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

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55

56 **Keywords**

57 Health-Related Quality of Life, Advanced Breast Cancer, Systematic Review, Randomized

58 Controlled Trials, Statistical Methodology, Patient Reported Outcomes

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63 **Summary**

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

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

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

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

83

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87 help in extracting the treatment arms and pointing out which trials are practice changing.

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91 unrestricted education grant from Boehringer Ingelheim.

92

93

94 **Introduction**

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

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

117 The Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life
118 Endpoints Data for Cancer Clinical Trials (SISAQOL) Consortium was established to respond to
119 a clear need to develop standards, guidelines, and recommendations for the analyses of PRO data
120 in cancer RCTs. This Consortium involves a wide range of international experts - leading PRO
121 researchers and statisticians as well as key individuals from different international oncological
122 and medical societies, advisory and regulatory bodies, academic societies, the pharmaceutical
123 industry, cancer institutes, and patient advocacy organizations¹¹. A key task identified by the
124 Consortium was to undertake systematic literature reviews to describe the current state of PRO
125 analyses in RCTs of cancer treatment. The current article examines how analyses of PRO such as
126 HRQOL are conducted in RCTs, in this case using anti-cancer treatments for advanced breast
127 cancer as an example set of trials commonly seen in the literature. Since maintaining HRQOL is
128 important in the care of advanced breast cancer patients, it was a reasonable expectation that a
129 considerable number of advanced breast cancer RCTs would have included PROs in their
130 assessments ¹².

131

132 **Methods**

133 **Search strategy and selection criteria**

134 We followed the methodology noted in the guidelines for the Cochrane Handbook for Systematic
135 Reviews of Interventions¹³ and the results of this review are reported in accordance with
136 PRISMA guidelines (see Appendix page 35-36 for the PRISMA checklist)¹⁴. We did not publish
137 a review protocol for this study. A literature search was performed in PubMed on March 30,
138 2016 (and updated on February 7, 2018) with the following keywords: (quality of life[MeSH
139 Terms] OR quality of life[Text Word] OR patient reported outcomes[Text Word]) AND
140 (advanced[All Fields] OR metastatic[All Fields]) AND breast cancer[Text Word] AND
141 (Randomized Controlled Trial) AND (breast neoplasm[MeSH Terms]) AND (Clinical
142 Trial[ptyp] AND ("2001/01/01"[PDat] : "2017/10/30"[PDat]) AND Humans[Mesh]). Using this
143 search strategy, 323 potentially eligible articles were identified. Checking of references of
144 publications were also undertaken. In addition, we performed a Web of Science search at a later
145 date (April 22, 2018), but no further articles were found.

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

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

156 Exclusion criteria were any RCTs which evaluated psychological, supportive or supplementary
157 interventions. Supplementary treatments were defined as any other interventions that did not
158 include anti-cancer therapy. Purely methodological or review publications were also excluded.
159 Quality-adjusted life years (QALY) endpoints were not considered as PRO endpoints.
160 Publications that reported interim analysis or the analyses of subgroups of patients (i.e.,
161 subgroups within the PRO cohort) were excluded since we wanted to limit the reporting to the
162 top-level PRO results of the RCTs. Figure 1 presents the search strategy flowchart and the
163 inclusion and exclusion criteria.

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

169

170 [Insert Figure 1 here]

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

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

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

187

188 **Results**

189 Table 1 summarizes the overall main findings of this systematic review. To assess whether
190 practices were improving over time, results were grouped into three periods (2001-2006; 2007-
191 2012; 2013-2017) in Table 2. Details about individual papers included in this review are in the
192 Appendix, page 1-28.

193 **Descriptive Statistics**

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

206 [Insert Table 1 here]

207 **Reporting of research objectives**

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

214 Statistical analysis and clinical relevance

215 The majority of the trials (59/66, 89%) reported analyzing multivariate data, with multiple PRO
216 scales/domains and/or with repeated assessments, to assess the PRO endpoint. Scales/domains
217 refer to PRO variables that were analyzed in the trial. Thirty-eight RCTs analyzed multiple PRO
218 scales/domains (38/66, 58%); and 21 RCTs analyzed a single PRO scale/domain (21/66, 32%).

