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From: STRESS-L, resource
Sent: 30 July 2019 12:11
Subject: STRESS-L July 2019 Newsletter

STRESS-L July Newsletter, Issue 10

@StressLTrial Trial Website

Welcome to the STRESS-L Newsletter!
Please let us know if you have any suggestions for improvements or information you would like to see included on a monthly basis.

Please click on the headers below which will take you to the different sections.

Trial Update

The STRESS-L trial team hopes you all have a rejuvenating summer!

Royal Liverpool Hospital

Well done to Royal Liverpool Hospital for recruiting your first 2 participants back-to-back in June and July!

Milestones

54 patients recruited so far

29 sites open to recruitment

32 sites initiated to date

Protocol Amendment v4.0 02/Apr/2019

As you will have seen from the recent notification of amendment email, dated 12th July, substantial amendment 10 has been submitted. Sites have 35 days from this date to raise any objections and the amendment can be implemented once HRA, REC and local R&D approvals are granted.

The main changes to the protocol are outlined below. Please refer to Protocol Version log V4.0 for a comprehensive list.

Changes to the Exclusion Criteria

Addition of:

- Any form of compensatory tachycardia
- Any form of vasodilatory shock that is not caused by sepsis
- Decision of withdrawal of care is in place or imminently anticipated

Removal of:

- Having been treated with any beta blocker during in the seventy two hours prior to randomisation

Amendment and clarification of Efficacy Secondary Outcomes

Removal of:

- Individual organ failure days in 28 day survivors through measures of oxygenation, renal, hepatic and coagulation function
- Changes in ECG between Randomisation and End of ICU

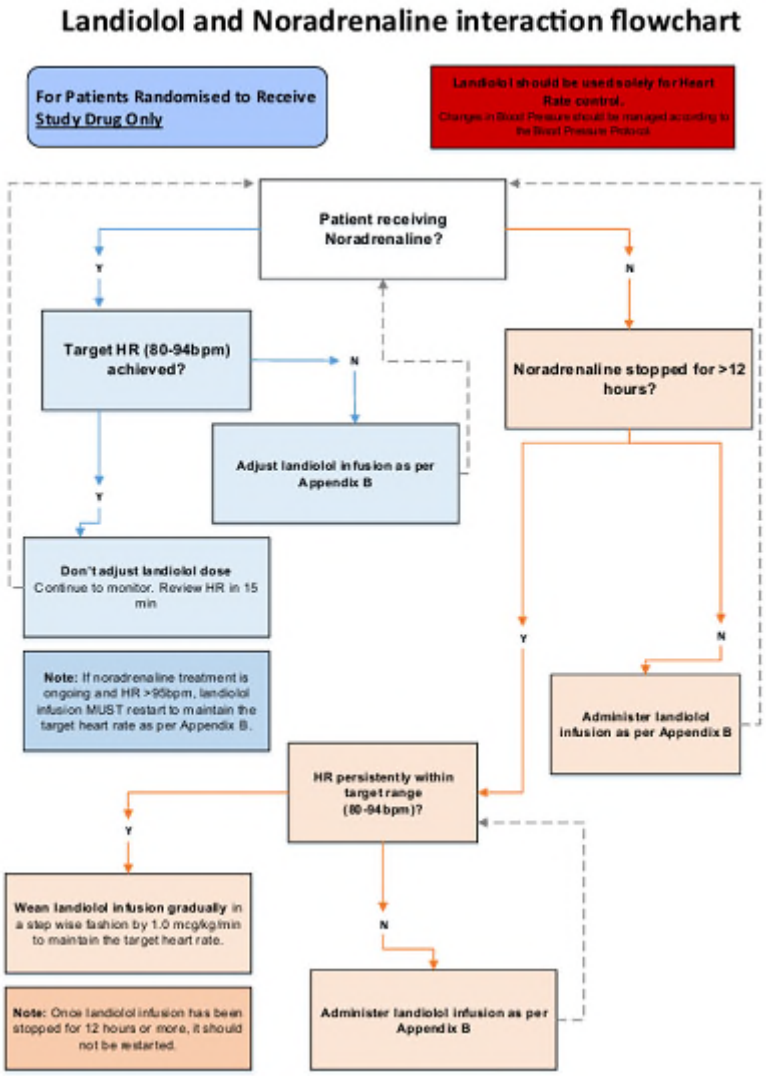
Clarification of landiolol infusion and stopping infusion

Please see updated landiolol dosing laminate (v3.0) for guidance.

