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Dear Niklas

29 November 2024

Re: STEPCARE trial, Data Safety Monitoring Board

I write as Chair of the STEPCARE Data Safety Monitoring Board (DSMB). The DSMB met on 27 November 2024, to review the results from the first interim analysis. In attendance, including myself, was Professor David Harrison, Professor Tim Walsh and Professor Joyce Yeung. A follow-up meeting with Professor Kathy Rowan was held on 29 November. Due to difficulties arranging the meeting the trial team were not in attendance at an open session.

We reviewed the updated external evidence, the progress of the trial, the completeness of the data, the delivery of the intervention, interim analysis (from the first 500 patients recruited) including safety data. As a DMEC, we would like to congratulate the trial team with the progress of the trial. Of particular note, at the time of the report:

- 41 sites from 11 countries were actively recruiting participants (now 44 from 12 countries)
- Site recruitment is averaging almost 6 patients a day
- Missing data for the mortality outcomes is exceedingly low (1.4% at day 30)
- Minimal eligible patients are being missed for recruitment (approximately 25%)
- There is clear separation between the groups across the three trials, especially in the blood pressure and sedation trials
- The DSMB agreed the external evidence did not change the need for STEPCARE

In terms of separation, we would like to note the convergence of temperatures between the groups at approximately 36 hours, and would encourage the trial team to further understand whether this is a potential issue with delivery of the intervention for the full 72 hours.

Please can you pass on our thanks to Professor Michael Bailey for the high-quality report and his quick response to requests from the DSMB. We would request that for future reports: (1) 'Death' is removed from the baseline table (unless justified)in the open report; (2) a consort flow is added outlining the screening process/failures; (2) details regarding consent are added to the open report; and (2) Baseline characteristics by the six treatment arms is provided in the closed report.

For the interim analysis we reviewed: potential interactions between the trials; 6-month mortality (or hospital discharge); functional outcome at 30 days; and serious adverse events. I can confirm that the DSMB recommendation is for STEPCARE to **continue without any changes**.

As outlined in the Charter, our suggestion for the next interim analysis is to occur when 1250 patients reach at least 30-day follow-up. We would expect the third and final interim analysis to occur at 2000 patients in line with the suggested three interim analyses. As the trial is progressing so quickly, we would appreciate an efficient turnaround of the report and the meeting to be booked in to allow the trial team to attend an open session. In addition, the protocol states that the statistical analysis plan would be published by the first interim analysis, please could this be shared with the DSMB?

Congratulations again from the DSMB for your fantastic progress made already in the trial. I would be happy either to discuss the above and/or to provide any further information, if useful.

Yours Sincerely

Paul Mouncey
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