

# BMJ Open Failure to address potential bias in non-randomised controlled clinical trials may cause lack of evidence on patient-reported outcomes: a method study

Frank Peinemann,<sup>1</sup> Alexander Michael Labeit,<sup>2</sup> Christian Thielscher,<sup>3</sup> Michael Pinkawa<sup>4</sup>

**To cite:** Peinemann F, Labeit AM, Thielscher C, *et al.* Failure to address potential bias in non-randomised controlled clinical trials may cause lack of evidence on patient-reported outcomes: a method study. *BMJ Open* 2014;**4**:e004720. doi:10.1136/bmjopen-2013-004720

► Prepublication history for this paper is available online. To view these files please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2013-004720>).

Parts of the study have been presented at 19th Cochrane Colloquium 19–22 October 2011 in Madrid, Spain.

Received 19 December 2013  
Revised 28 April 2014  
Accepted 13 May 2014



CrossMark

For numbered affiliations see end of article.

**Correspondence to**  
Frank Peinemann;  
[pubmedprjournal@gmail.com](mailto:pubmedprjournal@gmail.com)

## ABSTRACT

**Objectives:** We conducted a workup of a previously published systematic review and aimed to analyse why most of the identified non-randomised controlled clinical trials with patient-reported outcomes did not match a set of basic quality criteria.

**Setting:** There were no limits on the level of care and the geographical location.

**Participants:** The review evaluated permanent interstitial low-dose rate brachytherapy in patients with localised prostate cancer and compared that intervention with alternative procedures such as external beam radiotherapy, radical prostatectomy and no primary therapy.

**Primary outcome measure:** Fulfilment of basic inclusion criteria according to a Participants, Interventions, Comparisons, Outcomes (PICO) framework and accomplishment of requirements to contain superimposed risk of bias.

**Results:** We found that 21 of 50 excluded non-randomised controlled trials did not meet the PICO inclusion criteria. The remaining 29 studies showed a lack in the quality of reporting. The resulting flaws included attrition bias due to loss of follow-up, lack of reporting baseline data, potential confounding due to unadjusted data and lack of statistical comparison between groups.

**Conclusions:** With respect to the reporting of patient-reported outcomes, active efforts are required to improve the quality of reporting in non-randomised controlled trials concerning permanent interstitial low-dose rate brachytherapy in patients with localised prostate cancer.

## INTRODUCTION

The present paper reports a workup of a previously published systematic review.<sup>1</sup> It may be regarded as a methodological supplement adding information on a subset of excluded studies. We have compared permanent interstitial low-dose rate brachytherapy, with radical prostatectomy, external beam

## Strengths and limitations of this study

- We conducted a comprehensive literature search and strictly adhered to the projected methodology.
- We identified a lack of quality in non-randomised controlled clinical trials reporting patient-reported outcomes, analysed the cause and suggested possible improvements in designing studies in the future.
- The analysis is confined to a single disease and a specific treatment and conclusions drawn from its results may not be generalisable to other diseases and treatments.
- The limits for the inclusion of studies are arbitrarily set.

radiotherapy and ‘no primary therapy’ in patients with localised prostate cancer categorised as T1 to T2. We used the term ‘no primary therapy’ to accommodate different types of observation including active surveillance, watchful waiting and observing without a distinctive management. As a result, we included one randomised controlled trial (RCT) and 30 non-randomised controlled clinical trials (CCT). The primary outcome was overall survival. The secondary outcomes were clinically defined disease-free survival, biochemical recurrence-free survival, physician-reported severe adverse events and patient-reported outcomes (PROs) such as function and bother scores as well as generic and disease-related health-related quality of life. We concluded that the current evidence is insufficient to allow a definitive conclusion about overall survival. Radical prostatectomy and external beam radiotherapy can severely affect the structural integrity of neighbouring organs and their functions and can also cause considerable long-term impairment of health-related quality of life. With a view of

expecting similar survival but a tremendous difference of adverse events between treatment alternatives, valid data on health-related quality of life could tip the balance. At the least, we assume that shared decision-making and consideration of patients' preferences in searching for the best individual treatment would rely on information on the health-related quality-of-life data. Of the 30 included non-randomised studies, 13 studies reported PROs, that is, only the patients provided the information.<sup>2</sup> During the study selection process, we experienced that we excluded another 50 non-randomised PRO studies. We found it a pity that we could not use the data. We had the impression that a considerable number of studies were excluded because of a lack in the quality of reporting. Therefore, we wanted to summarise the reasons for excluding those PRO studies and make the authors of PRO studies aware of some basic requirements for reporting of comparative PRO data to achieve higher acceptance in the scientific community. The importance of reporting PRO has been addressed by the Consolidated Standards of Reporting Trials (CONSORT) group<sup>3</sup> which recently published a PRO extension to their acclaimed previous statement.<sup>4</sup> It may be wise to build a PRO extension to the STrengthening the Reporting of OBServational studies in Epidemiology (STROBE) statement<sup>5</sup> that addresses specific issues of observational studies.

The first aim of this study was to assess whether the excluded studies met the basic inclusion criteria using the PICO framework. The second aim was to ensure whether the excluded studies met the requirements to contain high risk of bias.

## MATERIALS AND METHODS

### Study inclusion criteria

We defined the inclusion criteria according to the PICO framework that should include four essential constituents, that is, the type of participants (P), intervention (I), comparator (C) and outcome (O).<sup>6</sup> The four PICO items can be supplemented by timing (T) and setting (S), two other important features of a systematic review, to create the so-called PICOTS typology.<sup>7</sup> A further extension embraces the study design (SD) to complete all major items of a search strategy (PICOTS-SD).<sup>8</sup>

### Population

#### *Initial and present publication*

Localised prostate cancer is defined by the categories T1 to T2 of the tumour-node-metastasis staging system<sup>9</sup> if combined with the absence of regional lymph node metastasis and distant metastasis.