219 Among the 38 RCTs that used multiple PRO scales/domains, only six employed a statistical
220 correction to correct for multiple testing (6/38, 16%). Two RCTs reported PROs as an
221 exploratory endpoint and assessed multiple outcomes. It can be argued that exploratory
222 endpoints do not have to correct for multiple testing. Results remained relatively the same after
223 removing these two exploratory endpoints from the total score of PROs that assessed multiple
224 outcomes (6/36, 17%). Combined, these numbers demonstrate that 27 of the 66 trials (41%)
225 addressed the issue of multiple testing either by statistically correcting for multiple
226 scales/domains or assessing only one scale/domain (often identified a priori as the most relevant
227 scale/domain). There was no clear pattern in these findings (2001-2006: 11/20, 55%; 2007-2012:
228 7/24, 29%; 2013-2017: 9/22, 41%).

229 Fifty-three RCTs analyzed data with repeated assessments at follow-up (>1 follow-up
230 assessment; 53/66, 80%); and 8 RCTs analyzed data with a single follow-up assessment (8/66,
231 12%). Among the RCTs that used multiple follow-up assessment points in their primary PRO
232 analysis, 33 RCTs (33/53, 62%) used a statistical technique that took into account the repeated
233 measurements of the data (e.g., time to event, linear mixed models) or statistically corrected for
234 them if these repeated measures were tested independently from one another. Combined, these
235 findings show that 41 of the 66 trials (41/66, 62%) addressed the issue of multiple testing either
236 by statistically correcting for multiple domains, using a statistical technique that took into
237 account the repeated measurements, or by analyzing only one follow-up time point. These
238 findings remain consistent over time (2001-2006: 13/20, 65%; 2007-2012: 14/24, 58%; 2013-
239 2017: 14/22, 64%).

240 The majority of the RCTs reported PRO scores descriptively (55/66, 83%), such as mean scores
241 or mean change scores by trial arms, either on their own or as a support for a comparative
242 analysis; and this has been quite consistent over the years (2001-2006: 16/20, 80%; 2007-2012:
243 19/24, 79%; 2013-2017: 20/22, 91%).

244 When analyzing PRO data, we identified more than six primary statistical analysis techniques.
245 The top two most commonly used statistical techniques were (generalized) linear mixed models
246 (18/66, 25%) and Wilcoxon ranks sums test/t-test (11/66, 17%). Many RCTs did not report the
247 statistical technique used; a p-value was reported but it was not mentioned how this value was
248 obtained (15/66, 23%). When comparing findings over time, the most commonly used statistical
249 techniques between 2001-2006 were (generalized) linear mixed models (8/20, 40%) and
250 Wilcoxon ranks sums test/t-test (5/20, 25%); between 2007-2012 were ANOVA/linear

251 regression (7/24, 29%), (generalized) linear mixed models (3/24, 13%) and Wilcoxon ranks sums
252 test/t-test (3/24, 13%); and between 2013-2017 were (generalized) linear mixed models (7/22,
253 32%) and time to event (5/22, 23%). No single technique was used in a majority of the trials.
254 Moreover, across all periods, a substantial proportion of RCTs failed to report the statistical
255 technique used (2001-2006: 5/20, 25%; 2007-2012: 6/24, 25%; 2013-2017: 4/22, 18%).

