PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cost-effectiveness of enhanced recovery in hip and knee replacement: a systematic review protocol
AUTHORS	Murphy, Jacqueline; Pritchard, Mark; Cheng, Lok; Janarthanan, Roshni; Leal, Jose

VERSION 1 – REVIEW

REVIEWER	Howard Thom University of Bristol, United Kingdom
REVIEW RETURNED	10-Oct-2017

GENERAL COMMENTS	-It would be helpful if the introduction gave an example of an "enhanced recovery" pathway to help the reader understand what it is being studied. -The tense is occasionally wrong and refers to the work as being already conducted, rather than planned. For example, the second bullet point under strengths on page 4, or the "Study selection" paragraph on page 6. Check throughout. -The “outcomes” on page 7 should include incremental net benefit with 95% credible intervals, rather than just the point estimate ICER. The ICER has difficulties with interpretation (numerator and denominator having the same sign) and poor reporting of uncertainty. The probability of being cost-effective is not sufficient on its own for uncertainty representation, as interventions may have a high probability of having only a small benefit. -The results of value of information (VoI) analyses should be extracted if they are reported by any studies. In a developing field like these enhanced pathways VoI is useful for research planning. - Noting VoI analyses will help with the “data synthesis” aim on page 8 to “identify intelligence gaps”. The VoI will indicate if the intelligence gap can be filled by a well conducted study.

REVIEWER	Mark Pennington King's Health Economics King's College London UK
REVIEW RETURNED	26-Oct-2017

GENERAL COMMENTS	The protocol follows good practice and addresses an issue of

	sizeable impact to the health service. I raise only a few issues regarding the clarity of the text. In the abstract the authors suggest the use of published modelling checklists to assess the quality of studies. I suspect that many studies will not be modelling studies; do the authors mean they will use economic evaluation checklists? The inclusion criteria could be more clearly stated - it appears to be populations including patients with osteoarthritis. Is there a minimum proportion of osteoarthritis patients required? I was a little unclear regarding the piloting work, notably the comment that 'The search strategy and inclusion/exclusion criteria were piloted by two reviewers using 10|% of the initial study results.' Do the authors mean that the screening and inclusion criteria were piloted? Presumably the search has been undertaken prior to the selection of 10% of the hits.I was also thought that the database selection was rather narrow. Is there a reason for excluding HMIC or the grey literature? Finally, there is no date given for the proposed final search.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Howard Thom
Institution and Country: University of Bristol, United Kingdom Please state any competing interests or state ‘None declared’: None declared.

Please leave your comments for the authors below
1. -It would be helpful if the introduction gave an example of an "enhanced recovery" pathway to help the reader understand what it is being studied.

AUTHORS’ REPLY: We have added a more detailed description of enhanced recovery to the Introduction section.
‘Enhanced recovery programmes vary between hospitals, but generally include a combination of best practice initiatives and medical interventions. Examples of such interventions include: (pre-operative) patient education and setting of expectations around surgery and rehabilitation, nutrition, physiotherapy; (peri-operative) optimised anaesthesia, shortened surgical times, minimal use of drains and tubes; (post-operative) same day mobilisation and discharge, engagement of multidisciplinary teams in provision of physiotherapy and occupational therapy, clear rehabilitation instructions; and/or other interventions as agreed in each hospital.’

2. -The tense is occasionally wrong and refers to the work as being already conducted, rather than planned. For example, the second bullet point under strengths on page 4, or the "Study selection" paragraph on page 6. Check throughout.

AUTHORS’ REPLY: We have corrected the tense throughout.

3. -The “outcomes” on page 7 should include incremental net benefit with 95% credible intervals, rather than just the point estimate ICER. The ICER has difficulties with interpretation (numerator and denominator having the same sign) and poor reporting of uncertainty.

AUTHORS’ REPLY: We are planning on reporting the absolute and incremental costs and incremental QALYs in addition to the ICER. This will facilitate the interpretation of the ICER. We will also report an intervention to be dominated or dominant if that is the case. Although we agree with reporting incremental net benefit to be useful to some extent (albeit conditional on authors reporting the appropriate threshold for their setting) we think that reporting the disaggregated costs and outcomes will facilitate a better comprehension of the results. As a secondary outcome we will report

the probability being cost-effective at thresholds relevant to the study setting, if reported by the authors.
‘In order to inform policy and achieve comparable results between studies, the primary outcome of interest is cost-effectiveness findings in terms of the incremental cost per QALY gained. In addition we will report the absolute costs and QALYs per intervention being evaluated as well as the respective incremental values relative to current care. ‘

4. - The probability of being cost-effective is not sufficient on its own for uncertainty representation, as interventions may have a high probability of having only a small benefit. The results of value of information (VoI) analyses should be extracted if they are reported by any studies. In a developing field like these enhanced pathways VoI is useful for research planning.