Changes to Documentation following the Protocol Amendment v4.0

Following the protocol amendment, the following documents will be updated and circulated form implementation;

- Temporary Beta Blocker CRF - to collect any beta blocker the participants may be on prior to and after randomisation up to 14 days
- Updated Eligibility CRF - to amend the inclusion/exclusion criteria. **Please note** that whilst the paper CRF has been updated, the eCRF on the database is still the previous version, so please leave the Eligibility Form on the database blank until this has been resolved
- Updated Day 28 Follow Up CRF - to remove the collection of SOFA Score data. **Please note** that whilst the paper CRF has been updated, the eCRF on the database is still the previous version, so please leave the SOFA Score section of the eCRF blank until this has been resolved
- Updated Patient CRF Record - in line with the changes to the CRFs listed above
- Updated SAE Form - it will no longer be possible to fax SAE forms to the coordinating team. The coordinating team will also now be responsible for the expectedness assessment and the event classification, so these sections will no longer be completed by site staff.
- Updated Document and Protocol Version Logs
- Updated Screening Log - in line with the changes to to the inclusion/exclusion eligibility criteria
- Updated eligibility cards - these will be circulated to all sites following approval of the amendment



Beta Blocker Usage

Patients who have been treated with a beta blocker in the previous 72 hours can now be recruited to STRESS-L.

If a beta blocker has been administered for a pre-existing condition regardless of whether they are randomised to the Landiolol plus standard care or standard care only arm, it can be continued. Please complete the CRF to let us know the dose and type of additional beta blocker being administered. The only exception to this is if a patient received a beta blocker for Atrial Fibrillation in the current episode of septic shock. In that case, the beta blocker should be discontinued. We ask that AF is treated with amiodarone, magnesium or potassium as per protocol and at the discretion of the local treating clinician.

If a patient meets the tachycardia eligibility criteria for STRESS-L, then it is unlikely that the existing beta blocker is

working well and so landiolol can be titrated according to protocol if they are randomised to intervention arm. However, the decision to continue or stop pre-existing beta blockade remains at the discretion of the treating clinician.

Changes to IMP Management

As you will know the trial has recently transitioned to refrigerated IMP stock which must be stored between 2-8 degrees Celsius. Thank you for your assistance in ensuring this process has run smoothly.

If you have not done so already, please return;

- copies of your IMP Inventory Logs and IMP Destruction log to the coordinating team.
- copies of the calibration certificates for temperature monitoring devices both in pharmacy and on ICU

Care Withdrawal Guidance

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 the trial where a withdrawal of care decision is not in place.

Adverse event reporting

Please remember to document any adverse events on the adverse events form.

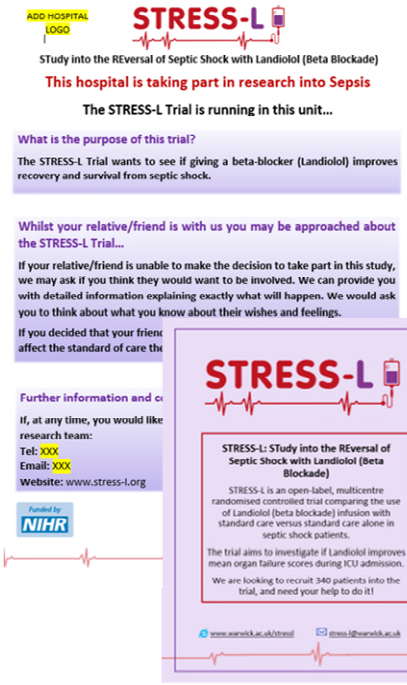
The following events are exempt from adverse event reporting AND serious adverse events as well as SUSAR's and SAR's UNLESS the investigator deems the event to be related to the administration of the study drug:

