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Research Ethics Coordinator,

21st December 2022

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 05** |

Please find enclosed documents pertaining to a substantial amendment for the EVIS Trial. Please note this amendment also includes the removal and addition of participating sites as per the completed amendment tool.

The full details of the proposed protocol changes are listed in the accompanying document ‘EVIS Summary of protocol changes v1.3 to V2.0 16 Dec 22’ and on the Amendment Tool.

In short, the main changes to the protocol and supporting documents are:

1. **Substantial Changes to the EVIS Trial Protocol (v2.0):**

A) Update to the risk assessment of extravasation with peripheral vasopressor administration – namely that extravasation is a local injury occurring due to damage to the peripheral vein where the PVC is sited, rather than a systemic effect of the norepinephrine infusion. Revised stopping criteria, have been implemented to allow for peripheral norepinephrine infusion to be restarted at a different peripheral venous cannula site in the cases where extravasation results in temporary tissue injury (grade 1 or 2).

(B) A new appendix has been inserted (Appendix B) that includes an extravasation assessment score.

(C) Specification of key secondary outcomes.

(D). Section added on concomitant administration of IMPs with interventions for management of COVID-19.

(E). Revision to dose titration requirements to allow for delay to treatment start and/or temporary halt to peripheral vasopressor administration in the event that the target MAP > 65 mmHg is achieved.

(F). Revision to the guidance for the administration of rescue vasopressors.

(G). Updates to the statistics and data analysis section of the protocol, in line with the specifics now to be captured in a separate statistical analysis plan.

(H) Inclusion that The University of Edinburgh will act as sole data controller for the purposes of data linkage only. Clarification on how data linkage will be conducted, which linkers will be collected and which specific NHS departments this information will be shared with.

1. **Non-Substantial Changes to the EVIS Trial Protocol (v2.0):**

(A) Administrative updates: versioning.

(B) Clarification regarding CTIMP to Non-CTIMP co-enrolment.

(C) Updated instructions in regards to archiving in line with sponsor SOP’s.

(D) Updated appendix A for dosing guidance. Please note that for clarity the mid-range dose of 0.10 micrograms/kg/min has been removed from the table in appendix A. This is to emphasise that norepinephrine dosing must be within the range of 0.05 – 0.15 micrograms/kg/min.

(E) Updated appendix E for SOFA score.

(F) Standardisation of MAP > 65 mmHG.

1. **Substantial updates to the EVIS PIS/ICF’s (v2.0) to reflect all applicable protocol changes**

A) Administrative updates: version and date

(B) Correction of previous error, from 180 day follow up to 90 days for the completion of the health questionnaire, in line with the protocol.

(C) Inclusion on information on data linkage: Clarification on data controllership for data linkage purposes, how data linkage will be conducted, which linkers will be collected and which specific NHS departments this information will be shared with.

1. **Minor updates to the clinical information sheets (V3.0) INTERVENTION & STANDARD CARE:**

(A) Administrative updates: version and date

(B) Updates to the wording to reflect all applicable protocol changes.

1. **IRAS form updated (20/12/2022):**

(A) Significant updates to the IRAS to reflect all applicable protocol changes.

(B) Non-Significant updates to the IRAS to reflect all applicable protocol changes from previous non-substantial amendment NSA04.

1. **EVIS CTA MhraProductsForm\_ReadyForSubmission\_20\_12\_22. Significant updates made to the EudraCT Application Form to better align with the approved/proposed protocol:**

(A) As per the approved protocol, revision to allow use of any brand of Noradrenaline (norepinephrine) 1mg/ml Concentrate for Solution for Infusion and Compound Sodium Lactate Solution for Infusion with a Marketing Authorisation in the UK.

(B) To list the specific vulnerable populations that will be included in EVIS namely, Women of Child-bearing Potential (WoCBP) not using contraception, WoCBP using contraception, Nursing women, Emergency Situations and Subject incapable of giving consent personally.

(C). Clarification that the comparator in EVIS is a medicinal product rather than a placebo.

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** |
| EVIS Clinical Information Sheet INTERVENTION  | v3.0 | 20.12.2022 |
| EVIS Clinical Information Sheet USUAL CARE  | v3.0 | 20.12.2022 |
| EVIS CTA MhraProductsForm\_ReadyForSubmission\_20\_12\_22 |  | 20.12.2022 |
| EVIS Locked Tool 307862\_Substantial Amendment 05\_ | V1.6 | 20.12.2022 |
| EVIS PIS ICF Personal Legal Rep (England, Wales & NI) v2.0 16 Dec 22 Clean | V2.0 | 16/12/2022 |
| EVIS PIS ICF Personal Legal Rep (England, Wales & NI) v2.0 16 Dec 22 TC | V2.0  | 16/12/2022 |
| EVIS PIS ICF Prof Legal Rep (England, Wales, NI) v2.0 16 Dec 22 Clean | V2.0 | 16/12/2022 |
| EVIS PIS ICF Prof Legal Rep (England, Wales, NI) v2.0 16 Dec 22 TC | V2.0 | 16/12/2022 |
| EVIS PIS ICF Prof Legal Rep (Scotland) v2.0 16 Dec 22 Clean | V2.0 | 16/12/2022 |
| EVIS PIS ICF Prof Legal Rep (Scotland) v2.0 16 Dec 22 TC | V2.0 | 16/12/2022 |
| EVIS PIS ICF Recovered Capacity (England, Wales NI) v2.0 16 Dec 22 Clean | V2.0 | 16/12/2022 |
| EVIS PIS ICF Recovered Capacity (England, Wales NI) v2.0 16 Dec 22 TC | V2.0 | 16/12/2022 |
| EVIS PIS ICF Recovered Capacity (Scotland) v2.0 16 Dec 22 Clean | V2.0 | 16/12/2022 |
| EVIS PIS ICF Recovered Capacity (Scotland) v2.0 16 Dec 22 TC | V2.0 | 16/12/2022 |
| EVIS PIS ICF Summary v2.0 16 Dec 22 Clean | V2.0 | 16/12/2022 |
| EVIS PIS ICF Summary v2.0 16 Dec 22 TC | V2.0 | 16/12/2022 |
| EVIS PIS ICF v2.0 16 Dec 22 Clean | V2.0 | 16/12/2022 |
| EVIS PIS ICF v2.0 16 Dec 22 TC | V2.0 | 16/12/2022 |
| EVIS PIS ICF Welfare Attorney Welfare Guardian Nearest Relative (Scotland) Clean | V2.0 | 16/12/2022 |
| EVIS PIS ICF Welfare Attorney Welfare Guardian Nearest Relative (Scotland) TC | V2.0 | 16/12/2022 |
| EVIS Protocol V2.0 16 Dec 22 Final Clean | V2.0 | 16/12/2022 |
| EVIS Protocol V2.0 16 Dec 22 Final TC | V2.0 | 16/12/2022 |
| EVIS Summary of Protocol Changes V1.3 to V2.0 16 Dec 22 | V1.3 to V2.0 | 16/12/2022 |
| IRASEudractExport (.xml) |  | 20/12/2022 |
| IRASForm\_20\_12\_22 (pdf) |  | 20/12/2022 |