Author's response to reviews

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

Authors:

Mark Coburn (mcoburn@kaachen.de)
Robert D Sanders (robert.sanders@imperial.ac.uk)
Mervyn Maze (MazeM@anesthesia.ucsf.edu)
Rolf Rossaint (rrossaint@ukaachen.de)
Javier Belda (Fco.Javier.Belda@uv.es)
Battist Borghi (battista.borghi@ior.it)
Nadja Rosencher (nadja.rosencher@cch.aphp.fr)
Glenn Arnold (Glenn.Arnold@imperial.nhs.uk)
Pierre Albaladejo (PALbaladejo@chu-grenoble.fr)
Xavier Capdevila (x-capdevila@chu-montpellier.fr)
Vincent Minville (minville.v@chu-toulouse.fr)
Peter Kienbaum (Peter.Kienbaum@med.uni-duesseldorf.de)
Vanessa Mynard (Vanessa.MYNARD@AirLiquide.com)
Chui F Chong (Chui-Fung.CHONG@AirLiquide.com)
Oliver Kunitz (Oliver.Kunitz@mutterhaus.de)

Version: 2 Date: 12 August 2012

Author's response to reviews: see over
Dear Editors-in-Chief, dear Referee,

We would like to thank you for your interest in our manuscript. Your comments and the referee’s comments are very helpful for us. We revised the manuscript according to the suggestions. A point-by-point description is given below. We hope that the revision fulfils your expectation, and we are looking forward to hear from you.

Thank you very much.

Yours sincerely,
Mark Coburn

**Editorial request:**

1) Please include a discussion section:

   *A Discussion section is now included*

2) As your research involves humans please include a statement of ethical approval in the Methods section of the manuscript, including the name of the body which gave approval, with a reference number where appropriate:

   “The design of the study was approved by the clinical ethical review committee (Clinical Ethical Review Committee; Medical Faculty; RWTH Aachen; EK 050/10) and by the local ethical review committees of the participating centres and competent authorities of the five participating countries.”

**Responses to Referee’ s Comments:**

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?
“All Adverse Events (AEs) occurring during the whole study period will be recorded by the investigators. Physicians will record all AEs apart from those occurring on the day of the surgery, between the time of admission of the patients in the operating room to the time of discharge of the patients from the Post-Anaesthesia Care Unit (PACU). The information recorded in the Case Report Forms for each AE experienced by the patients throughout their whole study period will include the nature of the events, their onset date and time, their end date and time, their severity, the corrective treatment(s) started if applicable, the outcome of the events and their relationship to the investigational inhaled gas and to the intravenous line applied separately as assessed by the investigator who records the AE. Physicians will record the relationships of each AE described to the investigational inhaled gas and to the intravenous line applied separately without knowing the nature of the study drugs administered.”

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?

“The study will be monitored regularly (visits and telephone monitoring) by AIR LIQUIDE Santé INTERNATIONAL personnel or any company appointed by the latter. During the monitoring visits, the Clinical Research Associate (CRA) will verify the consistency of the data recorded on the CRFs with the source documents (patient’s medical file, nurse’s chart, etc.). The CRA will also verify the management of therapeutic batches, the presence and completeness of the investigator file and general study compliance with Good Clinical Practice guidelines. An on-site audit may be requested and performed by the sponsor or designee personnel at any time.”

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).

We are awaiting the results of this trial to plan the next trial. We anticipate that a phase 3 / 4 trial would have slightly different inclusion/exclusion criteria to be more pragmatic.

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?
If we show efficacy in the Phase 2 trial we will apply for ethical approval to include patients with reduced capacity. This was not felt to be necessary for the phase 2 trial where we need to establish some form of efficacy.

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?
An interesting point. We have removed mention of these. It is unclear whether treatment for depression and MCI changes baseline connectivity and thus whether treatment reverses the status as a modifiable risk factor for delirium. In fact anti-depressants are actually associated as a risk factor for delirium in patients with depression (Gail et al., 2007).

6. The plans for the economic analysis are not given in any detail?
“Economic parameters, i.e., time to readiness to be discharged from the operating room, effective times of admission and discharge from the operating room, onset and end times of the general anaesthesia and surgical procedure (onset and end times of induction, time of intubation, onset and end times of the administration of the study treatments, time of skin incision and end of wound dressing, time of extubation), total drugs (xenon or sevoflurane) consumption per patient, are to be recorded by Physicians 2, as well as the type of hip fracture surgery performed (such as total hip replacement, hemi-arthroplasty of the hip, dynamic hip screw, cemented or not cemented).”

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?
This is now commented in the discussion section: “A big effort was made to design this study in a double blinded way and to keep the non-blinded bias as low as possible. Throughout the study, there will be two teams of physicians involved in the patient’s follow-up. Physicians 1 will perform the visits which include selection of patients, follow-up visits and study end visit. Physicians 1 will be kept blinded regarding the natures and doses of all study drugs administered throughout the study. Physicians 2 will perform randomisation and surgical procedure under general anaesthesia. However, physician 2 who is performing anaesthesia is not blinded due to technical reasons applying xenon anaesthesia. Yet, the bias of Physician 2, who is aware of the randomisation allocation, is kept minimal. Physician 2 is not involved in the assessment of the outcome parameters. Furthermore, the Case Report Forms are strictly separated and kept locked so Physician 2 is not able to access the Case Report Forms of Physician 1 and vice versa.”
7. Is the Confusion Assessment Method validated for use in clinical trials in this specific age group?
   The Confusion Assessment Method is validated for use in the elderly (see multiple publications by Prof Sharon Inouye, Harvard, USA and Van Munster et al., 2008 for example).

8. What is the rationale for considering the first 4 days post surgery as the primary outcome period?
   Postoperative delirium occurs predominantly in the first 4 days following hip fracture surgery (Kalisvaart et al., 2005), during this period it declines rapidly (peak on day 1, nadir on day 4). Thereafter it plateaus. Delirium occurring after 4 days is unlikely to be due to the anesthetic technique, therefore we only included the first 4 days for the primary endpoint.

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?
   This is true. However, for some of the participating centers this was a problem.

10. What is the current status of recruitment?
   “So far 121 patients have been randomized (July 2012).”

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?
   “A registration number in sequential numerical order in each center separately will be assigned to each eligible patient. Before induction, Physician 2 will open the individual randomization envelope allocated to the patient in order to prepare all equipments required and study drugs needed during the general anaesthesia. Prior to the study start, one randomisation list has been computer pre-established by the sponsor.”

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? I am not quite sure if I understood the question. The treatment is randomized.