NHS
Health Research Authority

Dr Tony Whitehouse
Queen Elizabeth Hospital Birmingham NHS Foundation Trust
Mindelsohn Way
Birmingham
B15 2GW
tony.whitehouse@uhb.nhs.uk

Email: hra.approval@nhs.net

10 November 2017

Dear Dr Whitehouse

Letter of HRA Approval

Study title:	**STRESS-L: STudy into the REversal of Septic Shock with Landiolol (Beta Blockade)**
IRAS project ID:	**213669**
EudraCT number:	**2017-001785-14**
Protocol number:	**STRESS-L**
REC reference:	**17/EE/0368**
Sponsor	**University Hospitals Birmingham NHS Foundation Trust**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The document *"After Ethical Review – guidance for sponsors and investigators",* issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/.

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

Your IRAS project ID is **213669**. Please quote this on all correspondence.

Yours sincerely

Gemma Oakes
Assessor

Email: hra.approval@nhs.net

Copy to: *Miss Nafisa Boota, University Hospital Birmingham NHS Foundation Trust [Sponsor Contact]*
STRESS-L@warwick.ac.uk
Dr Chris Counsell, University Hospital Birmingham NHS Foundation Trust [Lead NHS R&D Contact]
chris.counsell@uhb.nhs.uk

Appendix A - List of Documents

The final document set assessed and approved by HRA Approval is listed below.

Document	*Version*	*Date*
Contract/Study Agreement template [modified mNCA template]		21 September 2017
Contract/Study Agreement template [Statement of Activities]	1	04 September 2017
Contract/Study Agreement template [Schedule of Events]	1	04 September 2017
GP/consultant information sheets or letters [GP Letter]	1.0	10 August 2017
IRAS Application Form [IRAS_Form_01092017]		01 September 2017
IRAS Application Form XML file [IRAS_Form_01092017]		01 September 2017
Letter from funder [NIHR funding application]	1.0	01 June 2017
Letter from funder		07 April 2017
Other [REC cover letter]	1.0	20 October 2017
Other [patient information sheet_tracked changes]	2.0	17 October 2017
Other [SHORT PIS_tracked changes]	2.0	17 October 2017
Other [Legal Representative Information Sheet_tracked changes]	2.0	17 October 2017
Other [Patient Consent Form_tracked changes]	2.0	17 October 2017
Other [Legal Rep Consent Form_tracked changes]	2.0	17 October 2017
Participant consent form [Patient Consent Form]	2.0	17 October 2017
Participant consent form [Legal Representative Consent Form]	2.0	17 October 2017
Participant information sheet (PIS) [Patient Information Sheet]	2.0	17 October 2017
Participant information sheet (PIS) [SHORT patient information sheet]	2.0	17 October 2017
Participant information sheet (PIS) [Legal Representative Information Sheet]	2.0	17 October 2017
Research protocol or project proposal [STRESS-L Protocol]	1.0	10 August 2017
Summary CV for Chief Investigator (CI) [CV Dr Tony Whitehouse]		07 October 2016
Summary of product characteristics (SmPC) [SPC landiolol (MALTA)]		29 June 2016

Appendix B - Summary of HRA Assessment

This appendix provides assurance to you, the sponsor and the NHS in England that the study, as reviewed for HRA Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England to assist in assessing and arranging capacity and capability.

For information on how the sponsor should be working with participating NHS organisations in England, please refer to the, *participating NHS organisations*, *capacity and capability* and *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* sections in this appendix.

The following person is the sponsor contact for the purpose of addressing participating organisation questions relating to the study:

Name: Nafisa Boota
Tel: 02476 572 905
Email: STRESS-L@warwick.ac.uk

HRA assessment criteria

Section	HRA Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	IRAS [Part C] does not list all participating NHS sites involved in the study. The addition of any new sites following REC final opinion requires submission of an amendment.
2.1	Participant information/consent documents and consent process	Yes	The applicant has confirmed members of the research team that form part of the routine care team will make the initial approach to patients/legal representatives about the study.
3.1	Protocol assessment	Yes	No comments
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	The sponsor has provided statement of activities and schedule of events and an **unmodified** mNCA. The mNCA will be used with participating NHS sites in England, and a copy has been