### Intervention

#### *Initial and present publication*

Brachytherapy<sup>10</sup> is short-distance radiotherapy placing radiation sources with different duration and rates of dose delivery in or near tumours.<sup>11</sup> Permanent

interstitial low-dose rate brachytherapy means implanting of low-energy radioactive sources emitting radiation, which are contained in titanium pellets of the size of rice grains called seeds.<sup>12</sup>

### Comparator

#### *Initial and present publication*

The European Association of Urology suggested three different treatment concepts for localised prostate cancer in addition to permanent interstitial low-dose rate brachytherapy<sup>10</sup>: radical prostatectomy, external beam radiotherapy and different types of observation including active surveillance, watchful waiting and observing without distinctive management.

### Outcome

#### *Initial publication*

Overall survival, cancer-specific survival, disease-free survival, biochemical recurrence-free survival, severe adverse events and PROs. PROs comprised function and bother scores as well as generic and disease-related health-related quality of life.

#### *Present publication*

Fulfilment of basic inclusion criteria according to a PICO framework by the excluded CCT. Accomplishment of requirements to contain superimposed risk of bias in addition to the high risk of bias caused by the lack of randomisation framework by the excluded CCT.

### Timing

#### *Initial and present publication*

We did not set limits on the length of the observation period.

### Setting

#### *Initial and present publication*

We did not set limits on the setting such as type of country, year of recruitment or level of healthcare.

### Study design

#### *Initial publication*

We included RCT and CCT evaluating permanent interstitial low-dose rate brachytherapy as monotherapy in patients with localised prostate cancer. The proportion of relevant patients was required to be at least 80% of the study population and the response rate of questionnaires was expected to be at least 70%. For CCT to be included, comparable baseline characteristics between treatment groups or adjustment for imbalances of these data were required. Limits on year of publication or language were not applied.

#### *Present publication*

We included specifically the CCT that were excluded in the initial publication.

## Search strategy

The search strategy was reported previously.<sup>1</sup>

## Study selection

In the present study, we selected only those 50 non-randomised studies on PRO that were excluded from the evaluation in the initial publication. In the study selection process, two reviewers independently judged whether a study was included or excluded. Differences were resolved by discussion without the need for a third opinion.

## Data collection and analysis

The reasons for exclusion were extracted independently by two reviewers. We sought for the following data: the inclusion criteria using the PICO framework, the proportion of response of participants to questionnaires, which was required to be at least 70%, the reporting of separate baseline characteristics for each treatment group, the reporting of comparable baseline characteristics or adjustment for imbalances of these data such as the use of a Cox proportional hazard model and the reporting of statistics comparing treatment groups. Sufficient comparability was defined as a difference between baseline values that were not statistically significant. If a statistical test was not reported, we assumed two comparable values if the greater of the two values was less than 10% above the smaller one. We also required that authors reported effect measures and statistics testing the difference between treatment groups, for example, p values or effect measures including 95% CIs. Reporting of within group comparisons or before-and-after analyses was not deemed sufficient for inclusion. We did not apply a principal summary measure as we aimed to synthesise the information in a qualitative way.

## Assessment of risk of bias and quality of reporting

Two reviewers independently assessed the quality of reporting of CCT according to the criteria specified in the previous paragraph. We did not specifically assess the risk of bias because we decided to exclude all papers with regard to a lack of reporting essential data.

## RESULTS

Of a total of 462 full-text articles assessed for eligibility in the previously published systematic review, 31 studies were included and 431 studies were excluded. Among the 431 excluded articles, we identified 50 non-randomised studies that were reporting on PRO (figure 1). We evaluated the reasons for exclusion of those 50 studies and documented the results in table 1. In 42% (21 of 50) studies, the essential PICO framework was simply not met. In the majority of 58% (29 of 50) studies, the predefined requirement to apply measures to contain high risk of bias was not met. Of these 29 studies, 19 reported a proportion of patients responding to questionnaires of less than 70% or did not address this item. Baseline characteristics were not presented for treatment groups in three studies. In another

six studies, baseline characteristics were not comparable between treatment groups or there was no confounder control in the analysis adjusting for important different factors such as mean age. The statistical comparison between treatment groups was deemed not appropriate in one study.

