Dr Alasdair Corfield

NHS Greater Glasgow & Clyde

Royal Alexandria Hospital

Corsebar Road

Paisley

PA2 9PN

[Alasdair.Corfield2@nhs.scot](mailto:Alasdair.Corfield2@nhs.scot)

Research Ethics Coordinator,

09th December 2024

Dear Sir/Madam,

Re: EVIS Study

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| --- | --- |
| **Study title:**  **REC Reference:** | **EVIS - Early vasopressors in Sepsis**  **22/SS/0009** |
| **Protocol number:** | **GN20AE342** |
| **EudraCT number:** | **2021-006886-39** |
| **IRAS project ID:** | **307862** |
| **Substantial amendment:** | **Sub Amend 09** |

Please find enclosed documents pertaining to a substantial amendment for the EVIS Trial.

Please note that following ongoing discussions with the EVIS Trial Funder (the NIHR) the decision has been made to revise the primary outcome of the EVIS Trial from ‘All-Cause Mortality at 30 Days’ to ‘Days Alive and Out of Hospital at 90 Days (DAOH-90)’. This decision has the support of the EVIS independent study Statistician, the Independent Data Monitoring Committee, Trial Steering Committee and Sponsor. 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 proposed re-design has also be included in this amendment pack (13.08.24 - HTA Contract Variation Request Outcome).

The main focus of Substantial Amendment 09 is to address the change to the primary outcome, along with all necessary associated changes such as reducing the target sample size, extending the recruitment period, follow-up period end date and end date for all study activities.

The full details of the proposed protocol changes are listed in the accompanying document ‘EVIS Summary of protocol changes V3.0 to V4.0 09 Dec 24’ and on the Amendment Tool. The principle changes are as follows:

1. **Substantial Changes to the EVIS Trial Protocol (V4.0):**

(A). A 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 new primary end point of DAOH-90.

(B). 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. As a result of a reduction in sample size, EVIS' new targets are now to open 30 participating sites across the UK (a reduction of 30 from the previous target of 60). The monthly recruitment target for participating organisations is also being reduced from 2 participants, per site, per month, to 1 participant, per site, per month.

(C). Update to the primary Objective/Outcome.

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

(E). 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.

1. **Non-Substantial Changes to the EVIS Trial Protocol (V4.0):**

(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.

1. **Minor updates to the clinical information sheets (V4.0) INTERVENTION & STANDARD CARE (V5.0):**

(A) Administrative updates: version and date

(B) Updated wording to confirm to titrating to a MAP of greater than or equal to (≥) 65mmHG to reflect all applicable protocol changes.

1. **Minor updates to the EVIS PIS/ICF’s (V4.0) to reflect all applicable protocol changes**

(A) Update the stated follow up period, to match the updated windows for completion of follow-up activities in the protocol.

(B). Include additional wording for participants regarding the legal basis for the processing of participant data.

1. **Minor Changes to the EVIS Sub-Study Consent Form, PIS and Interview Guide for the Qualitative Research in the context of the Early Vasopressors in Sepsis (EVIS) Trial imbedded EVIS Process Evaluation**

(A) Explicitly ask for consent to record the staff interviews.

(B). Provide further information regarding how the data will be collected and stored.

(C). Include additional wording on the legal basis for the processing of participant data.

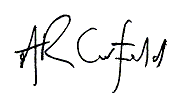
(D). Include in the interview guide the specific questions asked by the EVIS Sub-Study Team, relating to the collection of identifiable staff data, for transparency.

(E.). List the identifiable data being collected in the Consent Form, Interview Guide and PIS.

1. **EVIS CTA MhraProductsForm\_snapshot\_12\_12\_24. Significant updates made to the EudraCT Application Form to better align with the approved/proposed protocol:**
2. Changes to the Sponsor Contact person
3. Change to the principal research question/objective
4. Change to the primary outcome measure for the study and the time point(s) of evaluation of this end point
5. Update to the number of sites anticipated in the Member state concerned
6. Update to the Planned end dates, for clinical interventions and for all trial procedures
7. Reduction of the planned number of subjects to be included
8. Inclusion of additional principal investigators who have joined the Trial since the last time the EudraCT Application Form was updated

Thank you for considering this application.

