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13th March 2025

Dear Sir/Madam,

**Study Title:** EVIS - Early vasopressors in Sepsis

**IRAS Number:** 307862

**CTA:** 24712/0060/001-0003

**European Clinical Trials Database (EudraCT) Number:** 2021-006886-39

**Sponsor:** NHS Greater Glasgow and Clyde

**Current Protocol Version:** V4.0 – 09/12/2024

**Substantial amendment:** SA09

In response to the received Notice of Non-acceptance on the 10th of March for EVIS amendment SA09, I would be very grateful if you would consider the enclosed response in order to address the concerns set out in the grounds for non-acceptance.

1. The last version of the protocol approved by the MHRA is V2.0 – 16/12/2022. During this CTA the sponsor has not declared or provided to the MHRA details of all substantial amendments perform to the protocol from the last version approved by the MHRA (version 2.0 dated 16/12/2022) and the submitted version 4.0 dated 09/12/2024. This is not acceptable; therefore, the application is rejected.

The Sponsor in error only declared and provided a tracked changes documents detailing the changes between V3.0 – 14/02/2024 and V4.0 – 09/12/2024 of the EVIS protocol.

EVIS Substantial Amendment 07 included Non-Substantial changes to Protocol V2.1 – 10/10/2023, this was therefore reviewed by the REC only as indicated by the amendment tool.

As per the SA07 Amendment tool enclosed, the changes to the protocol in V2.1 – 10/10/2023 were not deemed significant by the Sponsor and are as follows:

(A) Administrative updates: versioning.

(B) Update to the sponsor representative contact.

(C) SMG updated to TMG throughout the protocol for consistency.

(D) Schedule of Assessments updated for consistency with the study visits.

(E) SOFA score changed from a secondary outcome to an exploratory outcome. As routine bloods are optional at all time points apart from at baseline, data collection for the SOFA score is not mandatory and therefore has been changed to an exploratory outcome only.

(F) Clarity added to the inclusion and exclusion criteria regarding assessing eligibility.

(G) Additions to the description of the consent process to add additional clarifications.

(H) Clarity added regarding randomisation and eligibility assessment.

(I) Further information provided in relation to time frames for the measurement of vital signs and the serum lactate used for determining eligibility.

(J) Study Visits updated for consistency to match the updated schedule of assessments table.

EVIS Substantial Amendment 08 included further Non-Substantial changes to the Protocol V3.0 – 14/02/2024, and again reviewed by the REC only as indicated by the amendment tool.

As per the SA08 Amendment tool enclosed, the changes to the protocol in V3.0 – 14/02/2024 were not deemed significant by the Sponsor and are as follows:

(A) Administrative updates: versioning.

(B) Added Appendix H to include further information regarding the imbedded process evaluation.

(C) Updated the description of the permitted medications to match the updated SpMC for noradrenaline.

(D) Updated the description of the imbedded process evaluation to match the addition of the new appendix H, to provide further information regarding the imbedded process evaluation sub-study.

(E) Updated the wording to clarify who will have access to the signed and uploaded informed consent forms.

(F) Updates to the data linkage description to clarify regarding where the responsibility for submitting the record linkage applications sits.

(G) Updates to the record retention and archiving arrangements to ensure consistency across study documentation, in relation to the length of time that study documents will be retained.

EVIS Protocol V2.0 – V4.0 TC FINAL – 13/03/2025, along with a summary of protocol changes V2.0 to V4.0 – 13/03/2025 have been enclosed to rectify this error.

1. The sponsor must clarify if the substantial changes performed between version 2.0 dated 16/12/2022 and version 2.1 dated 10/10/2023 and version 3.0 dated 14/02/2024 have been implemented by the sponsor without MHRA approval.

Protocol V2.1 and V3.0 were implemented in SA07 & SA08 respectively by the Sponsor, upon receiving the appropriate regulatory approvals from the HRA and the REC.

As referenced in the protocol Appendix I – Amendment History, the amendment numbers were SA07 and SA08. However, this is due to the amendment being substantial as opposed to the changes to the protocol.

Neither Full review, nor Notification Only to the MHRA were required for SA07 or SA08 according to the completed amendment tools for these amendments. This was due to the outcome of the Sponsor assessments for these amendments, with none of the changes outlined above deemed to have met the MHRA criteria for a Substantial amendment to the clinical trial authorisation i.e. likely to affect to a significant degree: the safety or physical or mental integrity of the subjects of the trial, the scientific value of the trial, the conduct or management of the trial, or the quality or safety of any investigational medicinal product used in the trial.