256 Less than half of the RCTs addressed the clinical relevance of the findings (28/66, 42%). Among
257 the trials that reported whether a finding was clinically relevant, the methods used varied: they
258 were reported either as a change of X points from baseline (18/28, 64%), an X points difference
259 between treatment arms (9/28, 32%) or both (1/28, 4%). The percentage of RCTs reporting the
260 clinical relevance of their findings increased somewhat over the years (2001-2006: 5/20, 25%;
261 2007-2012: 11/24, 46%; 2013-2017: 12/22, 55%)

262 Baseline assessment

263 The majority of the RCTs included a baseline PRO assessment (60/66, 91%). From these 60
264 studies, 36 (36/60, 60%) compared PRO baseline scores between treatment arms and 13 (13/60,
265 22%) included the baseline score as a covariate. That the majority of the RCTs included a
266 baseline PRO assessment has been consistent over the years (2001-2006: 18/20, 90%; 2007-
267 2012: 22/24, 92%; 2013-2017: 20/22, 91%); however, the number of studies reporting whether
268 PRO baseline scores are comparable between treatment arms seem to have declined over the
269 years (2001-2006: 13/18, 72%; 2007-2012: 14/22, 64%; 2013-2017: 9/20, 45%); and including
270 baseline scores as a covariate has not necessarily improved over the years (2001-2006: 2/18,
271 11%; 2007-2012: 6/22, 27%; 2013-2017: 5/20, 25%).

272

273

274 Amount of and handling of missing data

275 Many studies (24/66, 36%) did not report or did not clearly specify the analysis population for
276 the primary PRO analysis; and this is still the case in the recent years (2001-2006: 6/20, 15%;
277 2007-2012: 8/24, 33%; 2013-2017: 10/22, 45%). Fourteen RCTs (14/66, 21%) reported using the
278 intent-to-treat (ITT) population in their analysis; and a greater number of RCTs reported using a
279 modified intent-to-treat (mITT) population (28/66, 42%). These numbers were relatively
280 comparable over the years (see Table 2). Five different definitions of mITT were found,
281 demonstrating that there is no consistent definition of mITT (64% with baseline PRO and ≥ 1
282 post-assessment (18/28); 14% with baseline PRO (4/28); 7% with at least one PRO data point
283 (2/28); and 7% with baseline PRO and trial-specific follow-up point of interest (2/28). See
284 Appendix, page 21-28, for the analysis population used by each RCT).

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

291

292

293 **Discussion**

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

297 Most trials failed to report a specific research hypothesis (88%), even in the last six years (2012-
298 2017: 82%). This is consistent with previous reviews¹⁸⁻²¹. This may reflect lack of knowledge
299 about the likely HRQOL trajectory for novel treatments or a lack of consideration of PRO
300 specific hypotheses at the design stage and specification in the trial protocol. This is consistent
301 with recent reviews of trial protocol content^{22,23}. Our findings highlight an area of poor practice
302 which does not meet ISOQOL and CONSORT-PRO reporting standards^{24,25}. Failure to state a
303 clear PRO hypothesis a priori opens up the possibility that inappropriate statistical techniques
304 may be used. For instance, if a study had the objective about HRQOL changes over a six-week
305 period, a cross-sectional HRQOL analysis at six weeks is not equivalent to an area under the
306 curve analysis within the same time frame; in fact, it is possible that these two analytical
307 techniques may yield different results. If the PRO objective is not stated or too vaguely stated,
308 different statistical approaches may be reported as equivalent ways of addressing the same PRO
309 objective, when in fact, they focus on different aspects of the data; and therefore respond to
310 different research objectives. Divergent findings, however, may not necessarily invalidate the
311 PRO data analysis but rather illustrate the importance of a well-defined a priori hypothesis, and
312 responding to them with an appropriate statistical technique. Therefore, it is critical that
313 researchers clearly define their hypotheses and appropriate corresponding statistical analyses in
314 the protocol or statistical analysis plan in sufficient detail²⁶; and results are described in a way

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

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

326 Analysis of a PRO endpoint, such as HRQOL, often involves multiple outcomes. When drawing
327 conclusions about treatment efficacy, it is advisable to avoid the risk of accumulating type 1
328 errors (false positive findings) by adjusting critical p-values for multiple comparisons when
329 multiple outcomes are used to test a multi-dimensional endpoint, such as HRQOL. A large
330 number of RCTs did not do this (30/38, 79%); and this has still been the case in the last six years
331 (10/11, 91%), which may have led to erroneous conclusions about the PRO endpoint due to
332 excess type 1 errors²⁷. Given that results of these RCTs can lead to setting new standards of care,
333 this practice should be avoided. On-going work from SPIRIT-PRO to standardize what needs to
334 be included in the design stage of a trial (protocol) and statistical analysis plans may help
335 promote better reporting on these issues²⁶.

