Reviewer's report

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

Version: Date: 15 March 2015

Reviewer: Joanne Lord

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.

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.

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.

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.

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.

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?

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.

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.

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.
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.

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests