

Statistical analysis of patient-reported outcome data in randomised controlled trials of locally advanced and metastatic breast cancer

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**Current State of Statistical Analysis of Patient Reported Outcomes Data in Cancer
Randomized Controlled Trials on Locally Advanced and Metastatic Breast Cancer – A
Systematic Review**

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Summary

Although patient reported outcomes (PROs) such as health-related quality of life (HRQOL) are important endpoints in randomized controlled trials (RCTs), there is little consensus about analysis, interpretation and reporting of these data.

A systematic review was conducted to assess variability, quality, and standards of PRO data analyses in advanced breast cancer RCTs. We searched through PubMed for English language articles published in peer-reviewed journals between January 2001 and October 2017. Eligible articles reported PRO results from RCTs involving adult advanced breast cancer patients receiving anti-cancer treatments with reported sample sizes of at least 50 patients.

Sixty-six RCTs met the selection criteria. A small number of RCTs reported a specific PRO research hypothesis (8/66, 12%). There was heterogeneity in the statistical methods used to assess PRO data, with a mixture of longitudinal and cross-sectional techniques. Not all articles addressed the problem of inflated type I error resulting from multiple testing. Fewer than half of RCTs reported the clinical significance of their findings (28/66, 42%). The majority of trials did not report how missing data was handled (48/66, 73%).

Our review demonstrates a need to improve standards in analysis, interpretation and reporting of PRO data in cancer RCTs. Lack of standardization makes it difficult to draw robust conclusions and compare findings across trials. The Setting International Standards in the Analyzing Patient-Reported Outcomes and Quality of Life Data (SISAQOL) Consortium was set up to address this need and develop recommendations on the analysis of PRO data in RCTs.

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Introduction

In a breakthrough report, the Institute of Medicine highlighted *patient-centered care* as a critical component of quality health care¹. Patient-centered care is defined as “respectful of, and responsive to the individual patient preferences, needs, and values and that patient values guide all clinical decisions”¹. The incorporation of patient reported outcomes (PROs) in randomized controlled trials (RCTs) is one concrete way of responding to this imperative. Increasingly, PRO endpoints are being included in RCTs to assess clinical benefit alongside overall and progression-free survival². PRO is any outcome^{3,4} that is reported directly by the patient^{3,4}. By including PRO endpoints, such as health-related quality of life (HRQOL), the patient’s perspective is obtained, providing better patient information and supporting shared decision making in the development of new therapies^{5,6}.

However, the lack of standards and clear guidelines on how these patient-reported data should be analyzed and interpreted in RCTs diminishes their recognized and important value by making it difficult to compare results across trials and draw conclusions about the patient experience of new types of cancer treatment⁷. Data generated from certain PROs, such as HRQOL, are complex: they (a) are multidimensional, with several subscales to characterize patients’ symptoms and their impact on aspects of patient functioning; (b) require repeated measurements in order to capture changes in these outcomes; and (c) are prone to missing data since it is often difficult to obtain complete PRO follow-up data from all randomized patients^{8,9}. Inappropriate handling of these critical statistical issues could bias findings and lead to inaccurate conclusions. Current guidelines do not provide concrete suggestions on how to deal with statistical issues concerning PROs and need to be supplemented with more detailed strategies on how to address these concerns^{3,10}.

The Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data for Cancer Clinical Trials (SISAQOL) Consortium was established to respond to a clear need to develop standards, guidelines, and recommendations for the analyses of PRO data in cancer RCTs. This Consortium involves a wide range of international experts - leading PRO researchers and statisticians as well as key individuals from different international oncological and medical societies, advisory and regulatory bodies, academic societies, the pharmaceutical industry, cancer institutes, and patient advocacy organizations¹¹. A key task identified by the Consortium was to undertake systematic literature reviews to describe the current state of PRO analyses in RCTs of cancer treatment. The current article examines how analyses of PRO such as HRQOL are conducted in RCTs, in this case using anti-cancer treatments for advanced breast cancer as an example set of trials commonly seen in the literature. Since maintaining HRQOL is important in the care of advanced breast cancer patients, it was a reasonable expectation that a considerable number of advanced breast cancer RCTs would have included PROs in their assessments¹².

Methods

Search strategy and selection criteria

We followed the methodology noted in the guidelines for the Cochrane Handbook for Systematic Reviews of Interventions¹³ and the results of this review are reported in accordance with PRISMA guidelines (see Appendix page 35-36 for the PRISMA checklist)¹⁴. We did not publish a review protocol for this study. A literature search was performed in PubMed on March 30, 2016 (and updated on February 7, 2018) with the following keywords: (quality of life[MeSH Terms] OR quality of life[Text Word] OR patient reported outcomes[Text Word]) AND (advanced[All Fields] OR metastatic[All Fields]) AND breast cancer[Text Word] AND (Randomized Controlled Trial) AND (breast neoplasm[MeSH Terms]) AND (Clinical Trial[ptyp] AND ("2001/01/01"[PDat] : "2017/10/30"[PDat]) AND Humans[Mesh]). Using this search strategy, 323 potentially eligible articles were identified. Checking of references of publications were also undertaken. In addition, we performed a Web of Science search at a later date (April 22, 2018), but no further articles were found.

The inclusion and exclusion criteria for the RCTs were similar to that of Ghislain and colleagues¹⁵. The inclusion criteria were: articles should report PRO findings from RCTs involving adult advanced breast cancer patients (18 years or older), receiving anti-cancer treatments (chemotherapy, targeted therapy, endocrine therapy) with sample sizes of at least 50 patients. Advanced breast cancer refers to either metastatic breast cancer or locally advanced breast cancer (see ESO-ESMO international consensus guidelines for more information)¹². Only articles published in a peer-reviewed journal between January 2001 and October 2017 were included, regardless of starting or completion date of the study. It was originally considered to do

a search from 1997 to have exactly 20 years of review. However, due to the difficulty of retrieving articles before 2001, it was decided to begin the search from 2001.

Exclusion criteria were any RCTs which evaluated psychological, supportive or supplementary interventions. Supplementary treatments were defined as any other interventions that did not include anti-cancer therapy. Purely methodological or review publications were also excluded.

Quality-adjusted life years (QALY) endpoints were not considered as PRO endpoints.

Publications that reported interim analysis or the analyses of subgroups of patients (i.e., subgroups within the PRO cohort) were excluded since we wanted to limit the reporting to the top-level PRO results of the RCTs. Figure 1 presents the search strategy flowchart and the inclusion and exclusion criteria.

Two reviewers (MP and LDo) received the initial list of the 323 potentially eligible articles and the list of inclusion and exclusion criteria. They independently screened the articles based on these criteria. One reviewer (LDo) checked both assessments for any disagreements. Any disagreements were resolved through discussion. A third reviewer (CC) was available when no consensus could be reached.

[Insert Figure 1 here]

Evaluation criteria were adapted from previous reviews^{16,17} with adjustments to enable in-depth assessment of statistical issues critical for PRO analysis. The initial data extraction sheet was developed by MP and CC and pilot-tested on three randomly-selected included studies and was further refined. This resulted in 23 evaluation criteria, classified into five broad categories: (1)

general description of the article, (2) reporting of research objectives, (3) statistical analysis and clinical relevance, (4) baseline assessment, and (5) assessing the amount of, and handling of missing data (see Appendix, page 29-34, for more details on the list of variables that were extracted). Two reviewers (MP and LDo) independently evaluated all identified studies on this predefined checklist of 23 criteria. One reviewer (LDo) checked the completed data extraction sheets for any disagreements. In case of disagreement, the article was reassessed by both reviewers together. If no consensus could be reached, a third reviewer (CC) served as a mediator to resolve disagreements.

When multiple publications for one RCT were identified, the article with the more comprehensive PRO statistical reporting was included in the review (see articles with bold formatting in the Appendix, page 1-28). Therefore, findings reported in this systematic review are based on the number of unique RCTs.

Results

Table 1 summarizes the overall main findings of this systematic review. To assess whether practices were improving over time, results were grouped into three periods (2001-2006; 2007-2012; 2013-2017) in Table 2. Details about individual papers included in this review are in the Appendix, page 1-28.

Descriptive Statistics

The search identified 335 eligible articles, of which a total of 66 eligible RCTs in advanced breast cancer were included, involving a total of 26,905 patients. No disagreements occurred between the 2 independent reviewers. The sample size ranged between 66 and 1102, with an average of 407. From the 66 trials, 12 were considered to be practice changing trials. The most commonly used PRO measures were two cancer-specific HRQOL questionnaires: the EORTC QLQ-C30 (35/66, 53%) and the FACT-B (22/66, 33%). Almost half of the RCTs (27/66, 41%) used multiple assessment tools to measure PROs, of which six trials (6/27, 22%) used an instrument that was not validated (e.g., ad-hoc trial specific checklists) in addition to a validated questionnaire. The majority of the PRO endpoints were reported as secondary endpoints (46/66 trials; 70%), with only three RCTs using a PRO as a primary endpoint (3/66, 5%). The other RCTs either reported PRO as an exploratory endpoint (3/66, 5%) or did not clearly report the PRO endpoint (14/66, 21%).

[Insert Table 1 here]

Reporting of research objectives

Only eight of 66 RCTs (12%) reported a hypothesis specific enough to inform the analysis of the PRO endpoint (i.e., the direction of hypothesis is stated with the domain of interest and specified time frame). The majority of the articles either reported a broad hypothesis (25/66, 38%; e.g., “to evaluate HRQOL between treatment arms”) or no hypothesis (33/66, 50%). The majority of RCTs failed to report a specific PRO hypothesis, and there was no consistent improvement over time (2001-2006: 0/20, 0%; 2007-2012: 4/24, 17%; 2013-2017: 4/22, 18%).

Statistical analysis and clinical relevance

The majority of the trials (59/66, 89%) reported analyzing multivariate data, with multiple PRO scales/domains and/or with repeated assessments, to assess the PRO endpoint. Scales/domains refer to PRO variables that were analyzed in the trial. Thirty-eight RCTs analyzed multiple PRO scales/domains (38/66, 58%); and 21 RCTs analyzed a single PRO scale/domain (21/66, 32%). Among the 38 RCTs that used multiple PRO scales/domains, only six employed a statistical correction to correct for multiple testing (6/38, 16%). Two RCTs reported PROs as an exploratory endpoint and assessed multiple outcomes. It can be argued that exploratory endpoints do not have to correct for multiple testing. Results remained relatively the same after removing these two exploratory endpoints from the total score of PROs that assessed multiple outcomes (6/36, 17%). Combined, these numbers demonstrate that 27 of the 66 trials (41%) addressed the issue of multiple testing either by statistically correcting for multiple scales/domains or assessing only one scale/domain (often identified *a priori* as the most relevant scale/domain). There was no clear pattern in these findings (2001-2006: 11/20, 55%; 2007-2012: 7/24, 29%; 2013-2017: 9/22, 41%).

Fifty-three RCTs analyzed data with repeated assessments at follow-up (>1 follow-up assessment; 53/66, 80%); and 8 RCTs analyzed data with a single follow-up assessment (8/66, 12%). Among the RCTs that used multiple follow-up assessment points in their primary PRO analysis, 33 RCTs (33/53, 62%) used a statistical technique that took into account the repeated measurements of the data (e.g., time to event, linear mixed models) or statistically corrected for them if these repeated measures were tested independently from one another. Combined, these findings show that 41 of the 66 trials (41/66, 62%) addressed the issue of multiple testing either by statistically correcting for multiple domains, using a statistical technique that took into account the repeated measurements, or by analyzing only one follow-up time point. These findings remain consistent over time (2001-2006: 13/20, 65%; 2007-2012: 14/24, 58%; 2013-2017: 14/22, 64%).

The majority of the RCTs reported PRO scores descriptively (55/66, 83%), such as mean scores or mean change scores by trial arms, either on their own or as a support for a comparative analysis; and this has been quite consistent over the years (2001-2006: 16/20, 80%; 2007-2012: 19/24, 79%; 2013-2017: 20/22, 91%).

When analyzing PRO data, we identified more than six primary statistical analysis techniques. The top two most commonly used statistical techniques were (generalized) linear mixed models (18/66, 25%) and Wilcoxon ranks sums test/t-test (11/66, 17%). Many RCTs did not report the statistical technique used; a p-value was reported but it was not mentioned how this value was obtained (15/66, 23%). When comparing findings over time, the most commonly used statistical techniques between 2001-2006 were (generalized) linear mixed models (8/20, 40%) and Wilcoxon ranks sums test/t-test (5/20, 25%); between 2007-2012 were ANOVA/linear

regression (7/24, 29%), (generalized) linear mixed models (3/24, 13%) and Wilcoxon ranks sums test/t-test (3/24, 13%); and between 2013-2017 were (generalized) linear mixed models (7/22, 32%) and time to event (5/22, 23%). No single technique was used in a majority of the trials. Moreover, across all periods, a substantial proportion of RCTs failed to report the statistical technique used (2001-2006: 5/20, 25%; 2007-2012: 6/24, 25%; 2013-2017: 4/22, 18%).