336 The sample size estimation required for a trial is typically calculated only for the primary clinical
337 endpoint. Since PRO endpoints, such as HRQOL, are often secondary endpoints, the sample size
338 may be much larger (or smaller) than what is needed for that endpoint. Since statistical
339 significance is highly dependent on sample size, having a large sample size can produce
340 statistically significant results, but the clinical relevance of the change in the PRO endpoint may
341 be negligible²⁸. It is therefore recommended that clinical relevance should always be reported
342 alongside statistical significance. Similar to other reviews^{18-21,29}, our review showed it is still not
343 common practice to report the clinical relevance of PRO findings: less than half of the RCTs
344 (28/66, 42%) reported whether their findings were clinically relevant; although this practice has
345 shown some improvement in the last six years (from 2001-2006: 5/20, 25% to 2013-2017: 12/22,
346 55%).

347 The majority of the RCTs in this review reported having a baseline assessment (90%) and this
348 has been consistent over the years. These findings demonstrate wide acceptance of this practice.
349 Assessing baseline (or pre-treatment) scores is essential in any PRO analysis. Since individuals
350 can differ in their baseline levels, it is important to take this into account when assessing
351 individual changes over time and differences between treatment arms. This makes the statistical
352 analysis more efficient by reducing the influence of baseline differences in the analysis³⁰. A large
353 number of articles collected baseline PRO information (60/66, 91%) and 40% of RCTs did not
354 subsequently check whether there were baseline differences between treatment arms (24/60).
355 Additionally, only a small number of trials reported using the baseline PRO scores as a covariate
356 (13/60, 22%). These findings remain comparable over the years. This highlights the lack of
357 consistency between investigators on how to use baseline information in their analyses.

358 To assess the amount of missing data, it is critical that trials report the set or subset of trial
359 participants that will be used in the analysis (the “analysis population”) ³¹, as well as PRO
360 completion (or “compliance rates”) over time³². Only a small number of the publications used
361 intent-to-treat (ITT) as the analysis population (14/66, 21%); and this has still been the case in
362 the recent years (2013-2017: 4/22, 18%). Additionally, some papers that purported to use ITT
363 apparently did not adhere to the ITT principle (i.e., all randomized subjects should be analyzed
364 according to the allocated treatment³³). For example, some RCTs reported that they would use
365 ITT for analysis, but their statistical techniques removed a patient if an assessment was missing
366 (e.g., when a statistical test involves calculating a change score^{34,35}). Probably because of the
367 difficulty of using the ITT population for PRO analysis, a number of articles opted for a
368 modified intent-to-treat approach (mITT). However, there is no consensus on which mITT
369 approach should be used as demonstrated by the variety of ways these RCTs have defined their
370 mITT (e.g., patients with baseline PRO; patients with baseline PRO + 1 follow-up assessment).

371
372 Compliance rates are another way of understanding the amount of missing data in a trial³².
373 However, our findings showed that although more than half of the RCTs reported baseline
374 compliance rates, a smaller number of publications reported follow-up compliance rates within
375 their time frame of interest; and not all articles compared compliance rates between treatment
376 groups. This lack of information on compliance rates makes it difficult to evaluate whether a
377 statistical technique is appropriate for the analysis population (e.g., some statistical techniques
378 assume that the dataset has no missing data or that missing data is missing completely at random)
379 and whether the conclusions are generalizable to the population of interest.