## DISCUSSION

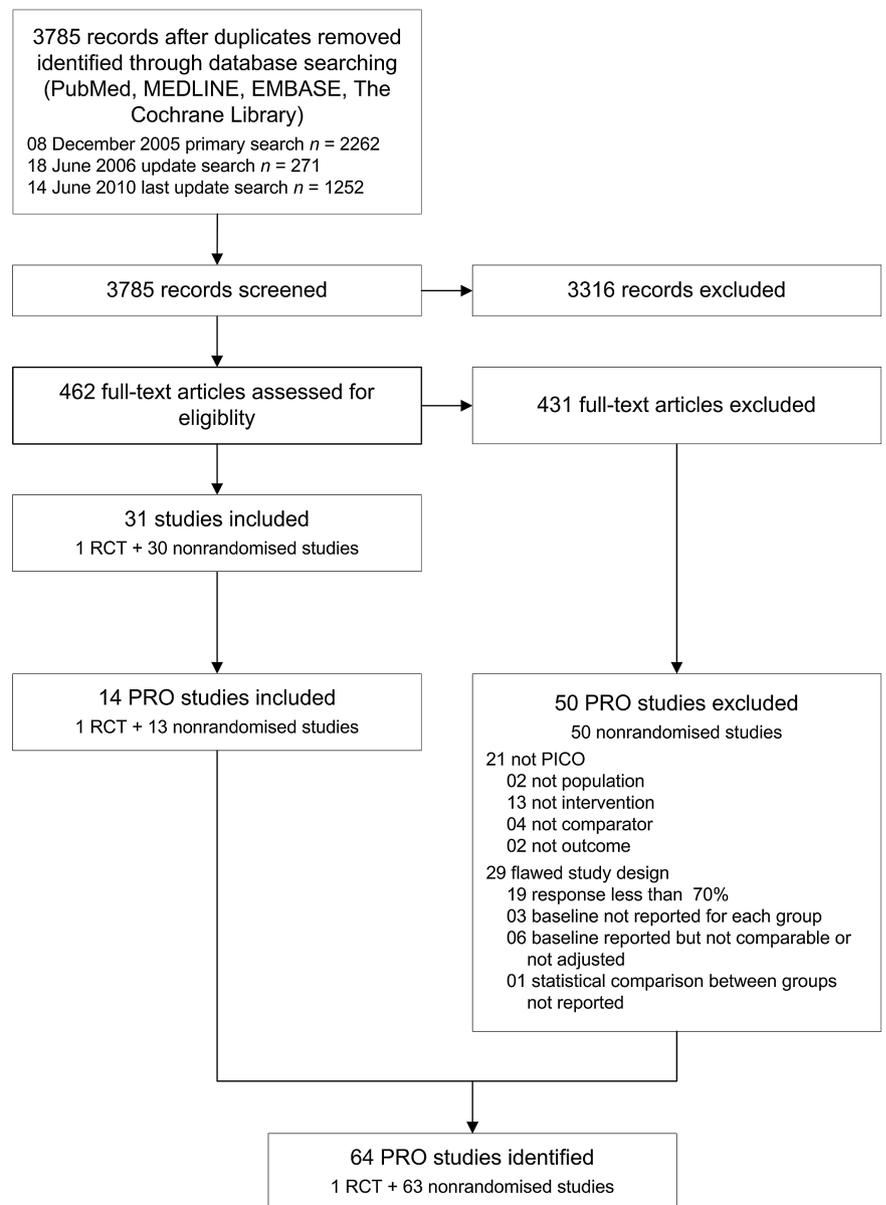
### Main results

In summary, we found that roughly 4 of 10 excluded PRO studies did not meet the essential inclusion criteria using the PICO framework. This result is consistent with the problem of information retrieval aiming at a high recall and ending up with a low precision. The papers were obviously not relevant to the research question and we did not further examine the quality of reporting. We also found that roughly 6 of 10 excluded PRO studies met the PICO framework but did not provide the predefined requirements to care sufficiently enough for a low response of patients to questionnaires, for reporting baseline characteristics between treatment groups, for adjusting differences in those baseline characteristics between treatment groups and to use appropriate statistics to compare the outcome between treatment groups.

### Quality of reporting of PROs

We identified a lack in the quality of reporting in many excluded CCT and wish to stress the importance of considering a series of requirements while conducting a study on PRO. Other authors have reported recently that, concerning disease-specific mortality or disease-free survival, the available studies did not show significant differences between treatment groups.<sup>13 14</sup> In the view of unknown or small differences in survival measures, the results of PRO studies could have a noticeable impact on medical decision-making.<sup>15 16</sup> None of the 50 excluded studies reported a non-responder analysis, although it is known that non-responders may have different attitudes than responders. Etter and Perneger<sup>17</sup> concluded that low response rates may be associated with overestimating an effect and that the strength and direction of a non-response bias may depend on the mechanism of non-response. Therefore, results may be confounded if the proportion of included data not available for analysis such as data from non-responders or due to loss to follow-up is considerable. We believe that a value of 30% or more can be denoted as considerable. Lowering this threshold, for example, to 20%, would have resulted in less included studies. However, others suggested that 20% or more loss would be sufficient for a high risk of bias threatening the validity of results.<sup>18</sup> Concerning questionnaires, we recommend taking measures that are known to improve response rates.<sup>19 20</sup> Edwards<sup>21</sup> conducted a systematic review to identify effective strategies to increase the response to postal and electronic questionnaires. The authors found several strategies to increase the response, for example,

**Figure 1** Study flow. PICO: population, intervention, comparator, outcome; PRO: patient-reported outcomes; RCT: randomised controlled trial.



prenotification, follow-up contact, shorter questionnaires, mentioning an obligation to respond, university sponsorship, non-monetary incentives, a statement that others had responded, an offer of survey results, giving a deadline. We did not use a strict algorithm to differentiate between comparable and not comparable baseline values between treatment groups. A statistically significant difference was judged as not comparable. Non-significant differences were also regarded as not comparable if the difference was at least 10% of the lower of two values. Using this approach we tried to reduce subjective decisions. We are not aware of published strict algorithms in this matter.

#### High risk of bias inherent in non-RCTs

With a view to include only one RCT, the initial publication was based almost exclusively on CCT. However, the

lack of randomisation poses a very large challenge to the authors who are advised to deal with essential problems such as selection bias and confounding. Otherwise, the findings may not be valid and of limited usefulness and the many efforts may be in vain. We wish to stress that the non-randomised design is associated with a high risk of bias because known and unknown characteristics may be distributed unequally between groups.<sup>22</sup> Certain study characteristics, such as prospective design, concurrent control group, adjustment of results with respect to different baseline values and confounder control, can limit additional bias. For example, Ioannidis *et al*<sup>23</sup> reported that discrepancies between RCT and CCT were less common when only CCT with a prospective design were considered. The Cochrane Collaboration offers a guide for inclusion of non-randomised studies<sup>24</sup> and it has developed a tool for assessing the risk of bias in RCT

