PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Failure to address potential bias in nonrandomized controlled clinical trials may cause lack of evidence on patient-reported outcomes - a method study
AUTHORS	Peinemann, Frank; Labeit, Alexander; Thielscher, Christian; Pinkawa, Michael

VERSION 1 - REVIEW

REVIEWER	Christopher Carroll University of Sheffield, UK
REVIEW RETURNED	26-Feb-2014

GENERAL COMMENTS	I think the title is misleading: the paper considers reasons for excluding non-RCT evidence that includes PROMs, not the exclusion of any study with relevant PROMS. The abstract also seems to reflect something different. Basically, this is an incomplete systematic review, which includes non-RCT evidence and then considers a question around reporting of PROMS. This is not apparent from the title or abstract. And it is not exclusion from "a systematic review", but from the authors' own review, which I feel weakens their case. The authors claim that it was unfortunate that they were previously unable to include PROMS data from certain excluded NRCTs - but as far as I can tell, this is not an issue with systematic review methods - or the field - but rather was their choice based on quality criteria - they did include other non-RCT evidence. This paper then considers exclusion based on whether there was a sufficient number of the relevant population reporting the outcome in the trial (a standard inclusion criterion - but usually applied to primary outcomes) and whether there was sufficient between-group comparability, as the quality criteria (pp.8-9) I appreciate the authors' points about the importance of PROMS and that non-RCT studies in this field should seek to achieve higher response rates for QoL or PROMS and achieve better comparability between groups (difficult for NRCTs, but capable of being managed as the authors state), in order to render such study data more usable by secondary researchers. However, I do not think this finding is of sufficient novelty or interest for the BMJ. It might be of interest to a clinical journal in the field.

REVIEWER	James A. Talcott Continuum Ccancer Centers of New York Mt. Sinai Beth Israel Medical Center

	New York, NY USA
REVIEW RETURNED	29-Mar-2014

GENERAL COMMENTS	The reported study describes and classifies the reasons for excluding 50 reports of the outcomes of standard low dose rate brachytherapy (LDR-BT) from a systematic review. The investigators first examined whether the reports met the PICO reporting criteria, including the type of participants (P), intervention (I), comparator (C), adding timing (T) and setting (S) to create the more inclusive PICOTS typology and study design (SD) for a complete a search strategy (PICOTS-SD). Because evidence is inadequate to define a survival difference, the authors focused on QOL outcomes. Having reported the results of their review in another publication, they report the reason for excluding 50 of 63 reports. After excluding the 21 reports not meeting the PICO standard, they found another 29 did not adequately protect against bias, by not reporting addressing the proportion of patients approached who were included, reporting pretreatment status, adjusting for confounders or making an appropriate control comparison. The report provides an opportunity to document the prevalence of failure to address potential bias, essential in a non-randomized trial. It is a useful if not unexpected result. The methodology is appropriate. Minor Comments It is confusing to have 2 outcomes, overall and disease-specific survival described as the primary outcome, altho subsequent text suggests it is the former. Local therapy is usually administered to patients with Nx, not No staging, since N0 status can only be determined definitively with surgery. It should state "N0 or Nx." The report makes a useful point. The editors should decide whether it is sufficiently important to merit publication in this journal. I see no reason not to accept it.

VERSION 1 – AUTHOR RESPONSE

General comment by the authors:

We thank the reviewers for checking our manuscript and for helpful additional comments. Below, we respond to each of their remarks and questions/concerns. The comments of each referee were placed in a separate ordered list using Arabic numbers. Each statement was copied from the feedback form and listed in a separate row.

- *Quotes from the manuscript typed in italic.*
- ~~*Removed text marked with a horizontal line*~~
- *Introduced text marked with a different font color and an underscore*