380

381 Strategies to deal with missing data in the statistical analyses were reported in only 27% of RCTs
382 (18/66); and this practice has not changed in the recent years (from 2001-2006: 4/20, 20% to
383 2013-2017: 5/22, 23%). However, it is known that missing data is a challenge in the analysis of
384 PRO data in cancer trials^{8,30,36}. As cancer patients often experience disease- and treatment-related
385 illness and mortality, missing assessments are often inevitable³⁷. Since missing data can bias
386 results, it is strongly advised that sensitivity analyses should be conducted to explore the
387 robustness of the primary findings³⁸. That is, investigators are encouraged to reanalyze the data
388 with a statistical model that makes different missing data assumptions than that of the primary
389 analysis. If results are reasonably consistent across the different analyses, there is increased
390 confidence that the presence of missing data did not compromise the original findings.³⁹ The lack
391 of information on how missing data were handled suggests that this problem is often ignored or
392 regarded as unimportant when reporting PRO findings. This situation should not be acceptable.

393

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

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

417
418 In conclusion, our review highlights the many statistical issues that need to be addressed to
419 improve the analysis and interpretation of PRO data, including HRQOL. The lack of consensus
420 on how to analyze PRO data makes it difficult to draw robust conclusions regarding PRO
421 endpoints and compare findings across trials. Although the increased inclusion of PRO endpoints
422 in RCTs is a substantial step toward a more patient-centered approach, standards and guidelines
423 are needed for how to analyze PRO data in cancer RCTs. The SISAQOL Consortium was set up
424 to address this need and develop recommendations on how to analyze PRO data in RCTs¹¹ and
425 will produce such guidelines in the future.

426

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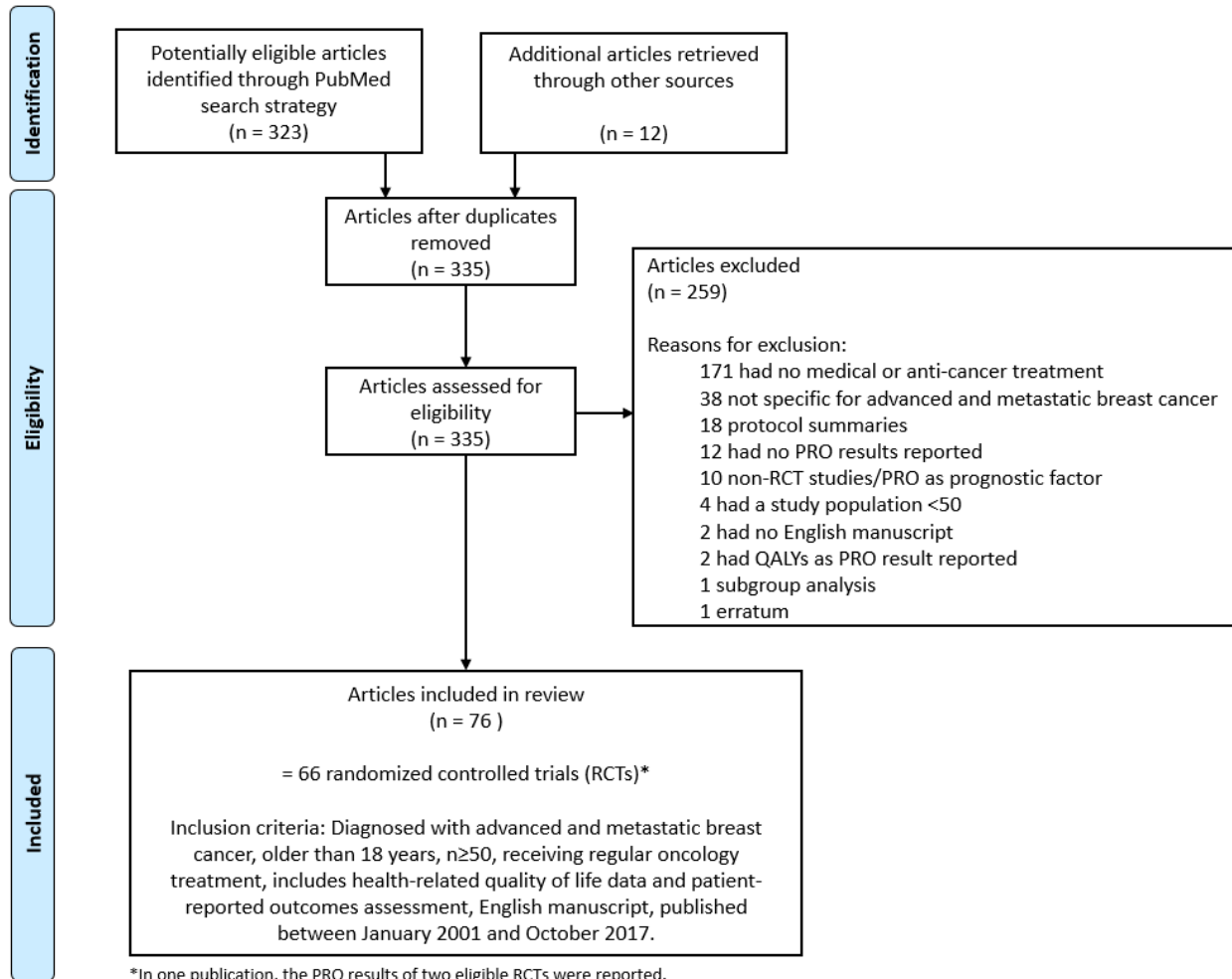
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837 **Figure 1: Search Strategy flowchart for the inclusion and exclusion of RCTs**