**Table 1** Reasons for excluding PRO articles

Non-randomised studies	Inclusion criteria				Requirements to contain high risk of bias			Statistical comparison between groups	Comments
	P	I	C	O	Response ≥70%	Baseline each group	Baseline comparable/or adjusted		
Bacon <i>et al</i> <sup>29</sup>	Yes	Yes	No	–	–	–	–	–	No concurrent group
Ball <i>et al</i> <sup>30</sup>	Yes	Yes	No	–	–	–	–	–	Cryotherapy
Befort <i>et al</i> <sup>31</sup>	Yes	Yes	Yes	Yes	No	–	–	–	Low response
Bergman <i>et al</i> <sup>32</sup>	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No appropriate test
Bergman <i>et al</i> <sup>33</sup>	Yes	Yes	Yes	Yes	No	–	–	–	Low response
Brandeis <i>et al</i> <sup>34</sup>	Yes	No	–	–	–	–	–	–	29% LDR-BT+EBRT
Brown <i>et al</i> <sup>35</sup>	Yes	No	–	–	–	–	–	–	EBRT
Burnett <i>et al</i> <sup>36</sup>	Yes	Yes	Yes	Yes	No	–	–	–	Response not reported
Chaikin <i>et al</i> <sup>37</sup>	No	–	–	–	–	–	–	–	Staging not reported
Chen <i>et al</i> <sup>38</sup>	Yes	Yes	Yes	Yes	Yes	Yes	No	–	No confounder control
Choo <i>et al</i> <sup>39</sup>	Yes	Yes	Yes	Yes	Yes	No	–	–	Baseline not reported
Clark <i>et al</i> <sup>40</sup>	Yes	Yes	Yes	Yes	No	–	–	–	Low response
Downs <i>et al</i> <sup>41</sup>	Yes	Yes	Yes	Yes	Yes	Yes	No	–	No confounder control
Eton <i>et al</i> <sup>42</sup>	Yes	Yes	Yes	Yes	No	–	–	–	Low response
Frank <i>et al</i> <sup>43</sup>	Yes	Yes	Yes	Yes	No	–	–	–	Low response
Fulmer <i>et al</i> <sup>44</sup>	Yes	Yes	Yes	Yes	No	–	–	–	Response not reported
Gore <i>et al</i> <sup>45</sup>	Yes	Yes	Yes	Yes	No	–	–	–	Low response
Guedea <i>et al</i> <sup>46</sup>	Yes	Yes	Yes	Yes	Yes	Yes	No	–	No confounder control
Hashine <i>et al</i> <sup>47</sup>	Yes	Yes	Yes	Yes	Yes	Yes	No	–	No confounder control
Hashine <i>et al</i> <sup>48</sup>	Yes	Yes	Yes	Yes	Yes	Yes	No	–	No confounder control
Hervouet <i>et al</i> <sup>49</sup>	No	–	–	–	–	–	–	–	≥20% T3–T4 in control groups
Hollenbeck <i>et al</i> <sup>50</sup>	Yes	No	–	–	–	–	–	–	LDR-BT+EBRT
Jo <i>et al</i> <sup>51</sup>	Yes	No	–	–	–	–	–	–	High-dose rate brachytherapy
Johnstone <i>et al</i> <sup>52</sup>	Yes	No	–	–	–	–	–	–	EBRT
Joly <i>et al</i> <sup>53</sup>	Yes	No	–	–	–	–	–	–	LDR-BT+EBRT
Takehi <i>et al</i> <sup>54</sup>	Yes	Yes	Yes	Yes	Yes	No	–	–	Baseline not reported
Lev <i>et al</i> <sup>55</sup>	Yes	No	–	–	–	–	–	–	LDR-BT+EBRT
Lilleby <i>et al</i> <sup>56</sup>	Yes	No	–	–	–	–	–	–	EBRT
Litwin <i>et al</i> <sup>57</sup>	Yes	Yes	Yes	Yes	No	–	–	–	Low response
Litwin <i>et al</i> <sup>58</sup>	Yes	No	–	–	–	–	–	–	25% LDR-BT+EBRT
Mehta <i>et al</i> <sup>59</sup>	Yes	Yes	Yes	No	–	–	–	–	“Fear of cancer”*
Miller <i>et al</i> <sup>60</sup>	Yes	No	–	–	–	–	–	–	44% LDR-BT+EBRT
Miller <i>et al</i> <sup>61</sup>	Yes	Yes	Yes	Yes	Yes	No	–	–	Baseline not reported
Monahan <i>et al</i> <sup>62</sup>	Yes	Yes	Yes	Yes	No	–	–	–	Low response
Namiki <i>et al</i> <sup>63</sup>	Yes	Yes	Yes	Yes	No	–	–	–	Low response
Namiki <i>et al</i> <sup>64</sup>	Yes	Yes	Yes	Yes	No	–	–	–	Low response