Section	HRA Assessment Criteria	Compliant with Standards	Comments
			provided.
4.2	Insurance/indemnity arrangements assessed	Yes	Where applicable, independent contractors (e.g. General Practitioners) should ensure that the professional indemnity provided by their medical defence organisation covers the activities expected of them for this research study
4.3	Financial arrangements assessed	Yes	The study is funded by the NIHR. The sponsor has confirmed that a per-patient recruitment and follow up fee will be paid to participating NHS sites. Pharmacy set up, maintenance and close down fees will also be covered. Further details are to be provided in the agreement between the sponsor and participating NHS sites.
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	No comments
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Yes	The sponsor has confirmed in addition to the IMP information contained in the protocol, further details will be provided in the IMP Management Manual that will be provided to sites.
5.3	Compliance with any applicable laws or regulations	Yes	<u>Human Tissue Act</u> A separate MTA will not be required for the sample arrangements. The sponsor has confirmed a Trial Laboratory Manual will be provided to sites. The sponsor has also confirmed that a site specific laboratory manual will be provided to participating NHS sites that will retain part of the fresh research samples to measure changes in neutrophil function and oxidative burst activity. These additional activities will

Section	HRA Assessment Criteria	Compliant with Standards	Comments
			form part of the contract negotiations between the participating NHS site and sponsor.
6.1	NHS Research Ethics Committee favourable opinion received for applicable studies	Yes	REC Favourable Opinion was issued on 09 November 2017.
6.2	CTIMPS – Clinical Trials Authorisation (CTA) letter received	Yes	MHRA Clinical Trials Authorisation was issued on 18 September 2017.
6.3	Devices – MHRA notice of no objection received	Not Applicable	No comments.
6.4	Other regulatory approvals and authorisations received	Not Applicable	No comments.

Participating NHS Organisations in England

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.
There is one site type participating in this study. All research activity is the same at all participating NHS organisations as detailed in the study protocol and accompanying documentation. As part of contract negotiations, the Sponsor will discuss with participating NHS sites those that are able to provide fresh blood samples to the Sysmex analysers (described in the study protocol as being part of secondary outcomes). A Site Specific Laboratory Manual will be provided to the participating NHS sites that are carrying out this additional activity. The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. For NIHR CRN Portfolio studies, the Local LCRN contact should also be copied into this correspondence. For further guidance on working with participating NHS organisations please see the HRA website. If Chief Investigators, sponsors or Principal Investigators are asked to complete site level forms for participating NHS organisations in England which are not provided in IRAS or on the HRA website, the Chief Investigator, sponsor or Principal Investigator should notify the HRA immediately at hra.approval@nhs.net. The HRA will work with these organisations to achieve a consistent approach to information provision.

Confirmation of Capacity and Capability

This describes whether formal confirmation of capacity and capability is expected from participating NHS organisations in England.

Participating NHS organisations in England **will be expected to formally confirm their capacity and capability** to host this research.

- The sponsor should ensure that participating NHS organisations are provided with a copy of this letter and all relevant study documentation, and work jointly with NHS organisations to arrange capacity and capability whilst the HRA assessment is ongoing.
- Further detail on how capacity and capability will be confirmed by participating NHS organisations, following issue of the Letter of HRA Approval, is provided in the *Participating NHS Organisations* and *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* sections of this appendix.

The Assessing, Arranging, and Confirming document on the HRA website provides further information for the sponsor and NHS organisations on assessing, arranging and confirming capacity and capability.

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and the minimum expectations for education, training and experience that PIs should meet (where applicable).

The sponsor has confirmed a Local Principal Investigator is required at each participating NHS site and these have already been identified.

Training - The sponsor has confirmed that local research staff will receive protocol procedural training at a site initiation visit.

In addition to the above, site staff are expected to have training in GCP. Certificates confirming GCP training will be collected prior to or at the site initiation visit.

GCP training is not a generic training expectation, in line with the HRA statement on training expectations.

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken

As a study undertaken by local staff, it is unlikely that letters of access or honorary research contracts will be applicable, except where local network staff employed by another Trust (or University) are involved (and then it is likely that arrangements are already in place).

Where arrangements are not already in place, network staff (or similar) undertaking any research activities that may impact on the quality of care of the participant (such as blood sampling), would be expected to obtain an honorary research contract from one NHS organisation (if university employed), followed by Letters of Access for subsequent organisations. This would be on the basis of a Research Passport (if university employed) or an NHS to NHS confirmation of pre-engagement checks letter (if NHS employed). These should confirm enhanced DBS checks, including appropriate barred list checks, and occupational health clearance.

For research team members undertaking activities that do not impact on the quality of care of the participant (for example, administering questionnaires), a Letter of Access based on standard DBS checks and occupational health clearance would be appropriate.

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England to aid study set-up.
The applicant has indicated that they intend to apply for inclusion on the NIHR CRN Portfolio.