Less than half of the RCTs addressed the clinical relevance of the findings (28/66, 42%). Among the trials that reported whether a finding was clinically relevant, the methods used varied: they were reported either as a change of X points from baseline (18/28, 64%), an X points difference between treatment arms (9/28, 32%) or both (1/28, 4%). The percentage of RCTs reporting the clinical relevance of their findings increased somewhat over the years (2001-2006: 5/20, 25%; 2007-2012: 11/24, 46%; 2013-2017: 12/22, 55%)

Baseline assessment

The majority of the RCTs included a baseline PRO assessment (60/66, 91%). From these 60 studies, 36 (36/60, 60%) compared PRO baseline scores between treatment arms and 13 (13/60, 22%) included the baseline score as a covariate. That the majority of the RCTs included a baseline PRO assessment has been consistent over the years (2001-2006: 18/20, 90%; 2007-2012: 22/24, 92%; 2013-2017: 20/22, 91%); however, the number of studies reporting whether PRO baseline scores are comparable between treatment arms seem to have declined over the years (2001-2006: 13/18, 72%; 2007-2012: 14/22, 64%; 2013-2017: 9/20, 45%); and including baseline scores as a covariate has not necessarily improved over the years (2001-2006: 2/18, 11%; 2007-2012: 6/22, 27%; 2013-2017: 5/20, 25%).

Amount of and handling of missing data

Many studies (24/66, 36%) did not report or did not clearly specify the analysis population for the primary PRO analysis; and this is still the case in the recent years (2001-2006: 6/20, 15%; 2007-2012: 8/24, 33%; 2013-2017: 10/22, 45%). Fourteen RCTs (14/66, 21%) reported using the intent-to-treat (ITT) population in their analysis; and a greater number of RCTs reported using a modified intent-to-treat (mITT) population (28/66, 42%). These numbers were relatively comparable over the years (see Table 2). Five different definitions of mITT were found, demonstrating that there is no consistent definition of mITT (64% with baseline PRO and ≥ 1 post-assessment (18/28); 14% with baseline PRO (4/28); 7% with at least one PRO data point (2/28); and 7% with baseline PRO and trial-specific follow-up point of interest (2/28). See Appendix, page 21-28, for the analysis population used by each RCT).

Regarding compliance rates, among the RCTs that assessed baseline PRO (60/66, 91%), twenty-eight of them (28/60, 47%) reported baseline PRO compliance rates for each treatment arm. Nineteen RCTs (19/66, 29%) reported whether compliance rates between treatment groups differed throughout the follow-up assessments. Most studies (48/66, 73%) did not report how missing data were dealt with. These findings were relatively comparable across the years (see Table 2).

Discussion

The aim of this systematic review was to assess the current state of PRO analysis in RCTs in advanced breast cancer. Our findings showed that in the 66 eligible RCTs, there was clear heterogeneity on how PRO data were analyzed.

Most trials failed to report a specific research hypothesis (88%), even in the last six years (2012-2017: 82%). This is consistent with previous reviews¹⁸⁻²¹. This may reflect lack of knowledge about the likely HRQOL trajectory for novel treatments or a lack of consideration of PRO specific hypotheses at the design stage and specification in the trial protocol. This is consistent with recent reviews of trial protocol content^{22,23}. Our findings highlight an area of poor practice which does not meet ISOQOL and CONSORT-PRO reporting standards^{24,25}. Failure to state a clear PRO hypothesis *a priori* opens up the possibility that inappropriate statistical techniques may be used. For instance, if a study had the objective about HRQOL changes over a six-week period, a cross-sectional HRQOL analysis at six weeks is not equivalent to an area under the curve analysis within the same time frame; in fact, it is possible that these two analytical techniques may yield different results. If the PRO objective is not stated or too vaguely stated, different statistical approaches may be reported as equivalent ways of addressing the same PRO objective, when in fact, they focus on different aspects of the data; and therefore respond to different research objectives. Divergent findings, however, may not necessarily invalidate the PRO data analysis but rather illustrate the importance of a well-defined *a priori* hypothesis, and responding to them with an appropriate statistical technique. Therefore, it is critical that researchers clearly define their hypotheses and appropriate corresponding statistical analyses in the protocol or statistical analysis plan in sufficient detail²⁶; and results are described in a way

that accurately represents the key patterns in the data and able to be understood by non-statistical readers.