*In one publication, the PRO results of two eligible RCTs were reported.

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841 Table 1. Summary of the key parameters relevant for PRO analysis.

	Yes (%)	No (%)	Not reported / unclear (%)
Reporting of research objectives			
Specific hypothesis	8 (12%)	25 ^a (38%)	33 ^a (50%)
Statistical significance & clinical relevance			
Multiple domains (>1 scale or domain included in analysis)	38 (58%)	21 (32%)	7 (11%)
If yes: employed statistical correction (multiple domains were independently tested)	6/38 (16%)	30/38 (79%)	2/38 (5%)
Repeated assessments (>1 follow-up assessment included in the analysis)	53 (80%)	8 (12%)	5 (8%)
If yes: employed a statistical technique that allowed inclusion of repeated assessment points; or employed a statistical correction (if repeated assessments were independently tested)	33/53 (62%)	12/53 (23%)	8/53 (15%)
Reporting of descriptive data	55 (83%)	11 (17%)	0 (0%)
Primary statistical technique employed			
Not reported or unclear	15 (23%)	NA	NA
(Generalized) linear mixed models, including pattern mixture models	18 (27%)	NA	NA
Wilcoxon ranks sums test / between subjects t-test	11 (17%)	NA	NA
ANOVA / linear regression	9 (14%)	NA	NA
Time to event	6 (9%)	NA	NA

Repeated measures ANOVA	2 (3%)	NA	NA
Proportion of patients/responder analysis	2 (3%)	NA	NA
Others	3 (5%)	NA	NA
Reporting of clinical relevance	28 (42%)	38 (58%)	0 (0%)
Change of X points from baseline)	18/28 (64%)	NA	NA
X points difference (between arms)	9/28 (32%)	NA	NA
Change of X points from baseline and X points differences (between arms)	1/28 (4%)	NA	NA
Baseline assessment			
Assessed baseline	60 (91%)	6 (9%)	0 (0%)
Compared baseline scores between treatment arms	36/60 (60%)	24/60 (40%)	0/60 (0%)
Included baseline as a covariate ^b	13/60 (22%)	35/60 (58%)	12/60 (20%)
Assessing the prevalence of and handling of missing data			
Intention-to-treat population (ITT) ^c	14 (21%)	28 ^c (42%)	24 ^c (36%)
Baseline compliance rates for each treatment arm ^d	28/60 (47%)	32/60 (53%)	NA
Follow-up compliance rates for each treatment arm	19 (29%)	47 (71%)	NA
Strategy to handle missing data	18 (27%)	48 (73%)	NA

842 Note. n = 66, unless otherwise indicated.

843 ^a "No" means that a broad hypothesis was reported. "Not reported/unclear" means no hypothesis was reported

844 ^b *The remaining RCTs were coded as “not applicable” because the statistical method used does not allow for an*
845 *inclusion of a covariate.*

846 ^c *“No” means modified ITT was used. “Not reported/unclear” means analysis population was not reported.*

847 ^d *n is based on the number of studies that included a baseline assessment in their study design.*

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Table 2. Summary of the key parameters relevant for PRO analysis from 2001-2006, 2007-2012, 2013-2017.