Continued



Table 1 Continued

Non-randomised studies	Inclusion criteria				Requirements to contain high risk of bias			Statistical comparison between groups	Comments
	P	I	C	O	Response ≥70%	Baseline each group	Baseline comparable/or adjusted		
Ohashi <i>et al</i> <sup>65</sup>	Yes	Yes	Yes	Yes	No	–	–	–	Low response
Pinkawa <i>et al</i> <sup>66</sup>	Yes	Yes	No	–	–	–	–	–	LDR-BT+hormones†
Roach <i>et al</i> <sup>67</sup>	Yes	No	–	–	–	–	–	–	EBRT, single-arm trial
Sanda <i>et al</i> <sup>68</sup>	Yes	Yes	Yes	Yes	No	–	–	–	Low response
Schover <i>et al</i> <sup>69</sup>	Yes	Yes	Yes	Yes	No	–	–	–	Low response
Soderdahl <i>et al</i> <sup>70</sup>	Yes	Yes	Yes	Yes	No	–	–	–	Low response
Speight <i>et al</i> <sup>71</sup>	Yes	Yes	Yes	Yes	No	–	–	–	Response not reported
Stone <i>et al</i> <sup>72</sup>	Yes	Yes	No	–	–	–	–	–	LDR-BT+hormones†
Trojan <i>et al</i> <sup>73</sup>	Yes	Yes	Yes	Yes	No	–	–	–	Low response
Tward <i>et al</i> <sup>74</sup>	Yes	Yes	Yes	No	–	–	–	–	Mortality differs§
Valicenti <i>et al</i> <sup>75</sup>	Yes	Yes	Yes	Yes	No	–	–	–	Response not reported
Van de Poll-Franse <i>et al</i> <sup>76</sup>	Yes	No	–	–	–	–	–	–	LDR-BT+EBRT
Wyler <i>et al</i> <sup>77</sup>	Yes	Yes	Yes	Yes	Yes	Yes	No	–	No confounder control
Zagar <i>et al</i> <sup>78</sup>	Yes	No	–	–	–	–	–	–	LDR-BT+EBRT
'NO' counts	2	13	4	2	19	3	6	1	Total: 50 studies
	PICO not met: 21				High risk of bias: 29				

–: not appropriate.

\*Mehta *et al*<sup>69</sup>: no appropriate endpoint.

†Pinkawa *et al*<sup>66</sup>; Stone *et al*<sup>72</sup>: neoadjuvant hormonal therapy.

§Tward *et al*<sup>74</sup>: non-disease-related mortality differs greatly. C, comparison of interest is radical prostatectomy, external beam radiotherapy, or no primary therapy; EBRT, external beam radiotherapy; I, intervention of interest is low-dose rate brachytherapy as monotherapy; LDR-BT, permanent interstitial low-dose rate brachytherapy; O, outcome of interest is function, bother, or generic health-related quality of life; P, patients with localised prostate cancer; PRO, patient-reported outcomes.

and CCT.<sup>25</sup> Guidelines for reporting observational studies have been published to improve their quality.<sup>5</sup> Cox regression analysis, propensity-score-based analysis and instrumental variable analysis are methods that have been used for correction of confounding bias in non-randomised studies.<sup>26</sup> Different values of various outcome measures between groups may be simply caused by different baseline data in lieu of absent significant treatment effects. We accepted any type of method adjusting or stratifying for one or more known differences in baseline characteristics. Nevertheless, it should be kept in mind that methods of adjustment do not guarantee removal of bias and that residual confounding may remain high.<sup>22</sup> Concerning the non-randomised design, we strongly recommend the use of methods for adjusting the results for confounders to aim for a less-biased estimation of the treatment effect<sup>27</sup> and the adoption of guidelines for the reporting of observational studies.<sup>5</sup>

### Strengths and limitations

The strengths of the present study are a comprehensive literature search, strict adherence to the projected methodology, the identification of a lack of quality in PRO studies and addressing the specific problems of PRO studies. We should consider some limitations: the study is confined to a single disease, so conclusions drawn from its results may not be generalisable to other diseases. The arbitrary limits set for inclusion of studies are responsible for the extent of excluded studies. These limits may be questioned by other investigators. During the re-evaluation of study quality, we found that one study fulfilled all criteria, although, this study was excluded in previous reports.<sup>28</sup> The minimum follow-up of 70% for inclusion was set arbitrarily and others might find this threshold too low. We did not endorse the recently published reporting of PRO in randomised trials, an extension of the CONSORT statement.<sup>4</sup> All included studies in the present review are non-randomised. We think that the lack of randomisation is the prevailing issue. We did not endorse the CONSORT PRO extension for another reason. The included studies were published many years before this extension was published. There might be a need to develop an extension of the STROBE statement<sup>5</sup> with the aim of improving the reporting of PRO in non-randomised studies. This extension could emphasise the specific challenges of reporting PRO with respect to lack of randomisation.

### CONCLUSIONS

We found that a considerable number of non-randomised controlled reporting PROs were excluded from a systematic review because of a lack of predefined reporting requirements. The assumed overall risk of bias was regarded as too high to consider the data of these studies for inclusion in the systematic review. With respect to the reporting of PROs, active efforts are

required to improve the quality of reporting in non-randomised controlled trials and to increase the number of randomised controlled trials.

### Author affiliations

<sup>1</sup>Children's Hospital, University of Cologne, Cologne, Germany

<sup>2</sup>Outcomes Research Center, University of Illinois, Peoria, Illinois, USA

<sup>3</sup>FOM University of Applied Science for Economics & Management, Essen, Germany

<sup>4</sup>Department of Radiotherapy, University Hospital, Aachen, Germany

**Contributors** FP conceived, designed and performed the experiments. FP and MP analysed the data. FP, AML, CT and MP wrote the manuscript.

