**Dr Alasdair Corfield**

**NHS Greater Glasgow & Clyde**

**Royal Alexandria Hospital**

**Corsebar Road**

**Paisley**

**PA2 9PN**

**Alasdair.Corfield2@nhs.scot**

09th December 2024

Dear Sir/Madam,

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

**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

I would be very grateful if you would consider the enclosed application for a Clinical Trial Authorisation for a substantial amendment (SA09) to the Clinical Trial Authorisation for the above study.

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 proposed revision underwent a formal internal and external review by the NIHR. 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. 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.
2. 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).
3. 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.

In addition, several changes have been made to the EudraCT Application Form to better align with the approved/proposed protocol. The following changes of note have been made:

* Changes to the Sponsor Contact person
* Key change to the principal research question/objective and associated changes

The following additional documents are provided in support of this 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 |

Please don’t hesitate to contact me at Alasdair.Corfield2@nhs.scot should you have any questions regarding this submission.

Many thanks for considering this request.

Yours sincerely,



Dr. Alasdair Corfield