In relation to the protocol changes submitted in SA09, the Sponsor has determined the following Substantial changes to the EVIS Trial Protocol (V4.0):

(A). Revision of the primary end point - The EVIS Funder (NIHR) approved a Re-design to the EVIS Trial on the 13/08/2024, to update the primary objective. The primary objective is to determine whether early PVI (within 12 hours of admission) targeted to MAP of ≥65 mmHg improves clinical effectiveness in hospitalised adult patients with septic shock compared with usual care, in the first 48 hours. The primary objective is currently measured by the Primary outcome of 'All-Cause Mortality at 30 Days', the proposed re-design revises this Primary Outcome to 'Days Alive and Out of Hospital at 90 Days'. This decision has the support of the EVIS independent study Statistician, IDMC, TSC and Sponsor. The NIHR conducted a formal internal and external review of the revised primary outcome prior to approval. The justification for the change has been enclosed separately in this amendment pack ". Justification for the EVIS change to the Primary Outcome V1.0 09.12.24" which provides a summary of the justification provided to the Funder for review. The approval by the EVIS Funder to proceed with the change/suggested re-design has also be included in this amendment pack (13.08.24 - HTA Contract Variation Request Outcome).

(B). A significant change to the sample size - Reduction to the target sample size from 3286 patients overall to 1005. This is as a result of new sample size calculations being conducted for the revised primary end point of Days Alive and Out of Hospital at 90 Days.

(C). Extension to the planned trial period. As part of the approval to change the primary outcome, the EVIS Funder (NIHR) approved an extension on the 13/08/2024. Current recruitment end date is 30/06/2025, with current study end date 30/09/2025. This amendment will extend the recruitment period, with the new recruitment end date 31/11/2026, a 3 month follow up period ending on the 28/02/2027 and the end date for all study activities to be 31/10/2027.

(D). Revised the Statistics and data analysis section of the protocol for the change to the primary outcome. Includes updated sample size calculations, recruitment rate and primary outcome analysis for the new primary outcome.

Further Non-Substantial Changes made to the EVIS Trial Protocol (V4.0) are:

(A) Administrative updates: versioning.

(B) Updated Schedule of Assessments for clarity and to match the change to the primary objective/outcome.

(C) Updated wording from Patients and Participants used interchangeably throughout the protocol, to Participants throughout for consistency.

(D) Additional description added to the Co-enrolment process, to provide further guidance when a patient would be eligible to co-enrol with more than one additional approved study.

(E) Additional clarity added to the Withdrawal process for patients.

(F) Updated Study Visits to ensure consistency with the updated Schedule of Assessments.

(G). Updated the description of the imbedded process evaluation in Appendix H and the main body of the protocol, to provide further information regarding how the data will be collected and stored.

(H). Included information regarding the National Data Opt Out and how this applies to EVIS Participant data.

(I). Standardisation of MAP ≥ 65mmHG, noticed previous protocols listed MAP > 65mmHG in error.

(J). Updated the rationale section to provide the scientific basis for the new Primary Outcome.

(K). Reduction in number of UK NHS Sites from 60 to 30

We apologise for the oversight in not declaring the non-substantial protocol changes of V2.1 and V3.0 and including this documentation in the original submission.

We hope that this response addresses all of the concerns raised in the grounds for non-acceptance.

The following **additional** documents are provided in support of this application grounds for non-acceptance response:

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|  | **Document Name** | **Version** | **Date** |
| 1. | 307862\_Substantial Amendment 07\_locked | SA07 | 10/10/2023 |
| 2. | 307862\_Substantial Amendment 08\_ | SA08 | 14/02/2024 |
| 3. | EVIS Protocol V2.0 - V4.0 - TC FINAL 13.03.25 | V4.0 | 13/03/2025 |
| 4. | EVIS Summary of Protocol Changes V2.0 to V4.0 13 March 25 | V4.0 – V2.0 | 13/03/2025 |
| 5. | EVIS MHRA Cover Letter – GNA SA09 Response (this document) |  | 13/03/2025 |

Documents provided in support of the initial SA09 Application:

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|  | **Document Name** | **Version** | **Date** |
| 1. | EVIS\_CTA\_MhraProductsForm\_snapshot\_12\_12\_24 |  | 12/12/2024 |
| 2. | EVIS\_CTA\_IRASEudractExport\_12\_12\_24 |  | 12/12/2024 |
| 3. | 307862\_SA\_09\_13Dec2024\_Locked19Dec24\_141613.pdf | V1.6 | 13/12/2024 |
| 4. | EVIS Protocol V4.0 09.12.24 CLEAN FINAL | V4.0 | 09/12/2024 |
| 5. | EVIS Protocol V4.0 09.12.24 Tracked Changes FINAL | V4.0 | 09/12/2024 |
| 6. | EVIS Summary of Protocol Changes V4.0 to V3.0 09.12.24 | V4.0 to V3.0 | 09/12/2024 |
| 7. | Justification for the EVIS Change to the Primary Outcome V1.0 09.12.24 | V1.0 | 09/12/2024 |
| 8. | 13.08.24 - HTA Contract Variation Request Outcome |  | 13/08/2024 |
| 9. | EVIS MHRA Cover Letter |  | 09/12/2024 |

Please don’t hesitate to contact me at Louise.Ner@nhs.scot should you have any questions regarding this submission.

Many thanks for considering this request.

Yours sincerely,

Louise Ner