Study Title: EVIS - Early vasopressors in Sepsis
European Clinical Trials Database (EudraCT) Number: 2021-006886-39
Sponsor: NHS Greater Glasgow and Clyde
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Substantial amendment: SA09

Justification for the EVIS Change to the Primary Outcome

The Early Vasopressors in Sepsis (EVIS) study aims to answer an important research question about the approach to resuscitation of adults with septic shock, namely whether low volume intravenous fluid resuscitation facilitated by early use of peripheral vasopressors leads to improved outcomes compared with standard care. The research question at the heart of the EVIS study remains unanswered, of high clinical importance [1] and relevant to patients and their families [2]. The target population of the study are an underserved population in research due to their severity and acuity of illness, temporary incapacity and socioeconomic profile.

We have submitted evidence to the NIHR (National Institute for Health Research) which shows that currently, the study has:

- recruited the anticipated target critically ill population
- an outcome event rate that was anticipated in this population, and confirms the severity of illness
- demonstrated that interventions are being delivered as planned
- demonstrated the capability of integrating process evaluation work with the main trial
- delivered added value, such as high multi-specialty and multi-disciplinary engagement with the API scheme

We believe that the central research question is still highly relevant, and we are proposing changes to the design of the project to allow the research question to be answered, in a timely manner and appropriate financial envelope. We still believe that regardless of whether the trial results are positive, negative or neutral, the trial will deliver meaningful results for clinicians, patients and the wider health service, with the potential to change practice nationally and internationally.

Proposed redesign

Primary outcome

We are proposing changing the primary outcome to Days Alive and Outside of Hospital at 90 days (DAOH-90). Septic shock is associated with significant mortality and reduced quality of life in survivors. The primary outcome of DAOH-90 is a patient-centred outcome measure that will capture both death and morbidity. DAOH has been validated in other settings where mortality alone is insufficient to capture the burden of disease, particularly the longer-term functional outcome sequelae [3,4]. The choice of DAOH-90 was informed in consultation with our public and patient partners. They felt that time spent out of hospital and at home is an important outcome and may be more of an acceptable outcome to patients than the current 30 day mortality, as it also captures the impact on patients as well as their rehabilitation journey. DAOH is readily quantifiable and is currently being used as an outcome measure in other critical care trials [5,6]. It would also be a meaningful outcome from a clinical and NHS hospital usage perspective.

Statistical calculations

Overall, a sample size of 975 usable participants (1,005 overall allowing for 3% loss to follow up) will give 90% power using an ordinal logistic regression model for the equivalent of around 7 days

improvement in the mean DAOH-90. The 7 day difference in primary outcome is based on feedback from patients and clinicians.

We have used data from the ARISE-FLUIDS study currently recruiting in Australia in a similar population. Their observational study reported a standard deviation of 31 for DAOH-90. For a two-sample t-test, assuming that DAOH-90 has a symmetric distribution summarised by its location (mean) and spread (SD), to detect a mean difference of 7 units in a SD of 31 equates to an effect size of 7/31 or about 0.23. This requires a sample size of 414/group or 828 overall.

The distribution of DAOH-90 is not symmetric. By convention, deaths are scored as -1. We originally powered the study on any cause death and anticipated that in this sepsis population there would be 25% deaths in the control group and that the treatment has expected to reduce this to 20%. When around a quarter of the values of the primary outcome are at an extreme (here -1) there is no transformation that might map the transformed variate onto a more symmetric shape.

In addition, there may be a small subset who are going to be mildly ill and discharged quickly – at the other end of the spectrum there might be some who will be alive and at home for 90 days regardless. So, the natural distribution of the DAOH-90 in this population might be 'bath shaped', with concentrations (unequal) at the two extremes of -1 and 90, and then the remainder taking values between 1 and 89. We have then inflated 828 participants by 15% to allow for non-parametric distribution based on the accepted fact that the asymptotic relative efficiency (compared with the parametric two-sample t-test) of a ranked based test (e.g., Wilcoxon rank sum test) is never worse than 86.4% [7].

