occurs which is **not** included in one of the above outcomes, this must be reported as per safety reporting definitions. For example, if a patient has pyrexia and this is not related to the drug and not serious, this must be reported as an adverse event. Even though Pyrexia is expected in some cases to occur due to Sepsis, it should still be reported.