**Funding** This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** No additional data are available.

**Open Access** This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 3.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/3.0/>

### REFERENCES

1. Peinemann F, Grouven U, Bartel C, *et al.* Permanent interstitial low-dose rate brachytherapy for patients with localized prostate cancer—a systematic review of randomized and non-randomized controlled clinical trials. *Eur Urol* 2011;60:881–93.
2. Patrick D, Guyatt GH, Acquadro C. Chapter 17: Patient-reported outcomes. In: Higgins JPT, Green S, eds. *Cochrane handbook for systematic reviews of interventions Version 510* [updated March 2011]. Chichester: The Cochrane Collaboration, 2011. [www.cochrane-handbook.org](http://www.cochrane-handbook.org)
3. Schulz KF, Altman DG, Moher D, *et al.* CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *PLoS Med* 2010;7:e1000251.
4. Calvert M, Blazeby J, Altman DG, *et al.* Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. *JAMA* 2013;309:814–22.
5. von Elm E, Altman DG, Egger M, *et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Med* 2007;4:e296.
6. O'Connor D, Green S, Higgins JPT. Chapter 5: Defining the review question and developing criteria for including studies. In: Higgins JPT, Green S, eds. *Cochrane handbook for systematic reviews of interventions Version 510* [updated March 2011]. Chichester: The Cochrane Collaboration, 2011. [www.cochrane-handbook.org](http://www.cochrane-handbook.org)
7. Chang SM, Matchar DB, Smetana GW, Umscheid, CA. eds. *Methods guide for medical test reviews*. Rockville: Agency for Healthcare Research and Quality; 2012, AHRQ Publication No: 12-EC017.
8. White CM, Ip S, McPheeters M, *et al.* *Using existing systematic reviews to replace de novo processes in conducting comparative effectiveness reviews. Methods guide for comparative effectiveness reviews*. Rockville: Agency for Healthcare Research and Quality, 2009.
9. Ebele JN, Sauter G, Epstein JI, *et al.* *Pathology and genetics of tumours of the urinary system and male genital organs*. Lyon: IARC Press, 2004.
10. Heidenreich A, Bolla M, Joniau S, *et al.* *Guidelines on prostate cancer*. Arnhem: European Association of Urology, 2011.
11. Thompson I, Thrasher JB, Aus G, *et al.* *Prostate cancer. Guideline for the management of clinically localized prostate cancer: 2007 update*. Linthicum: American Urological Association, 2007.
12. Nath R. Overview of brachytherapy physics. In: Thomadsen BR, Rivard MR, Butler W, eds. *Brachytherapy physics*. 2nd edn. Madison: Medical Physics Publishing, 2005.
13. Wilt TJ, MacDonald R, Rutks I, *et al.* Systematic review: comparative effectiveness and harms of treatments for clinically localized prostate cancer. *Ann Intern Med* 2008;148:435–48.

