Author's response to reviews

Title: Local anaesthetic wound infiltration in addition to standard anaesthetic regimen in total hip and knee replacement: Long-term cost-effectiveness analyses alongside the APEX randomised controlled trials

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Author's response to reviews:

To: Dr Ursula D'Souza
Senior Editor
BMC Medicine

Local anaesthetic wound infiltration in addition to standard anaesthetic regimen in total hip and knee replacement: Long-term cost-effectiveness analyses alongside the APEX randomised controlled trials

Dear Dr D'Souza,

We have the pleasure of submitting our revised manuscript for consideration as a paper in BMC Medicine.

We are very thankful for the reviewers' comments to our manuscript and their recommendation. We have now addressed all of the reviewers requested revisions, including discretionary revisions, which we felt have improved our manuscript. We are submitting a revised version of the manuscript with tracked changes and new Tables 4a and 4b and Figures 2a and 2b, to account for revisions requested.

We have also addressed all editorial changes requested. We made efforts to comply with the BMC format requirements. We would appreciate if you would advise on further format changes required.

Thank you for your interest in our manuscript and for the excellent reviews. We
are very grateful for their recommendation.

With best wishes,

Elsa Marques, Ashley W Blom and Sian Noble on behalf of authors

Local anaesthetic wound infiltration in addition to standard anaesthetic regimen in total hip and knee replacement: Long-term cost-effectiveness analyses alongside the APEX randomised controlled trials

Elsa M. R. Marques, Ashley W. Blom, Erik Lenguerrand, Vikki Wylde, Sian M. Noble

Author’s response to reviewers and editor

REVIEWER 1

Reviewer’s report:

This is an excellent example of a 'within trial' economic evaluation. The background and rationale for the analysis is concisely and clearly described. THR and TKR are extremely common procedures, and although the addition of LAI is a minor (low cost) adaptation of existing procedures, the magnitude of estimated QALY gains and cost savings would be important at a population level, if robust. For THR in particular, the estimated gain of around 0.05 QALYs would be a meaningful benefit for patients, and greater than could be expected for many routine therapy and analgesic interventions provided for osteoarthritis.

Thus I do think this is an important topic.

The methods of data collection and analysis are of a good quality, thorough and well described. Although the rates of completion of resource use data are poor, this is extremely common in this type of cost-effectiveness analysis, certainly in countries such as England where there are no reliable information systems that record use of health and social services across hospital and community settings. The use of multiple imputation and adjustment for patient characteristics is appropriate and very clearly explained. The cost-effectiveness results are also clearly and appropriately reported and interpreted. I would support publication with only minor revisions, as suggested below.

AUTHORS RESPONSE: We would like to thank the reviewer for their comments and their recommendation of our work for publication. We acknowledge that missing patient self-report data was an issue, which was addressed though application of the best available methods. We feel our manuscript has been improved through the revisions requested by the reviewer.
MAJOR COMPULSORY REVISIONS
None

MINOR COMPULSORY REVISIONS

1. Please clarify in the Methods, under the ‘Resource use identification and collection’ section whether resources for all causes were included in the costing, or whether the analysis was restricted to hip/knee related services? There is no agreed rule over which costs should be included in this sort of analysis, but it should be clearly stated.

AUTHORS RESPONSE: We would like to thank the reviewer for pointing out this omission. We included only services related to their hip or knee function or surgery. Patient completed questionnaires enquired about services used for reasons related to their joint replacement. The hospital medical notes were reviewed by research nurses who coded visits as related to hip/knee surgery or complications, or not related. We now added to the first sentence of the “Resource use identification and collection” section, page 6:

(p6) “Collection of resource use data was identical for both the THR and TKR trials, and related to services used for reasons related to the patient’s joint replacement.”

2. Similarly, please clarify here whether patients were asked to report on use of health/social services provided by the NHS or Local Authorities, or whether they might also have reported on services paid for privately.

AUTHORS RESPONSE: Thank you for this point. Patients were asked whether they had to pay or make a contribution for services, equipment or changes made to their homes. Note questions M4 through to M7 in the resource use questionnaire available at the DIRUM website (reference 14 in the article). We costed services provided to patients by the NHS or the local authority, and excluded use of services, equipment or home changes paid for privately. We added a sentence in the “Resource use identification and collection” section, page 7, to clarify this:

(p7) “We excluded services, equipment and home changes paid for privately by patients.”