Reviewer #1: comment to Author **Christopher Carroll, University of Sheffield, UK**	**Response by author**
I think the title is misleading: the paper considers reasons for excluding non-RCT evidence that includes PROMs, not the exclusion of any study with relevant PROMS.	Thank you for pointing out a potentially misleading title. In an associated Cochrane Review (PMID: 21735436), we reported that a total of 461 of 462 references of the potentially relevant articles had a non-randomized design. In fact all excluded studies were non-randomized. In the current paper, we did not consider any excluded study but any RCTs and CCTs reporting PROMs. In response to your concern, we changed the title. Inserted: *Failure to address potential bias in nonrandomized controlled clinical trials may cause lack of evidence on patient-reported outcomes*
The abstract also seems to reflect something different. Basically, this is an incomplete systematic review, which includes non-RCT evidence and then considers a question around reporting of PROMS. This is not apparent from the title or abstract. And it is not exclusion from "a systematic review", but from the authors' own review, which I feel weakens their case.	Thank you for pointing out that the work is not a complete systematic review. The paper may be regarded as a methodological supplement that is associated with a previously conducted systematic review (PMID: 21763066). It addresses an additional issue and adds information that were not projected by this systematic review and that is usually not part of a systematic review. In response to your concern, we changed the abstract and the method section. Inserted: *Background* *The present paper reports a workup of a previously published systematic review that evaluated patient-reported outcomes of permanent interstitial low-dose rate brachytherapy in patients with localized prostate cancer.* *Objective* *We aimed to summarize qualitatively the reasons for exclusion of nonrandomized controlled clinical trials reporting patient-reported outcomes.* *Methods* *We searched PubMed, MEDLINE, EMBASE, and The Cochrane Library without restrictions on 14 June 2010. We defined the inclusion criteria according to the PICO framework. The outcomes of the present publication address methodological issues: fulfilment of basic inclusion criteria according to a PICO framework and accomplishment of requirements to address and protect against high risk of bias.*

The authors claim that it was unfortunate that they were previously unable to include PROMS data from certain excluded NRCTs - but as far as I can tell, this is not an issue with systematic review methods - or the field - but rather was their choice based on quality criteria - they did include other non-RCT evidence. This paper then considers exclusion based on whether there was a sufficient number of the relevant population reporting the outcome in the trial (a standard inclusion criterion - but usually applied to primary outcomes) and whether there was sufficient between-group comparability, as the quality criteria (pp.8-9)	We think that the type of inclusion and exclusion criteria in a determine the number and type of studies included in a systematic review. These criteria may comprise, for example, type of allocation, number of participants, proportion of relevant participants, proportion of returned questionnaires and many more. Among the excluded studies, we analyzed what predefined inclusion criteria were not met including the PICO criteria. We believe that all the criteria addressed in the paper are a potential issue with systematic reviews.
I appreciate the authors' points about the importance of PROMS and that non-RCT studies in this field should seek to achieve higher response rates for QoL or PROMS and achieve better comparability between groups (difficult for NRCTs, but capable of being managed as the authors state), in order to render such study data more usable by secondary researchers. However, I do not think this finding is of sufficient novelty or interest for the BMJ. It might be of interest to a clinical journal in the field.	Thank you for acknowledging our main points, no further comment.

Reviewer #2: comment to Author **James A. Talcott, Continuum Cancer Centers of New York, Mt. Sinai Beth Israel Medical Center; New York, NY, USA**	**Response by author**
The reported study describes and classifies the reasons for excluding 50 reports of the outcomes of standard low dose rate brachytherapy (LDR-BT) from a systematic review. The investigators first examined whether the reports met the PICO reporting criteria, including the type of participants (P), intervention (I), comparator (C), adding timing (T) and setting (S) to create the more inclusive PICOTS typology and study design (SD) for a complete a search strategy (PICOTS-SD). Because evidence is inadequate to define a survival difference, the authors focused on QOL outcomes.	Thank you for summarizing, no further comment.
Having reported the results of their review in another publication, they report the reason for excluding 50 of 63 reports. After excluding the 21 reports not meeting the PICO standard, they found another 29 did not adequately protect against bias, by not reporting addressing the	Thank you for summarizing, no further comment.

proportion of patients approached who were included, reporting pretreatment status, adjusting for confounders or making an appropriate control comparison.	
The report provides an opportunity to document the prevalence of failure to address potential bias, essential in a non-randomized trial. It is a useful if not unexpected result. The methodology is appropriate.	Thank you for appreciating and clarifying our intention, no further comment.
Minor comments: It is confusing to have 2 outcomes, overall and disease-specific survival described as the primary outcome, altho subsequent text suggests it is the former.	We have clarified overall outcome as the primary outcome.
Minor comments: Local therapy is usually administered to patients with Nx, not No staging, since N0 status can only be determined definitively with surgery. It should state "N0 or Nx."	We have removed the N and M codes.