14. Koukourakis G, Kelekis N, Armonis V, *et al.* Brachytherapy for prostate cancer: a systematic review. *Adv Urol* 2009;2009:327945.
15. Rosenthal SA, Bittner NH, Beyer DC, *et al.* American Society for Radiation Oncology (ASTRO) and American College of Radiology (ACR) practice guideline for the transperineal permanent brachytherapy of prostate cancer. *Int J Radiat Oncol Biol Phys* 2011;79:335–41.
16. Crook JM, Gomez-Iturriaga A, Wallace K, *et al.* Comparison of health-related quality of life 5 years after SPIRIT (Surgical Prostatectomy [RP] versus Interstitial Radiation [BT] Intervention trial ACOSOG Z0070). *Int J Radiat Oncol Biol Phys* 2010;78(3 Suppl 1):S76.
17. Etter JF, Perneger TV. Analysis of non-response bias in a mailed health survey. *J Clin Epidemiol* 1997;50:1123–8.
18. Schulz KF, Grimes DA. Sample size slippages in randomised trials: exclusions and the lost and wayward. *Lancet* 2002;359:781–5.
19. Smeeth L, Fletcher AE. Improving the response rates to questionnaires. *BMJ* 2002;324:1168–9.
20. Brealey SD, Atwell C, Bryan S, *et al.* Improving response rates using a monetary incentive for patient completion of questionnaires: an observational study. *BMC Med Res Methodol* 2007;7:12.
21. Edwards PJ, Roberts I, Clarke MJ, *et al.* Methods to increase response to postal and electronic questionnaires. *Cochrane Database Syst Rev* 2009;(3):MR000008.
22. Deeks JJ, Dinnes J, D'Amico R, *et al.* Evaluating non-randomised intervention studies. *Health Technol Assess* 2003;7:iii–x, 1–173.
23. Ioannidis JP, Haidich AB, Pappa M, *et al.* Comparison of evidence of treatment effects in randomized and nonrandomized studies. *JAMA* 2001;286:821–30.
24. Reeves BC, Deeks JJ, Higgins JPT, *et al.* Chapter 13: Including non-randomized studies. In: Higgins JPT, Green S. eds. *Cochrane handbook for systematic reviews of interventions Version 5.1.0* [updated March 2011]. Chichester: The Cochrane Collaboration, 2011. [www.cochrane-handbook.org](http://www.cochrane-handbook.org)
25. Higgins JPT, Altman DG, Sterne JAC. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S. eds. *Cochrane handbook for systematic reviews of interventions Version 5.1.0* [updated March 2011]. Oxford: The Cochrane Collaboration, 2011. [www.cochrane-handbook.org](http://www.cochrane-handbook.org)
26. Schmoor C, Gall C, Stampf S, *et al.* Correction of confounding bias in non-randomized studies by appropriate weighting. *Biom J* 2011;53:369–87.
27. Cox E, Martin BC, Van Staa T, *et al.* Good research practices for comparative effectiveness research: approaches to mitigate bias and confounding in the design of nonrandomized studies of treatment effects using secondary data sources: the International Society for Pharmacoepidemiology and Outcomes Research Good Research Practices for Retrospective Database Analysis Task Force Report—Part II. *Value Health* 2009;12:1053–61.
28. Pinkawa M, Asadpour B, Piroth MD, *et al.* Health-related quality of life after permanent I-125 brachytherapy and conformal external beam radiotherapy for prostate cancer: a matched-pair comparison. *Radiother Oncol* 2009;91:225–31.
29. Bacon CG, Giovannucci E, Testa M, *et al.* The impact of cancer treatment on quality of life outcomes for patients with localized prostate cancer. *J Urol* 2001;166:1804–10.
30. Ball AJ, Gambill B, Fabrizio MD, *et al.* Prospective longitudinal comparative study of early health-related quality-of-life outcomes in patients undergoing surgical treatment for localized prostate cancer: a short-term evaluation of five approaches from a single institution. *J Endourol* 2006;20:723–31.
31. Befort CA, Zelefsky MJ, Scardino PT, *et al.* A measure of health-related quality of life among patients with localized prostate cancer: results from ongoing scale development. *Clin Prostate Cancer* 2005;4:100–8.
32. Bergman J, Gore JL, Penson DF, *et al.* Erectile aid use by men treated for localized prostate cancer. *J Urol* 2009;182:649–54.
33. Bergman J, Kwan L, Litwin MS. Improving decisions for men with prostate cancer: translational outcomes research. *J Urol* 2010;183:2186–92.
34. Brandeis JM, Litwin MS, Burnison CM, *et al.* Quality of life outcomes after brachytherapy for early stage prostate cancer. *J Urol* 2000;163:851–7.
35. Brown MW, Brooks JP, Albert PS, *et al.* An analysis of erectile function after intensity modulated radiation therapy for localized prostate carcinoma. *Prostate Cancer Prostatic Dis* 2007;10:189–93.
36. Burnett AL, Aus G, Canby-Hagino ED, *et al.* Erectile function outcome reporting after clinically localized prostate cancer treatment. *J Urol* 2007;178:597–601.
37. Chaikin DC, Broderick GA, Malloy TR, *et al.* Erectile dysfunction following minimally invasive treatments for prostate cancer. *Urology* 1996;48:100–4.
38. Chen RC, Clark JA, Talcott JA. Individualizing quality-of-life outcomes reporting: how localized prostate cancer treatments affect patients with different levels of baseline urinary, bowel, and sexual function. *J Clin Oncol* 2009;27:3916–22.
39. Choo R, Long J, Gray R, *et al.* Prospective survey of sexual function among patients with clinically localized prostate cancer referred for definitive radiotherapy and the impact of radiotherapy on sexual function. *Support Care Cancer* 2010;18:715–22.
40. Clark JA, Inui TS, Silliman RA, *et al.* Patients' perceptions of quality of life after treatment for early prostate cancer. *J Clin Oncol* 2003;21:3777–84.
41. Downs TM, Sadetsky N, Pasta DJ, *et al.* Health related quality of life patterns in patients treated with interstitial prostate brachytherapy for localized prostate cancer—data from CaPSURE. *J Urol* 2003;170:1822–7.
42. Eton DT, Lepore SJ, Helgeson VS. Early quality of life in patients with localized prostate carcinoma: an examination of treatment-related, demographic, and psychosocial factors. *Cancer* 2001;92:1451–9.
43. Frank SJ, Pisters LL, Davis J, *et al.* An assessment of quality of life following radical prostatectomy, high dose external beam radiation therapy and brachytherapy iodine implantation as monotherapies for localized prostate cancer. *J Urol* 2007;177:2151–6.
44. Fulmer BR, Bissonette EA, Petroni GR, *et al.* Prospective assessment of voiding and sexual function after treatment for localized prostate carcinoma: comparison of radical prostatectomy to hormonobrachytherapy with and without external beam radiotherapy. *Cancer* 2001;91:2046–55.
45. Gore JL, Kwan L, Lee SP, *et al.* Survivorship beyond convalescence: 48-month quality-of-life outcomes after treatment for localized prostate cancer. *J Natl Cancer Inst* 2009;101:888–92.
46. Guedea F, Ferrer M, Pera J, *et al.* Quality of life two years after radical prostatectomy, prostate brachytherapy or external beam radiotherapy for clinically localised prostate cancer: the Catalan Institute of Oncology/Bellvitge Hospital experience. *Clin Transl Oncol* 2009;11:470–8.
47. Hashine K, Kusuhara Y, Miura N, *et al.* A prospective longitudinal study comparing a radical retropubic prostatectomy and permanent prostate brachytherapy regarding the health-related quality of life for localized prostate cancer. *Jpn J Clin Oncol* 2008;38:480–5.
48. Hashine K, Kusuhara Y, Miura N, *et al.* Health-related quality of life using SF-8 and EPIC questionnaires after treatment with radical retropubic prostatectomy and permanent prostate brachytherapy. *Jpn J Clin Oncol* 2009;39:502–8.
49. Hervouet S, Savard J, Simard S, *et al.* Psychological functioning associated with prostate cancer: cross-sectional comparison of patients treated with radiotherapy, brachytherapy, or surgery. *J Pain Symptom Manage* 2005;30:474–84.
50. Hollenbeck BK, Dunn RL, Wei JT, *et al.* Neoadjuvant hormonal therapy and older age are associated with adverse sexual health-related quality-of-life outcome after prostate brachytherapy. *Urology* 2002;59:480–4.
51. Jo Y, Junichi H, Tomohiro F, *et al.* Radical prostatectomy versus high-dose rate brachytherapy for prostate cancer: effects on health-related quality of life. *BJU Int* 2005;96:43–7.
52. Johnstone PA, Gray C, Powell CR. Quality of life in T1–3N0 prostate cancer patients treated with radiation therapy with minimum 10-year follow-up. *Int J Radiat Oncol Biol Phys* 2000;46:833–8.
53. Joly F, Brune D, Couette JE, *et al.* Health-related quality of life and sequelae in patients treated with brachytherapy and external beam irradiation for localized prostate cancer. *Ann Oncol* 1998;9:751–7.
54. Kakehi Y, Takegami M, Suzukamo Y, *et al.* Health related quality of life in Japanese men with localized prostate cancer treated with current multiple modalities assessed by a newly developed Japanese version of the Expanded Prostate Cancer Index Composite. *J Urol* 2007;177:1856–61.
55. Lev EL, Eller LS, Gejerman G, *et al.* Quality of life of men treated for localized prostate cancer: outcomes at 6 and 12 months. *Support Care Cancer* 2009;17:509–17.
56. Lilleby W, Fossa SD, Waehre HR, *et al.* Long-term morbidity and quality of life in patients with localized prostate cancer undergoing definitive radiotherapy or radical prostatectomy. *Int J Radiat Oncol Biol Phys* 1999;43:735–43.
57. Litwin MS, Sadetsky N, Pasta DJ, *et al.* Bowel function and bother after treatment for early stage prostate cancer: a longitudinal quality of life analysis from CaPSURE. *J Urol* 2004;172:515–19.
58. Litwin MS, Gore JL, Kwan L, *et al.* Quality of life after surgery, external beam irradiation, or brachytherapy for early-stage prostate cancer. *Cancer* 2007;109:2239–47.
59. Mehta SS, Lubeck DP, Pasta DJ, *et al.* Fear of cancer recurrence in patients undergoing definitive treatment for prostate cancer: results from CaPSURE. *J Urol* 2003;170:1931–3.