The most commonly used statistical technique (linear mixed models) was only employed in 27% of the RCTs (18/66). Wilcoxon-ranks-test/t-tests, statistical techniques appropriate for single time points or change scores, were also commonly used (11/66, 17%) although this strategy may not be appropriate since the majority of the trials involved analyzing data with more than two repeated assessments (53/66, 80%). There seems to be an increased interest in the use of time to event analysis in the recent years (from 2001-2007: 1/20, 5% to 2013-2017: 5/22, 23%) (see Table 2). However, a major concern remains that a number of RCTs (15/66, 23%) did not even (clearly) report the statistical technique they used to analyze PRO data, which is still evident in the recent years (2013-2017: 4/22, 18%).

Analysis of a PRO endpoint, such as HRQOL, often involves multiple outcomes. When drawing conclusions about treatment efficacy, it is advisable to avoid the risk of accumulating type 1 errors (false positive findings) by adjusting critical p-values for multiple comparisons when multiple outcomes are used to test a multi-dimensional endpoint, such as HRQOL. A large number of RCTs did not do this (30/38, 79%); and this has still been the case in the last six years (10/11, 91%), which may have led to erroneous conclusions about the PRO endpoint due to excess type 1 errors²⁷. Given that results of these RCTs can lead to setting new standards of care, this practice should be avoided. On-going work from SPIRIT-PRO to standardize what needs to be included in the design stage of a trial (protocol) and statistical analysis plans may help promote better reporting on these issues²⁶.

The sample size estimation required for a trial is typically calculated only for the primary clinical endpoint. Since PRO endpoints, such as HRQOL, are often secondary endpoints, the sample size may be much larger (or smaller) than what is needed for that endpoint. Since statistical significance is highly dependent on sample size, having a large sample size can produce statistically significant results, but the clinical relevance of the change in the PRO endpoint may be negligible²⁸. It is therefore recommended that clinical relevance should always be reported alongside statistical significance. Similar to other reviews^{18-21,29}, our review showed it is still not common practice to report the clinical relevance of PRO findings: less than half of the RCTs (28/66, 42%) reported whether their findings were clinically relevant; although this practice has shown some improvement in the last six years (from 2001-2006: 5/20, 25% to 2013-2017: 12/22, 55%).

The majority of the RCTs in this review reported having a baseline assessment (90%) and this has been consistent over the years. These findings demonstrate wide acceptance of this practice. Assessing baseline (or pre-treatment) scores is essential in any PRO analysis. Since individuals can differ in their baseline levels, it is important to take this into account when assessing individual changes over time and differences between treatment arms. This makes the statistical analysis more efficient by reducing the influence of baseline differences in the analysis³⁰. A large number of articles collected baseline PRO information (60/66, 91%) and 40% of RCTs did not subsequently check whether there were baseline differences between treatment arms (24/60). Additionally, only a small number of trials reported using the baseline PRO scores as a covariate (13/60, 22%). These findings remain comparable over the years. This highlights the lack of consistency between investigators on how to use baseline information in their analyses.

To assess the amount of missing data, it is critical that trials report the set or subset of trial participants that will be used in the analysis (the “analysis population”) ³¹, as well as PRO completion (or “compliance rates”) over time ³². Only a small number of the publications used intent-to-treat (ITT) as the analysis population (14/66, 21%); and this has still been the case in the recent years (2013-2017: 4/22, 18%). Additionally, some papers that purported to use ITT apparently did not adhere to the ITT principle (i.e., all randomized subjects should be analyzed according to the allocated treatment ³³). For example, some RCTs reported that they would use ITT for analysis, but their statistical techniques removed a patient if an assessment was missing (e.g., when a statistical test involves calculating a change score ^{34,35}). Probably because of the difficulty of using the ITT population for PRO analysis, a number of articles opted for a modified intent-to-treat approach (mITT). However, there is no consensus on which mITT approach should be used as demonstrated by the variety of ways these RCTs have defined their mITT (e.g., patients with baseline PRO; patients with baseline PRO + 1 follow-up assessment).