	2001 – 2006 (n=20)			2007-2012 (n=24)			2013-2017 (n=22)		
	Yes (%)	No (%)	Not reported / unclear (%)	Yes (%)	No (%)	Not reported /unclear (%)	Yes (%)	No (%)	Not reported /unclear (%)
Reporting of research objectives									
Specific hypothesis	0 (0%)	6 ^a (30%)	14 ^a (70%)	4 (17%)	14 ^a (58%)	6 ^a (25%)	4 (18%)	5 ^a (23%)	13 ^a (59%)
Statistical significance & clinical relevance									
Multiple domains (>1 scale or domain included in analysis)	9 (45%)	8 (40%)	3 (15%)	18 (75%)	4 (17%)	2 (8%)	11 (50%)	9 (41%)	2 (9%)
If yes: employed statistical correction (multiple domains were independently tested)	3/9 (33%)	5/9 (56%)	1/9 (11%)	3/18 (17%)	15/18 (83%)	0/18 (0%)	0/11 (0%)	10/11 (91%)	1/11 (9%)
Repeated assessments (>1 follow-up assessment included in the analysis)	14 (70%)	3 (15%)	3 (15%)	19 (79%)	4 (17%)	1 (4%)	20 (91%)	1 (5%)	1 (5%)
If yes: employed a statistical technique that allowed inclusion of repeated assessment points; or employed a statistical correction (if repeated assessments were independently tested)	10/14 (71%)	2/14 (14%)	2/14 (14%)	10/19 (53%)	7/19 (37%)	2/19 (11%)	13/20 (65%)	3/20 (15%)	4/20 (20%)

Reporting of descriptive data	16 (80%)	4 (20%)	0 (0%)	19 (79%)	5 (21%)	0 (0%)	20 (91%)	2 (9%)	0 (0%)
Primary statistical technique employed									
Not reported or unclear	5 (25%)	NA	NA	6 (25%)	NA	NA	4 (18%)	NA	NA
(Generalized) linear mixed models, including pattern mixture models	8 (40%)	NA	NA	3 (13%)	NA	NA	7 (32%)	NA	NA
Wilcoxon ranks sums test / between subjects t-test	5 (25%)	NA	NA	3 (13%)	NA	NA	3 (14%)	NA	NA
ANOVA / linear regression	1 (5%)	NA	NA	7 (29%)	NA	NA	1 (5%)	NA	NA
Time to event	1 (5%)	NA	NA	0 (0%)	NA	NA	5 (23%)	NA	NA
Repeated measures ANOVA	0 (0%)	NA	NA	2 (8%)	NA	NA	0 (0%)	NA	NA
Proportion of patients/responder analysis	0 (0%)	NA	NA	1 (4%)	NA	NA	1 (5%)	NA	NA
Others	0 (0%)	NA	NA	2 (8%)	NA	NA	1 (5%)	NA	NA

Reporting of clinical relevance	5 (25%)	15 (75%)	0 (0%)	11 (46%)	13 (54%)	0 (0%)	12 (55%)	10 (45%)	0 (0%)
Change of X points from baseline	5/5 (100%)	NA	NA	5/11 (45%)	NA	NA	8/12 (67%)	NA	NA
X points difference (between arms)	0/5 (0%)	NA	NA	6/11 (55%)	NA	NA	3/12 (25%)	NA	NA
Change of X points from baseline and X points differences (between arms)	0/5 (0%)	NA	NA	0/11 (0%)	NA	NA	1/12 (8%)	NA	NA