60. Miller DC, Sanda MG, Dunn RL, *et al.* Long-term outcomes among localized prostate cancer survivors: health-related quality-of-life changes after radical prostatectomy, external radiation, and brachytherapy. *J Clin Oncol* 2005;23:2772–80.
61. Miller DC, Wei JT, Dunn RL, *et al.* Use of medications or devices for erectile dysfunction among long-term prostate cancer treatment survivors: potential influence of sexual motivation and/or indifference. *Urology* 2006;68:166–71.
62. Monahan PO, Champion V, Rawl S, *et al.* What contributes more strongly to predicting QOL during 1-year recovery from treatment for clinically localized prostate cancer: 4-weeks-post-treatment depressive symptoms or type of treatment? *Qual Life Res* 2007;16:399–411.
63. Namiki S, Satoh T, Baba S, *et al.* Quality of life after brachytherapy or radical prostatectomy for localized prostate cancer: a prospective longitudinal study. *Urology* 2006;68:1230–6.
64. Namiki S, Kwan L, Kagawa-Singer M, *et al.* Distress and social dysfunction following prostate cancer treatment: a longitudinal cross-cultural comparison of Japanese and American men. *Prostate Cancer Prostatic Dis* 2009;12:67–71.
65. Ohashi T, Yorozu A, Toya K, *et al.* Serial changes of international prostate symptom score following I-125 prostate brachytherapy. *Int J Clin Oncol* 2006;11:320–5.
66. Pinkawa M, Fishedick K, Gagel B, *et al.* Association of neoadjuvant hormonal therapy with adverse health-related quality of life after permanent iodine-125 brachytherapy for localized prostate cancer. *Urology* 2006;68:104–9.
67. Roach M III, Chinn DM, Holland J, *et al.* A pilot survey of sexual function and quality of life following 3D conformal radiotherapy for clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys* 1996;35:869–74.
68. Sanda MG, Dunn RL, Michalski J, *et al.* Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med* 2008;358:1250–61.
69. Schover LR, Fouladi RT, Warneke CL, *et al.* Defining sexual outcomes after treatment for localized prostate carcinoma. *Cancer* 2002;95:1773–85.
70. Soderdahl DW, Davis JW, Schellhammer PF, *et al.* Prospective longitudinal comparative study of health-related quality of life in patients undergoing invasive treatments for localized prostate cancer. *J Endourol* 2005;19:318–26.
71. Speight JL, Elkin EP, Pasta DJ, *et al.* Longitudinal assessment of changes in sexual function and bother in patients treated with external beam radiotherapy or brachytherapy, with and without neoadjuvant androgen ablation: data from CaPSURE. *Int J Radiat Oncol Biol Phys* 2004;60:1066–75.
72. Stone NN, Marshall DT, Stone JJ, *et al.* Does neoadjuvant hormonal therapy improve urinary function when given to men with large prostates undergoing prostate brachytherapy? *J Urol* 2010;183:634–9.
73. Trojan L, Harrer K, Schafer J, *et al.* [Complications and side effects of low dose rate brachytherapy for the treatment of prostate cancer: data on a 13year follow-up study from Mannheim]. *Urologe A* 2007;46:1542–7.
74. Tward JD, Lee CM, Pappas LM, *et al.* Survival of men with clinically localized prostate cancer treated with prostatectomy, brachytherapy, or no definitive treatment: impact of age at diagnosis. *Cancer* 2006;107:2392–400.
75. Valicenti RK, Bissondtte EA, Chen C, *et al.* Longitudinal comparison of sexual function after 3-dimensional conformal radiation therapy or prostate brachytherapy. *J Urol* 2002;168:2499–504.
76. Van de Poll-Franse LV, Sadetsky N, Kwan L, *et al.* Severity of cardiovascular disease and health-related quality of life in men with prostate cancer: a longitudinal analysis from CaPSURE. *Qual Life Res* 2008;17:845–55.
77. Wyler SF, Engeler DS, Seelentag W, *et al.* Health-related quality of life after radical prostatectomy and low-dose-rate brachytherapy for localized prostate cancer. *Urol Int* 2009;82:17–23.
78. Zagar TM, Stock RG, Cesaretti JA, *et al.* Assessment of postbrachytherapy sexual function: a comparison of the IIEF-5 and the MSEFS. *Brachytherapy* 2007;6:26–33.