3. Confidence intervals are provided for ICERs in table 4a, and in the text under ‘Economic results: NHS perspective’ (p14). This is misleading, as it does not differentiate between negative ICERs in the South East quadrant (where the intervention is dominant), and those in the North West (where it is dominated).
Thus a negative ICER may be good or bad. And further, one cannot make any inference from the magnitude of negative ICERs (see reference by Hoch). The scatterplots for THR indicate that few bootstrap points lie in the North West, thus the lower confidence limit of £16,641 per QALY probably relates to a ‘good’ negative ICER in the South East (?). The lower limits for the ICER are therefore difficult to interpret. I would suggest removing these confidence intervals, and relying instead on the INMB approach, which is more robust and easy to interpret.

AUTHORS RESPONSE: On reflection, we agree with the reviewer. We planned to only report ICERs when the intervention was not dominant. However, given that the confidence interval still spans to a negative value, in this case due to dominance of the intervention, we agree that reporting this ICER estimate and CI is still misleading. We have therefore eliminated the ICER reports in relation to QALYs from the text and table 4a, and modified the abstract and page 14, “Economic results: NHS perspective” to read:

(p 2/ p14): “From an NHS perspective, LAI in addition to usual analgesia is no longer a dominant strategy in THR, albeit highly cost-effective, with an INMB of £961 (95% BCI £50 to £1,873)”

In addition, we recognise that the confidence interval for the ICER in relation to the WOMAC pain score in Table 4a also spans to a negative value due to dominance, which may also be misleading. In the absence of societal willingness to pain thresholds for a change in the WOMAC pain scale, we have not derived an INMB in relation to the WOMAC, but have now explained in a footnote of Table 4 that the negative values for the ICER confidence interval are due to dominance.

(Footnote of Table 4a): * This confidence interval includes negative ICER values. These negative values indicate that the intervention is dominant.

4. I would also question the p value cited for the Incremental cost per QALY gained in Table 4a. If this relates to a hypothesis that the intervention is cost-effective (at the £20,000 per QALY threshold), as suggested in the footnote, how can it give a different result (p<0.001) to the equivalent INMB test (0.039). Logically, these are testing the same thing: that the bootstrap dots on the cost-effectiveness plane lie below the diagonal with slope lambda. I would suggest removing the p values for the ICERs.

AUTHORS RESPONSE: We thank the reviewer for this comment that the p-values are misleading. The INBM regression estimate is adjusted, and with robust standard errors, whereas the ICER t-test was not and should not have been performed. We have deleted this ICER estimate and p-value in table 4a.
5. The final sentence in the first paragraph on page 15 states that: “The results of an NHS perspective only showed that results in the THR trial were sensitive to the inclusion of social care costs”. I don’t see how this follows from the results reported in Table 4a: the INMB is positive (and p<0.05) from both NHS and NHS+PSS perspectives. The incremental cost estimate does change sign, but the intervention is still cost-effective. Could you clarify this point please?

AUTHORS RESPONSE: We would like to apologise for the unclear statement. We meant to draw attention to the fact that, in THR, the inclusion of social services changes the intervention from non-dominant to dominant. We agree that it was not expressed as clearly as it could have been and have now rephrased the sentence in p15 to read:

(p15): “From an NHS perspective, in relation to THR, the intervention is no longer dominant, but still highly cost effective.”

6. Reference number 19 (Edwards et al) relates to an HESG presentation, which are usually ‘not for quotation’ and not publicly available, so permission from the authors would be needed for citation. But I don’t think that a citation is really necessary for the AUC method for estimating QALYs (it’s very common and well explained in the text). Or if you do want a reference, I think the following paper (number 19, Manca et al) would cover the point.

AUTHORS RESPONSE: We would like to thank the reviewer for this suggestion. We have erased the Edwards et al reference and used the Manca et al reference instead.

DISCRETIONARY REVISIONS

7. Local estimates were used for unit costs of some resources. I understand why, as national tariffs are not available to allow disaggregation of components of the index admission, which could have been affected by the intervention. However, this may limit the transferability of results to other hospitals around the country, where costs differ. It would help to add sensitivity analysis to test the impact of higher or lower local unit costs, and to add some discussion about whether this would be likely to change the results.

AUTHORS RESPONSE: Thank you for this suggestion. We have now included a sensitivity analysis to explore the variation in the local trust estimates for the initial inpatient stay, where all cost categories were microcosted. We have assumed a worst case scenario, where costs would be 50% higher and a best case scenario where costs would be 50% lower. We have added this to the
methods, the results and discussion. We also included these results in Tables 4a and 4b, and include cost-effectiveness plans and acceptability curves for these sensitivity analyses in revised Figures 2a and 2b.