Compliance rates are another way of understanding the amount of missing data in a trial ³². However, our findings showed that although more than half of the RCTs reported baseline compliance rates, a smaller number of publications reported follow-up compliance rates within their time frame of interest; and not all articles compared compliance rates between treatment groups. This lack of information on compliance rates makes it difficult to evaluate whether a statistical technique is appropriate for the analysis population (e.g., some statistical techniques assume that the dataset has no missing data or that missing data is missing completely at random) and whether the conclusions are generalizable to the population of interest.

Strategies to deal with missing data in the statistical analyses were reported in only 27% of RCTs (18/66); and this practice has not changed in the recent years (from 2001-2006: 4/20, 20% to 2013-2017: 5/22, 23%). However, it is known that missing data is a challenge in the analysis of PRO data in cancer trials^{8,30,36}. As cancer patients often experience disease- and treatment-related illness and mortality, missing assessments are often inevitable³⁷. Since missing data can bias results, it is strongly advised that sensitivity analyses should be conducted to explore the robustness of the primary findings³⁸. That is, investigators are encouraged to reanalyze the data with a statistical model that makes different missing data assumptions than that of the primary analysis. If results are reasonably consistent across the different analyses, there is increased confidence that the presence of missing data did not compromise the original findings.³⁹ The lack of information on how missing data were handled suggests that this problem is often ignored or regarded as unimportant when reporting PRO findings. This situation should not be acceptable.

While our review was robust and followed a systematic approach, our work also has several limitations. Findings from this review were based on published articles, and the articles selected may reflect publication bias, i.e., statistically significant “positive” results tend to have a better chance of being published⁴⁰. Protocols or *a priori* statistical analysis plans were not checked alongside these published reports. It is possible that information classified as “not reported” in this review may have been recorded in the protocol, but was not included in the article due to space limitations in the journals. However our findings are consistent with systematic reviews of protocols^{22,23} and other reviews of papers reporting RCTs^{18–21,29} demonstrating that these issues are indeed prevalent in the PRO field. We excluded non-English publications in our search, so some relevant trials may have been excluded. The focus of this systematic review was on

advanced breast cancer and thus may not be generalizable to all cancer types, although we have no reason to think that the analysis problems reported here would be different in other disease sites. Indeed, the converging results from other systematic reviews in different cancer sites point toward a general problem that is not specific to one cancer site^{16,17,19}. As there are no agreed-upon standards on how to conduct analyses of PROs in RCTs, the evaluation criteria of these trials were based on authors' selection of statistical issues that were deemed as critical for the analysis of PRO data, but remains broadly in line with on-going work on guidelines for statistical analysis plans²⁶. Although this review focuses on standards in statistical analysis, we would like to stress the importance of a high quality study design; and choosing appropriate PRO measures and assessment points that capture the impact of both the disease and treatment on the patient experience. Even if the most robust statistical approach is used, findings from a RCT would be of little relevance if the study design is of poor quality; and inappropriate outcomes and follow-up assessment points are used²⁶.

In conclusion, our review highlights the many statistical issues that need to be addressed to improve the analysis and interpretation of PRO data, including HRQOL. The lack of consensus on how to analyze PRO data makes it difficult to draw robust conclusions regarding PRO endpoints and compare findings across trials. Although the increased inclusion of PRO endpoints in RCTs is a substantial step toward a more patient-centered approach, standards and guidelines are needed for how to analyze PRO data in cancer RCTs. The SISAQOL Consortium was set up to address this need and develop recommendations on how to analyze PRO data in RCTs¹¹ and will produce such guidelines in the future.

