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**Paisley, PA2 7DE**

16th December 2022

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:** V1.3 – 03/11/2022

**Substantial amendment:** SA05

I would be very grateful if you would consider the enclosed application for a Clinical Trial Authorisation for a substantial amendment (SA05) to the Clinical Trial Authorisation for the above study.

The principle changes are as follows:

1. 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). A new appendix has been inserted (Appendix B) that includes an extravasation assessment score.
2. Clarifications regarding the specification of key secondary outcomes.
3. Section added on concomitant administration of IMPs with interventions for management of COVID-19.
4. 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
5. Acknowledgement that higher doses of peripheral norepinephrine may be required in the event the target MAP is not achieved and the decision that continued administration of vasopressors must be via a central line. Due to the very short half-life of norepinephrine, this is a temporary but necessary requirement and is standard care in UK centres that routinely administer norepinephrine via the peripheral route. This is considered as out with the scope of the protocol and should be managed as per clinical requirements.
6. 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.
7. Inclusion of section regarding data linkage.
8. Updated instructions in regards to archiving.

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.

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:

* 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
* 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
* Clarification that the comparator in EVIS is a medicinal product rather than a placebo

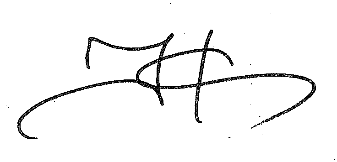
The following additional documents are provided in support of this application:

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| --- |
| 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 |
| EVIS Locked Tool 307862\_Substantial Amendment 05\_ |
| EVIS PIS ICF Personal Legal Rep (England, Wales & NI) v2.0 16 Dec 22 Clean |
| EVIS PIS ICF Personal Legal Rep (England, Wales & NI) v2.0 16 Dec 22 TC |
| EVIS PIS ICF Prof Legal Rep (England, Wales, NI) v2.0 16 Dec 22 Clean |
| EVIS PIS ICF Prof Legal Rep (England, Wales, NI) v2.0 16 Dec 22 TC |
| EVIS PIS ICF Prof Legal Rep (Scotland) v2.0 16 Dec 22 Clean |
| EVIS PIS ICF Prof Legal Rep (Scotland) v2.0 16 Dec 22 TC |
| EVIS PIS ICF Recovered Capacity (England, Wales NI) v2.0 16 Dec 22 Clean |
| EVIS PIS ICF Recovered Capacity (England, Wales NI) v2.0 16 Dec 22 TC |
| EVIS PIS ICF Recovered Capacity (Scotland) v2.0 16 Dec 22 Clean |
| EVIS PIS ICF Recovered Capacity (Scotland) v2.0 16 Dec 22 TC |
| EVIS PIS ICF Summary v2.0 16 Dec 22 Clean |
| EVIS PIS ICF Summary v2.0 16 Dec 22 TC |
| EVIS PIS ICF v2.0 16 Dec 22 Clean |
| EVIS PIS ICF v2.0 16 Dec 22 TC |
| EVIS PIS ICF Welfare Attorney Welfare Guardian Nearest Relative (Scotland) Clean |
| EVIS PIS ICF Welfare Attorney Welfare Guardian Nearest Relative (Scotland) TC |
| EVIS Protocol V2.0 16 Dec 22 Final Clean |
| EVIS Protocol V2.0 16 Dec 22 Final TC |
| EVIS Summary of Protocol Changes V1.3 to V2.0 16 Dec 22 |
| IRASEudractExport (.xml) |
| IRASForm\_20\_12\_22 (pdf) |

Please don’t hesitate to contact me at [Pamela.Sandu@ggc.scot.nhs.uk](mailto:Pamela.Sandu@ggc.scot.nhs.uk) or 0141 314 4414 should you have any questions regarding this submission.

Many thanks for considering this request.

Yours sincerely,



Pamela Sandu

Research Co-ordinator