Reviewer's report

Title: HIPELD: An international, multi-center, randomized, controlled trial evaluating the effect of xenon on post-operative delirium in elderly patients undergoing hip fracture surgery

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Reviewer: John Norrie

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HIPHELD An international multicenter randomised controlled trial evaluating the effect of xenon on post operative delirium in elderly patients undergoing hip fracture surgery

Statistical / methodological review

Discretionary revisions

1. The protocol could be improved by an explicit discussion of the safety issues and how adverse events are going to be both recorded and reported? There is good discussion about how vital parameters such as blood pressures will be monitored and corrective actions to be taken to keep these parameters within control, but this is more about unexpected safety events?

2. Following on from this, there is no mention of the oversight of the study, in particular an independent Data Monitoring Committee (which would see unblinded data as the study progressed) or an independent chair & members on a Trial Steering Committee, say?

3. The authors describe this as a phase 2 study, and there do seem to be the expectedly large number of inclusion / exclusion criteria. So although the study is undertaken in many centres, it would be useful to include a comment on what a subsequent phase 3/4 trial would look like in terms of a broader set of included patients, and possible size (for a pragmatic estimate of effectiveness rather than efficacy).

4. In particular excluding patients that are cognitively impaired (MMSE < 24) or demented, or even more intriguingly, depressed, should be justified more carefully, even within the context of a phase 2 study?

5. Background - wasn't really sure that depression should be labelled along with age as a 'non-modifiable' risk factor? There are effective treatments for depression? You might also argue that calling cognitive impairment as non-modifiable is contentious, too?

5. The plans for the economic analysis are not given in any detail?

6. The authors are clear on the blind in the study - but it would be useful to comment on what bias the decision making by Physician 2 who is aware of the randomised allocation might have on the various outcomes?
7. Is the Confusion Assessment Method validated for use in clinical trials in this specific age group?

8. What is the rationale for considering the first 4 days post surgery as the primary outcome period?

9. And the authors seem to indicate that collecting data for some of the outcomes post 5 days after surgery is optional e.g. SOFA and lab results - isn't there a risk of both imprecision (only partial returns) and also more seriously bias in this approach?

10. What is the current status of recruitment?

11. Using sealed envelopes is generally considered a sub optimal mechanism for delivering randomisation - open to manipulation - what reassurance is there that this isn't a problem here?

12. Not really sure I understood what the authors were proposing with the analysis 'in the subgroup of patients for whom POD is diagnosed at least once in the 4 days post surgery' - this would not of course be a randomised analysis?