Methods section, “Sensitivity Analysis” (p10): Secondly, we explored the potential variation in the local trust cost estimates for the initial inpatient stay: theatre and recovery costs, LAI injection, and daily admission rates to wards, using a worst and best case scenarios where local costs could be up to 50% higher; or 50% lower, than our local trust.

We further clarified in p10: Imputation models for all cost categories and utility scores were redone accounting for changes in sensitivity analysis.

Results section, “Sensitivity Analysis” (p15): Varying local trust cost estimates during the initial patient stay by a factor of 50% higher or lower did not alter our results, whereby the intervention is still dominant in both surgeries. In THR the INMB statistics range from £1,051, using lower local costs, to £1,151, when higher local costs were used, compared with £1,125 in the base case. In TKR, the respective figures are £253 and £159, compared with £264 in the base case. Due to changes in the components of the imputation model, QALY estimates vary slightly, particularly in TKR for these scenarios.

Discussion section, (p16): Local estimates for the initial hospital were used rather than national tariffs to allow for the disaggregation of this stay. This could potentially limit the generalisability of the results to other hospital locations. However, there were only minor differences in resource use in the microcosted items. A sensitivity analysis which altered these local unit costs showed the initial results to be robust.

8. Regressions to estimate between-group differences in costs and outcomes seem to have been conducted independently. It has been suggested that a seemingly unrelated regression method should be used to acknowledge the relationships between the dependent variables (cost and QALYs): e.g. Willan,AR; Briggs,AH; Hoch,JS. Health Econ., 2004, 13, 5, 461-475. I wouldn’t expect this to make much difference to the results, but it might be helpful to test this, and discuss.

AUTHORS RESPONSE: For this article regressions were conducted independently for costs and outcomes. SUR regressions would not have changed the coefficients reported but would produce a variance-covariance matrix and test the correlation coefficients between costs and outcomes. We felt that this added information may detract from the main message of the study: to report the economic results to inform decision-making. Additionally, we are in the process of conducting a separate methodological study, exploring the relationship between costs and outcomes in this patient group, which will use APEX data as a case study. Reporting on such a relationship within this
manuscript, would prevent us from reporting on this more in-depth evaluation.

9. The authors make a recommendation that LAI ‘should be recommended’ in THR. I don’t disagree with this (in fact I’d go further and suggest it should be recommended for TKR as well, even in countries with a very low willingness to pay per QALY). However, this does step over the line from reporting findings to making policy recommendations, which the funder (NIHR) generally discourages.

AUTHORS RESPONSE: We agree with the reviewer that this may have been too strong a statement. The NIHR reviewed the content of this manuscript and did not requested any changes. We have, however, amended the sentence in the abstract and the conclusions, and refrain from policy recommendations:

(p2/p16) “The evidence, because of larger QALY gains, is stronger for THR.”

REVIEWER 2

Reviewer’s report: The authors should be commend on the construct of such a robust study. I have no remarks or suggestion for revisions. Many thanks.

AUTHORS RESPONSE: We appreciated this approval and compliment and would like to thank the reviewer for the recommendation.

EDITORIAL CHANGES REQUESTED

1. Please provide details of the ethical approval and informed consent for your study in the Methods section. More information can be found at: http://www.biomedcentral.com/about/editorialpolicies#Ethics

AUTHORS RESPONSE: We have now added to page 5 of the Methods information on ethics approval and informed consent:

(p5) “The APEX trials were approved by Southampton and South West Hampshire Research Ethics Committee (09/H0504/94) and all participants provided informed, written consent. The trials were registered as an International Standardised Randomized Controlled Trial (96095682) and as a Clinical Trial of an Investigational Medicinal Product with the Medicine Healthcare and Regulatory Authority (18524/0215/001-0001) and EudraCT (2009–013817–93).”

2. Please include details of the RESTORE collaborators in the Acknowledgements section.
AUTHORS RESPONSE: We have now moved the collaborators section to the acknowledgements.

3. Please provide a list of abbreviations at the end of your manuscript

AUTHORS RESPONSE: We have now added a list of abbreviations to the end of the manuscript, in page 17.

4. Authors’ contributions: please confirm whether all authors approved the final version of the manuscript for submission

AUTHORS RESPONSE: All authors approved the final version of the manuscript and it is now stated in the authors’ contribution section.

5. Please include the date that the trial was registered after the registration number at the end of the abstract.

AUTHORS RESPONSE: We have now added the registration date at the ISRCTN registry.

Please also ensure that your revised manuscript conforms to the journal style (http://www.biomedcentral.com/info/ifora/medicine_journals ). It is important that your files are correctly formatted.

AUTHORS RESPONSE: Thank you. We believe we have formatted our files according to your guidelines. Please advise if there are any other format changes required.