AUTHORS’ REPLY: We have added VOI to the secondary outcomes (Outcomes) and Data Extraction sections.
’ The secondary outcomes of interest are the probability of being the most cost-effective intervention (to reflect uncertainty), value of information (VoI) if reported, study design and quality, model type, structure and validation status (for model-based studies), and the source and quality of the data used for the analysis. ’

5. - Noting VoI analyses will help with the “data synthesis” aim on page 8 to “identify intelligence gaps”. The VoI will indicate if the intelligence gap can be filled by a well conducted study.
AUTHORS’ REPLY: We have included a note in the Data Synthesis section around the uses of the VoI findings.
‘Using the results of sensitivity analyses and VoI methods (if available), we will report recommendations for further research to reduce decision uncertainty.’

Reviewer: 2
Reviewer Name: Mark Pennington
Institution and Country: King's Health Economics, King's College London, UK Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below The protocol follows good practice and addresses an issue of sizeable impact to the health service. I raise only a few issues regarding the clarity of the text.
1. In the abstract the authors suggest the use of published modelling checklists to assess the quality of studies. I suspect that many studies will not be modelling studies; do the authors mean they will use economic evaluation checklists?

AUTHORS’ REPLY: Yes, we will use modelling checklists where appropriate, and non-modelling checklists for non-modelling studies. We have clarified this in the Strengths section and have the following in the methods:
‘Risk of bias
In line with published recommendations , the quality of reporting and risk of bias of the economic evaluations will be assessed using published checklists from the Consensus on Health Economic Criteria project for economic evaluations and the International Society for Pharmacoeconomics and Outcomes Research taskforce for decision models.
Items in the checklists will be marked as Yes, No, Unknown or Not Applicable for each study, and a final assessment of the risk of bias will be made by the reviewer.’

2. The inclusion criteria could be more clearly stated - it appears to be populations including patients with osteoarthritis. Is there a minimum proportion of osteoarthritis patients required?

AUTHORS' REPLY: We have clarified the inclusion criteria in the Population section. We have not stated a minimum proportion but we will extract and report the full characteristics of the populations if reported by the authors.
'We will include studies with participants undergoing THR and TKR surgery for common indications. In the UK, osteoarthritis was the surgical indication in 90% of primary hip replacement procedures [16] and 96.1% of primary knee replacements in 2015 [17]. We will therefore include studies with osteoarthritis as an indication for surgery, though we do not intend to pre-specify a minimum required proportion of patients with this indication.'

3. I was a little unclear regarding the piloting work, notably the comment that 'The search strategy and inclusion/exclusion criteria were piloted by two reviewers using 10|% of the initial study results.' Do the authors mean that the screening and inclusion criteria were piloted? Presumably the search has been undertaken prior to the selection of 10% of the hits.

AUTHORS' REPLY: That is correct; we have clarified this in the Search Strategy section.
'The search strategy and inclusion/exclusion criteria were piloted by two reviewers. For the latter, the search was run and inclusion/exclusion criteria were applied to 10% of the search results to check consistency between reviewers.'

4. I was also thought that the database selection was rather narrow. Is there a reason for excluding HMIC or the grey literature?

AUTHORS' REPLY: We think that MEDLINE, EMBASE, ECONLIT and NHS EED databases are very comprehensive. We will also search the reference lists of the included studies as an additional check as well as the references from other literature reviews in hip and knee replacement (see Search strategy). We are not doing grey literature searches but rather focusing on published (formal) and peer-reviewed literature. We want to avoid including unfinished work or work that has not gone through a peer-reviewed process and may be considered to be of low quality.

5. Finally, there is no date given for the proposed final search.

AUTHORS' REPLY: The final search was conducted up to 1st March 2017 – see Search Strategy.

VERSION 2 – REVIEW

REVIEWER	Howard Thom School of Medicine: Population Health Sciences
REVIEW RETURNED	14-Dec-2017

GENERAL COMMENTS	Many thanks for addressing my concerns.

REVIEWER	Mark Pennington King's Health Economics King's College London, UK
REVIEW RETURNED	22-Nov-2017

GENERAL COMMENTS	The authors have addressed my comments on the previous draft. There are a couple of remaining grammatical errors to correct: In the second bullet on the strengths of the study - The review will follow the latest guidelines and assess the quality... In the methods, fourth paragraph under search strategy (line 56, P34) the tense seems incorrect still.