- 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

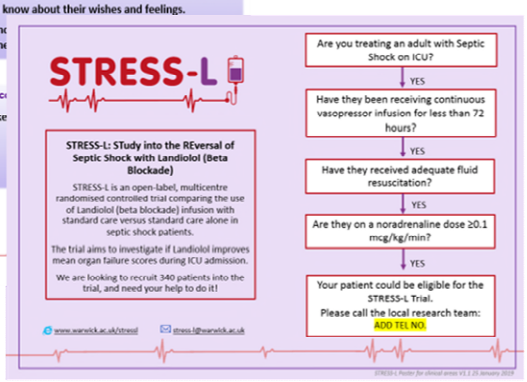
If an event occurs which is **not** included in one of the above outcomes, this must be reported as per safety reporting definitions. For example, if a patient has pyrexia and this is not related to the drug and not serious, this must be reported as an adverse event. Even though Pyrexia is expected in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

Trial Materials

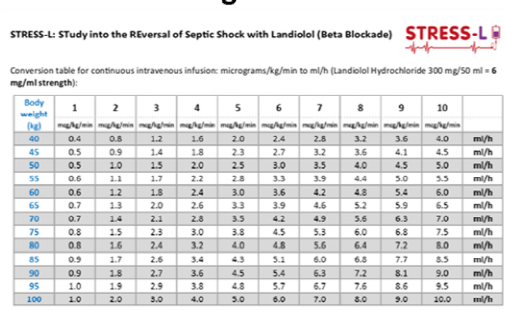
Please let us know if you would like to receive any of our trial materials below!



ICU Staff and Relative posters



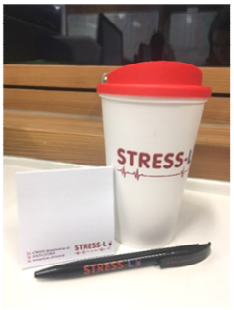
Landiolol dosage chart laminates


STRESS-L: STudy into the REversal of Septic Shock with Landiolol (Beta Blockade) STRESS-L

Conversion table for continuous intravenous infusion: micrograms/kg/min to ml/h (Landiolol Hydrochloride 300 mg/50 ml = 6 mg/ml strength):

Body weight (kg)	1 mcg/kg/min	2 mcg/kg/min	3 mcg/kg/min	4 mcg/kg/min	5 mcg/kg/min	6 mcg/kg/min	7 mcg/kg/min	8 mcg/kg/min	9 mcg/kg/min	10 mcg/kg/min	
40	0.4	0.8	1.2	1.6	2.0	2.4	2.8	3.2	3.6	4.0	ml/h
45	0.5	0.9	1.4	1.8	2.3	2.7	3.2	3.6	4.1	4.5	ml/h
50	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	ml/h
55	0.6	1.1	1.7	2.2	2.8	3.3	3.9	4.4	5.0	5.5	ml/h
60	0.6	1.2	1.8	2.4	3.0	3.6	4.2	4.8	5.4	6.0	ml/h
65	0.7	1.3	2.0	2.6	3.3	3.9	4.6	5.2	5.9	6.5	ml/h
70	0.7	1.4	2.1	2.8	3.5	4.2	4.9	5.6	6.3	7.0	ml/h
75	0.8	1.5	2.3	3.0	3.8	4.5	5.3	6.0	6.8	7.5	ml/h
80	0.8	1.6	2.4	3.2	4.0	4.8	5.6	6.4	7.2	8.0	ml/h
85	0.9	1.7	2.6	3.4	4.3	5.1	6.0	6.8	7.7	8.5	ml/h
90	0.9	1.8	2.7	3.6	4.5	5.4	6.3	7.2	8.1	9.0	ml/h
95	1.0	1.9	2.9	3.8	4.8	5.7	6.7	7.6	8.6	9.5	ml/h
100	1.0	2.0	3.0	4.0	5.0	6.0	7.0	8.0	9.0	10.0	ml/h

Travel mugs, post it notes & pens!



Eligibility card laminates

Please let us know if you have any further suggestions

Co-enrolment update

Please see below for our list of currently approved co-enrolling trials. Discussions are in progress with further studies but please let us know if there are any at your site which are a priority!

- A-STOP
- ADAPT-Sepsis
- BLING III
- CRYOSTAT-2
- FLO-ELA
- REST
- STARRT-AKI
- TAME
- VACIRiSS