Author's response to reviews

Title: Study Protocol: Intrathecal opioid versus ultrasound guided fascia iliaca plane block for analgesia after primary hip arthroplasty - a randomised, blinded noninferiority trial.

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Author's response to reviews: see over
Response to reviewer’s report

Dear Dr Moher,

Thank you for giving us the opportunity to revise and resubmit our manuscript entitled; “Intrathecal opioid versus ultrasound guided fascia iliaca plane block for analgesia after primary hip arthroplasty – a randomised controlled trial”.

We have revised our manuscript in response to your helpful suggestions and comments. Below please find an itemised summary of the suggestions, followed by our responses (in italics).

This is a protocol of a randomized trial comparing ultrasound block to no ultrasound block in 96 people receiving primary hip arthroplasty. The primary outcome is 24-hour post operative morphine consumption. Page numbering, and better still line numbering would greatly facilitate my peer review of the protocol

   This has now been addressed. Please see the revised manuscript.

The protocol is registered and the investigators are seeking funds. On this latter point, can the investigators provide a little more detail for readers about the funding request? For
example, are the investigators applying for peer review funding, funding from industry, or a combination?

This aspect has been expanded from line 393. A grant application has been submitted to the Chief Scientist’s Office (CSO). The CSO is part of the Scottish Government Health Directorate. Its role is to support research initiated by the research community in Scotland and to advise the Scottish Government on how research contributes to improvements in health and healthcare. Grant applications to the CSO undergo a stringent peer review process prior to any award being made.

A grant application has also been made to the European Society for Regional Anaesthesia and Pain Medicine. Once again, all applications are peer reviewed by experts in the field of regional anaesthesia prior to funds being awarded. These funders have no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The decision regarding any funding awards remains outstanding.

In the covering letter submitted along with the protocol the investigators consider this to be a pragmatic trial. I’m more used to thinking about pragmatic trials as ones involving several hundred participants across many different centres recruiting participants.

The word “pragmatic” has been removed.

In the body of the protocol (hypothesis section) the investigators state their interest in seeing whether ultrasound guided versus non-ultrasound block is “comparable”. When I read comparable in the context of a randomised trial I interpret this to mean interest in detecting equivalence or non-inferiority. The investigators need to clarify this point as it impinges upon several other aspects of the proposed trial, particularly the sample size section. Is the trial designed as a superiority trial or an equivalence or non-inferiority trial?
We thank the reviewer for these helpful comments. We have altered the manuscript to clarify that this is a noninferiority trial. As we had not originally categorised the trial in this manner, the statistical calculation to obtain the sample size has been revised (line 259). The number of patients now required has altered very slightly and the statistical derivation of this number is described in the revised manuscript.

First line of the “overview” section: the investigators should delete “prospective” and elsewhere in the text of the protocol.

The word “prospective” has been deleted as advised.

The consent section is rather long at about half a page. Is there something unusual about this trial, in terms of the intervention, safety profile that warrants this amount of space?

The consent process for this trial has been reviewed and approved by the West of Scotland Research Ethics Committee 4. The Research Ethics Committee did not feel that there was anything unusual or concerning about our trial. This section of the article has therefore been shortened accordingly. Please see the revised manuscript (line 166).

The randomisation section needs more clarification for readers. The investigators tell readers about how the generation of their sequence will be generated – computer generated. What’s less well described is how allocation concealment is be achieved and how the randomization will be implemented (e.g., Moher et al. CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomized trials. BMJ. 2010 Mar 23;340:c869)?

This section has now been extended to take into account the reviewers comments, many of which were addressed in our protocol but unfortunately omitted from the manuscript. Please see the revised manuscript (line 175).
Would readers find it more helpful if group 1 and group 2 were relabelled ‘experimental’ and ‘control’?

*Group 1 has been renamed Fascia Iliaca Group and Group 2, Spinal Morphine Group. See line 189.*

In the sample size and statistical considerations section the reader is not provided with information about the anticipated length of time the investigators will take to recruit and enrol the participants – how long will the trial take? Similarly, in this section, there are no details as to whether the investigators plan on establishing a data safety and monitoring committee as part of the trial conduct?

*It is anticipated that recruitment for this study will take between one and two years to complete if 1 to 2 patients are enrolled each week. We wish to work only with one surgeon to reduce inter-operator variability. At present he undertakes at least 4 total hip replacements every week. Data collection for each patient will occur during the first 48 hours post-operatively and at a routine 6 week follow up appointment. No further follow up will be routinely arranged. Any patients requiring specific follow up will have this arranged on an individual basis. (Line 306)*

*We value and respect the reviewer’s question on the need for a Data Monitoring Committee. However, we have not proposed to have an independent data monitoring committee. It is our understanding that the need for such committees in certain trials remains under debate. Our understanding is that Data Monitoring Committees are required where the trial meets the definition of ‘Randomised trial with mortality or major morbidity endpoints’. Respiratory depression or death are the only serious adverse events we would think worthy of the attention of the suggested additional data monitoring committee. These events are extremely rare and have not occurred in the context of intrathecal opioid use in our hospital in the last 5 years. Death would be picked up routinely by the Scottish Audit of Surgical Mortality. Both would be picked up at follow up in the*
first 48 hours by investigators. In addition all serious morbidity or mortality would be independently audited by our institution’s cardiac arrest audit, and / or the anaesthetic department’s well developed morbidity and mortality review process. In the event of either of these serious events, we would invite the Anaesthetic Clinical Governance Committee to review the results of the study up until that point.

Consistent with good clinical practice, we also intend to conduct monthly safety meetings in order to highlight and discuss any safety concerns. Whilst we appreciate that these will not be independent, all adverse events will be reviewed at these meetings and any serious adverse events (and suspected unexpected serious adverse reactions) communicated to the appropriate authority as detailed in the protocol, namely the Pharmacovigilance Office in the Robertson Centre for Biostatistics in Glasgow.

Yours sincerely,

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