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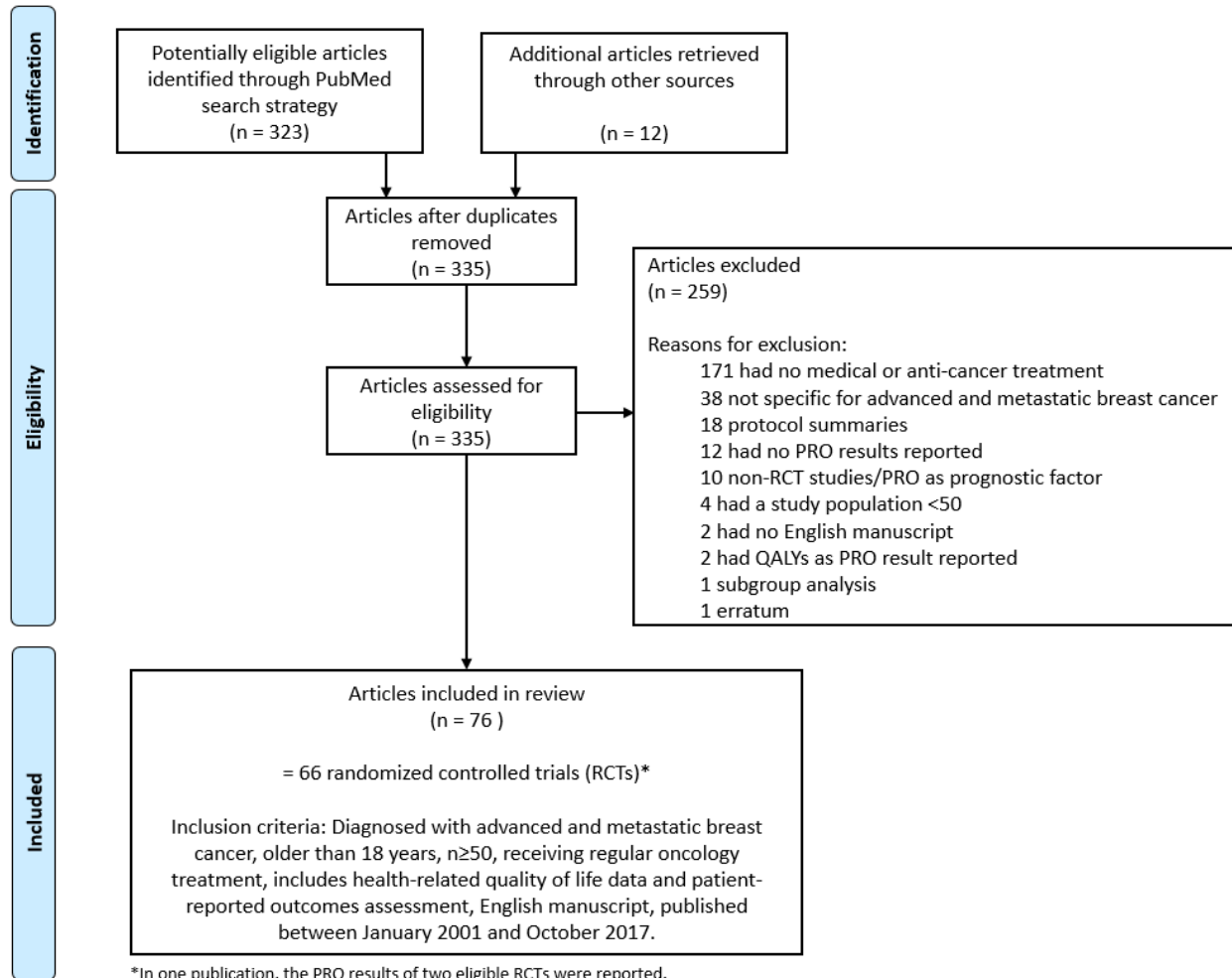
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Figure 1: Search Strategy flowchart for the inclusion and exclusion of RCTs



Authors' Contributions

All authors conceptualized the idea during the SISAQOL consortium meeting in Brussels in January 2016. M.Pe, and C. Coens conceptualized and developed the relevant statistical issues needed to be assessed for the analysis of PRO data. M.Pe carried out the systematic review with L. Dorme as the second reviewer. M.Pe, L. Dorme, C. Coens, A. Bottomley contributed to the initial interpretation of the results. M.Pe took the lead in drafting the manuscript. M. Pe and L. Dorme drafted the initial summary of findings. L. Dorme took the lead in the presentation of the raw results found in the Appendix. A. Bottomley supervised the findings and writing of this work. All authors discussed the results, provided critical feedback and reviewed the manuscript. All authors approved the final draft of the manuscript.

Conflict of Interest Statement

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