Baseline assessment

Assessed baseline	18 (90%)	2 (10%)	0 (0%)	22 (92%)	2 (9%)	0 (0%)	20 (91%)	2 (9%)	0 (0%)
Compared baseline scores between treatment arms	13/18 (72%)	5/18 (28%)	0 (0%)	14/22 (64%)	8/22 (36%)	0 (0%)	9/20 (45%)	11/20 (55%)	0 (0%)
Included baseline as a covariate ^b	2/18 (11%)	11/18 (61%)	5/18 (28%)	6/22 (27%)	12/22 (55%)	4/22 (18%)	5/20 (25%)	12/20 (60%)	3/20 (15%)

Assessing the prevalence of and handling of missing data

Intention-to-treat population (ITT) ^c	4 (20%)	10 ^c (50%)	6 ^c (15%)	6 (25%)	10 ^c (42%)	8 ^c (33%)	4 (18%)	8 ^c (36%)	10 ^c (45%)
Baseline compliance rates for each treatment arm ^d	7/18 (39%)	11/18 (61%)	NA	11/22 (50%)	11/22 (50%)	NA	10/20 (50%)	10/20 (50%)	NA
Follow-up compliance rates for each treatment arm	5 (25%)	15 (75%)	NA	6 (25%)	18 (75%)	NA	8 (36%)	14 (64%)	NA

Strategy to handle missing data	4 (20%)	16 (80%)	NA	9 (38%)	15 (63%)	NA	5 (23%)	17 (77%)	NA
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^a "No" means that a broad hypothesis was reported. "Not reported/unclear" means no hypothesis was reported

^b RCTs that used a statistical method that does not allow for an inclusion of a covariate were coded as "not applicable".

^c "No" means modified ITT was used. "Not reported/unclear" means analysis population was not reported.

^d n is based on the number of studies that included a baseline assessment in their study design.

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

AB reports grants from Boehringer Ingelheim, grants from EORTC cancer research fund, during the conduct of the study; grants from Merck, outside the submitted work; and member of the EORTC Quality of Life Group executive committee. AC reports other from Genentech, A Member of the Roche Group, employee, outside the submitted work. GV reports personal fees and non-financial support from Roche, personal fees and non-financial support from Eisai, personal fees from Novartis, grants from National Institute Health Research England, grants from Yorkshire Cancer Research, grants from Breast Cancer Now, grants from EORTC Quality of Life Group, outside the submitted work. IG reports being an employee of Boehringer Ingelheim which provided an unrestricted education grant to EORTC. KO reports grants for the International Brain Tumour Alliance (IBTA) from AbbVie, Accuray, Antisense Pharma, Apogenix, Archimedes, Ark Therapeutics, Astra Zeneca, Boehringer Ingelheim, Brain Tumour Network (USA), Brain Tumor Resource and Information Network (USA), Bristol-Myers Squibb (BMS) Celldex Therapeutics, Crusade, Dijon Designs (UK), Elekta, Eli Lilly, Gerry & Nancy Pencer Brain Trust (Canada), Gosling Foundation (UK), GlaxoSmithKline (GSK), Ivy Foundation (USA), Lilly, Link Pharmaceuticals, MagForce, Medac, Merck Serono, Merck, MGI Pharma, MSD Oncology, NeoPharm, Neuroendoscopy (Australia), Northwest Biotherapeutics, Novartis, Novocure, Pediatric Brain Tumor Foundation (USA), Pfizer, Photonamic, Roche, Schering-Plough (Global), Sontag Foundation (USA), Spink (UK), to-BBB, Vane Percy (UK), VBL Therapeutics and the Wallerstein Foundation (USA), all of which are outside the submitted work. KC reports other from Amgen, other from BMS, other from Celgene, other from Adelphi Values, other from Endomag, outside the submitted work. MC reports personal fees from Astellas, grants from NIHR, outside the submitted work; and International Society for Quality of Life Research, Best Practices for PRO in Trials Taskforce Chair. MKo reports grants from EORTC, Biofrontera, KFN, personal fees from Janssen-Cilag outside the submitted work. ND reports grants from the EuroQol Group, and grants from Association of the British Pharmaceutical Industry outside the submitted work

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