NHS
Blood and Transplant
Clinical Trials Unit
Long Road
Cambridge
CB2 0PT

14th June 2021

Dear London Queen Square Research Ethics Committee,

RE: SIGNET: Statins for Improving orGaN outcome in Transplantation
IRAS ID: 288722
CI's: Professor John Dark and Dr Dan Harvey
Sponsor: The Newcastle Upon Tyne Hospitals NHS Foundation Trust
Sponsor ref: 09691

Thank you for your review of our application, and please find below our responses to the Provisional Opinion:

Number	Action Required	Response from the applicant
1	The Committee requests the researchers amend the protocol to provide an approximate timeframe (in regard to the point that organ retrieval will occur) that details the earliest and latest possible time-points that consent will be requested and when Simvastatin can be administered effectively.	In almost all cases the consent for research is taken immediately after the consent for organ donation. The organ donation process is long and complex. In the intervention arm the statin will thus be given 20-30 hours before organ retrieval. In the very rare circumstance of late research consent (perhaps the family need to consult other members) we would not wish to limit the time of administration of the statin as the subsequent duration of donor management prior to organ retrieval remains difficult to predict even many hours after the process has started and potential benefit therefore remains. We agree with the committee this is a relevant consideration and we have a pre-specified statistical analysis to investigate the effect of duration of simvastatin action, but this is relatively unknown at the outset and we are keen to retain a range of durations within the study to answer this important

		question. We have added a specific statement to the statistics plan to clarify this point.
2	The Committee requests the PIS be amended to include details on what action will be taken if the family, friends or Next of Kin become distressed and that contact details for appropriate individuals/organisations they can contact for support be included.	The Specialist Nurses are very familiar with talking to distressed families; indeed, this is a core aspect of their role and would take precedence over research consent for example. In addition to this a range of support is available, varying in organisation at a local level. Family, friends or next of kin will be directed to these local bereavement charities or support groups. The PIS has been amended to signpost families to the SNOD or local hospital team who will be able to advise what support is available. Nationally the donor family network provide support and we have included a link to their website showing the support they offer.
3	The Committee agreed that the proposed use of a single electronic confirmation of consent for participating in the research and for the organ donation was appropriate, however there was concern that this could result in the research aspects being unclear. The Committee requests text be added to the consent form sticker to specify that the points the individual are consenting to are for research purposes, rather than what would be carried out under standard practice for organ donations.	We are very pleased that the committee agree with the use of the single consent form, as is the standard practice for all other research for which family consent is requested. The sticker has been appropriately modified.
4	The Committee agreed that the researchers had taken appropriate measures to protect the research participants by including a data monitoring committee that will cease the trial should the data indicate any risk to participants. The Committee requests the researchers provide confirmation of what specific outcomes would cause the data monitoring committee to cease the study	The DMC includes an international expert on trials in organ donors who brings critical care expertise, a European expert in abdominal transplantation, and an independent statistician. Their extensive experience will help them to assess the different organ outcomes in the study and make judgements about any safety concern for participants. At their first meeting we discussed the

	and confirmation that the research team were satisfied this was sufficient to protect the recipient's safety.	challenges of assessing outcomes across multiple types of organ transplant. The study design includes formal interim analyses after 50% and 75% of recruitment. These will look at the primary outcome of the study (in heart transplants) and use established statistical techniques to assess whether there is strong evidence of harm, benefit or futility at those points. To give an indication, the p-value thresholds at the 50% and 75% interim analyses would be 0.005 and 0.022. While the statistical methods only focus on the heart primary outcome, the DMC will review outcomes for all organs at every meeting and at these interim analyses. The DMC will also be provided with contextual data from the wider UK transplant programme to help interpret these trial data. The DMC will be provided with data on organ utilisation rates and early post-transplant patient and graft survival for each organ. These key safety outcomes will be carefully monitored for any concerns as the primary role of the committee. The research team are satisfied the DMC will be able to protect recipient's safety using the data available to them, but to bolster this will offer the DMC the opportunity to expand their number and add any additional expertise required at their discretion at the next meeting.

Assessment - Further information required

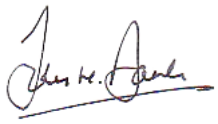
Assessment - Further Information Required	Response from the applicant
Please provide more information on withdrawal in the Donor Family PIS, specifically at what point withdrawal of the organ transplantation will no longer be possible. Please confirm whether recording verbal consent over the telephone is standard practice or whether it is being conducted solely for research purposes.	Withdrawal from the research is possible at any time. If this occurs after the intervention medication has been given, then no further donor data is required or collected. Withdrawal of consent for organ donation itself after confirmation of death by neurological criteria is unusual, and in practice only possible before the donor is transferred from ITU to the operating theatre. The option of withdrawing from research is clearly stated on the PIS, but withdrawal from organ donation itself is a complex clinical consideration managed by the specialist nurse and the ICU team. Although not referenced in the PIS this is extensively discussed within the organ donation consent process. Recording verbal consent over the telephone is standard practice for organ donation consent and research consent.

List of revised documents submitted:

- 09691 Patient Information Sheet v1.1 11/06/2021
- 09691 Patient Information Sheet v1.1 11/06/2021 - Tracked Changes
- 09691 Consent form sticker v1.1 11/06/2021
- 09691 Consent form sticker v1.1 11/06/2021 – Tracked Changes
- List of collaborating sites to date 14/06/2021

Please do not hesitate to contact us if you have any queries.

Kind regards,



Prof John Dark
Chief Investigator

Dr Dan Harvey
Chief Investigator