Yours sincerely,



Dr Alasdair Corfield

The following additional documents are provided in support of this application:

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| --- | --- | --- | --- |
|  | **Document Name** | **Version** | **Date** |
| 1. | EVIS Clinical Information Sheet INTERVENTION | V4.0 | 05/12/2024 |
| 2. | EVIS Clinical Information Sheet USUAL CARE | V5.0 | 05/12/2024 |
| 3. | EVIS\_CTA\_MhraProductsForm\_snapshot\_12\_12\_24 |  | 12/12/2024 |
| 4. | EVIS\_CTA\_IRASEudractExport\_12\_12\_24 |  | 12/12/2024 |
| 5. | 307862\_SA\_09\_13Dec2024\_Locked19Dec24\_141613.pdf | V1.6 | 13/12/2024 |
| 6. | EVIS PIS ICF Personal Legal Rep (England, Wales & NI) V4.0 09.12.24 Clean | V4.0 | 09/12/2024 |
| 7. | EVIS PIS ICF Personal Legal Rep (England, Wales & NI) V4.0 09.12.24 TC | V4.0 | 09/12/2024 |
| 8. | EVIS PIS ICF Prof Legal Rep (England, Wales, NI) V4.0 09.12.24 Clean | V4.0 | 09/12/2024 |
| 9. | EVIS PIS ICF Prof Legal Rep (England, Wales, NI) V4.0 09.12.24 TC | V4.0 | 09/12/2024 |
| 10. | EVIS PIS ICF Prof Legal Rep (Scotland) V4.0 09.12.24 Clean | V4.0 | 09/12/2024 |
| 11. | EVIS PIS ICF Prof Legal Rep (Scotland) V4.0 09.12.24 TC | V4.0 | 09/12/2024 |
| 12. | EVIS PIS ICF Recovered Capacity (England, Wales NI) V4.0 09.12.24 Clean | V4.0 | 09/12/2024 |
| 13. | EVIS PIS ICF Recovered Capacity (England, Wales NI) V4.0 09.12.24 TC | V4.0 | 09/12/2024 |
| 14. | EVIS PIS ICF Recovered Capacity (Scotland) V4.0 09.12.24 Clean | V4.0 | 09/12/2024 |
| 15. | EVIS PIS ICF Recovered Capacity (Scotland) V4.0 09.12.24 TC | V4.0 | 09/12/2024 |
| 16. | EVIS PIS ICF Summary V4.0 09.12.24 Clean | V4.0 | 09/12/2024 |
| 17. | EVIS PIS ICF Summary V4.0 09.12.24 TC | V4.0 | 09/12/2024 |
| 18. | EVIS PIS ICF V4.0 09.12.24 Clean | V4.0 | 09/12/2024 |
| 19. | EVIS PIS ICF V4.0 09.12.24 TC | V4.0 | 09/12/2024 |
| 20. | EVIS PIS ICF WA & Guardian (Scotland) V4.0 09.12.24 Clean | V4.0 | 09/12/2024 |
| 21. | EVIS PIS ICF WA & Guardian (Scotland) V4.0 09.12.24 TC | V4.0 | 09/12/2024 |
| 22. | EVIS Protocol V4.0 09.12.24 CLEAN FINAL | V4.0 | 09/12/2024 |
| 23. | EVIS Protocol V4.0 09.12.24 TC FINAL | V4.0 | 09/12/2024 |
| 24. | EVIS Protocol V4.0 09 Dec 24 Schedule of Assessments | V4.0 | 09/12/2024 |
| 25. | EVIS Sub-Study CF V2.0 09.12.24 CLEAN FINAL | V4.0 | 09/12/2024 |
| 26. | EVIS Sub-Study CF V2.0 09.12.24 TC FINAL | V4.0 | 09/12/2024 |
| 27. | EVIS Sub-Study Interview Guide V2.0 09.12.24 CLEAN FINAL | V4.0 | 09/12/2024 |
| 28. | EVIS Sub-Study Interview Guide V2.0 09.12.24 TC FINAL | V4.0 | 09/12/2024 |
| 29. | EVIS Sub-Study PIS V2.0 09.12.24 CLEAN FINAL | V4.0 | 09/12/2024 |
| 30. | EVIS Sub-Study PIS V2.0 09.12.24 TC FINAL | V4.0 | 09/12/2024 |
| 31. | EVIS Summary of Protocol Changes V4.0 to V3.0 09.12.24 | V4.0 to V3.0 | 09/12/2024 |
| 32. | Justification for the EVIS Change to the Primary Outcome V1.0 09.12.24 | V1.0 | 09/12/2024 |
| 33. | 13.08.24 - HTA Contract Variation Request Outcome |  | 13/08/2024 |