Analysis

If approved, we will update our Statistical Analysis Plan and seek approval from our independent oversight commitments (the iDMC and the TSC). The main analysis will be according to the intention to treat principle and use a logistic regression model for the new primary outcome of DAOH-90 adjusting for centre as a random effect (or e.g. centres combined at a regional level if there are many small centres) and any pre-specified baseline covariates strongly predictive of outcome. We will run sensitivity type analyses that investigate the robustness of the findings to any patterns of missing data (expected to be negligible for the primary mortality outcome).

The secondary outcomes, which will now include 30 day all-cause mortality, will be analysed in a similar way to the primary analysis, using statistical models appropriate to the distribution of the outcome (mainly linear or logistic mixed effects models).

Centres

In order to deliver this recruitment, we are now proposing recruitment from 30 centres across the UK, as opposed to the previously modelled 60 centres. We have currently opened 22 sites to recruitment, with a further 3 actively completing the site set up process. We are in conversation with a number of other potential sites currently, with their participation in EVIS under consideration, so we as a trial team believe it is feasible and deliverable to reach the new projection of 30 open and recruiting sites. We are aiming to recruit 1 patient per site per month, retaining the previously accounted for four month bedding in period, whereby newly opened participating sites are expected

to recruit 0 patients in the first four months, reaching the average of 1 patient per month, per site, by month 4.

Timelines

In order to deliver the revised recruitment target and number of sites, we have revised our study timelines. We now anticipate last patient recruitment by 30/11/2026, an extension of 1 year and 5 months from the previously projected recruitment end date of 30/06/2025. We have a 3 month (90 day) follow up period, so the new predicted end date for follow-up activities would be 28/02/2027. We have also in collaboration with the ECTU incorporated additional time in order to allow for routine data applications and receipt of this data, as well as data cleaning alongside database lock. So the new predicted end date for all study activities would be 31/10/2027.

Study design

Apart from those changes outlines above, the study will remain an open label two-arm, multicentre, pragmatic, parallel group randomised trial of adult patients with community acquired sepsis recruited from the Emergency Department and Medical and Surgical Assessment Units across 30 UK NHS Hospitals.

P: Adults presenting to an ED or AMU with signs or symptoms of community acquired sepsis and a SBP < 90 mmHg or MAP < 65mmHg and a venous lactate of > 2mmol/l

I: Intravenous norepinephrine infusion commenced via a peripheral intravenous cannula and titrated to a MAP ≥ 65mmHg for 48 hours after randomisation

C: Intravenous crystalloid administered as 250-1000ml boluses up to 30ml/kg in the first 3 hours after randomisation, and thereafter according to national guidelines for remaining 45 hours to a target MAP ≥65mmHg.

O: Days alive and out of hospital at day 90 (DAOH-90)

Support

The study Sponsor, Trial Steering Committee, Data Monitoring Committee and Clinical Trials Unit have reviewed the proposed re-design and support this change. The Trial Funder the NIHR underwent a formal internal and external review of the proposed redesign also, and approved this change – please see Funder Approval letter as part of this amendment submission pack as evidence.

References

1. De Backer D, Deutschman CS, Hellman J, et al. Surviving Sepsis Campaign Research Priorities 2023. Crit Care Med. 2024;52(2):268-296.
2. Smith J, Keating L, Flowerdew L on behalf of the JLA EM PSP Steering Group, et al An Emergency Medicine Research Priority Setting Partnership to establish the top 10 research priorities in emergency medicine. Emergency Medicine Journal 2017; 34:454-456

3. Myles, P.S., et al., Validation of days at home as an outcome measure after surgery: a prospective cohort study in Australia. BMJ Open, 2017. 7(8).
4. Fanaroff, A., et al., Days Alive and Out of Hospital: Exploring a Patient-Centered, Pragmatic Outcome in a Clinical Trial of Patients With Acute Coronary Syndromes. Circulation: Cardiovascular Quality and Outcomes, 2018. 11(12).
5. Presneill JJ, Bellomo R, Brickell K, et al. Protocol and statistical analysis plan for the phase 3 randomised controlled Treatment of Invasively Ventilated Adults with Early Activity and Mobilisation (TEAM III) trial. Crit Care Resusc. 2023;23(3):262-272.
6. ARISE-FLUIDS Clinicaltrials.gov.au (Registration No: NCT04569942)
7. RF Riffenburgh – Sample Size Estimation and meta-analysis Chapter 18, section 14 in Statistics in Medicine ed. Lachenbruch, 2012)