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REVIEW ARTICLE

Information about missing patient-reported outcome data in breast cancer trials is frequently not documented: a scoping review

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Abstract

Objectives: This review addresses the common problem of missing patient-reported outcome (PRO) data in clinical trials by assessing the current practice of their statistical handling as reported in publications of randomized controlled trials (RCTs) in patients with breast cancer.

Study Design and Setting: We searched PubMed to identify RCTs evaluating biomedical treatments in breast cancer patients with at least one PRO endpoint published between January 2019 and February 2022. Two reviewers independently assessed the eligibility of the publications for this scoping review and extracted prespecified information on missing PRO data and related statistical practices.

Results: Of 1,598 publications identified, 118 trials met the inclusion criteria. Eighty-eight (74.6%) trials reported the extent of missing data, with 11 (9.3%) not containing any missing PRO data. Twenty-one (19.6%) trials explicitly stated the statistical approach for handling missing data, with a preference for single imputation over multiple imputation approaches (57.2%/19.0%). Only six (5.6%) trials reported a sensitivity analysis to examine the extent to the results being affected by changes in assumptions made about missing PRO data.

Conclusion: International efforts to raise awareness of the importance of accurately reporting state-of-the-art handling of missing PRO data are not yet fully reflected in the current literature of breast cancer RCTs.

Keywords: Patient-reported outcomes; Missing data; Imputation; Sensitivity analysis; Breast cancer; Randomized controlled trials

1. Introduction

Patient-reported outcomes (PROs) complement traditional clinical endpoints such as survival or adverse events and serve the purpose of drawing a comprehensive picture of side effects that often accompany cancer treatment and may influence health-related quality of life (HRQoL), by definition directly experienced and reported by the patients [1,2]. Therefore, regulators encourage the incorporation of PROs as endpoints in cancer clinical trials, labeling claims and the evaluation of medical products [2,3]. This development is further strengthened by large-scale efforts to establish standards for PRO assessment, analysis (SISAQOL) [4], and reporting (CONSORT-PRO) [5] in clinical trials, and their protocols (SPIRIT-PRO) [6]. Furthermore, the *estimand framework,* recently described in the ICH E9(R1) addendum [7], aims to facilitate the understanding of patient-reported experience in cancer drug development by aligning design, conduct, and statistical analysis plan with the respective study objectives [8]. These standards provide the basis for transparent decision-making in policy-making and clinical practice while considering PRO results from clinical trials.

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EQUATOR guideline applied: Manuscript prepared in accordance with Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist.

Review protocol: The review protocol can be made available upon reasonable request.

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What is new?

Key findings

- Only 21 (19.6%) of breast cancer randomized controlled trials (RCTs) with patient-reported outcome (PRO) endpoints included an explicit statement on the statistical approach for handling missing PRO data.
- Additionally, very few trials (six (5.6%)) reported findings of a sensitivity analysis investigating possible bias due to missing data.

What this adds to what was known?

- The findings underscore the urgent need to fully address the current practice of missing PRO data reporting from the extent to the assumptions on mechanisms leading to the choice of statistical approach, being (ideally) concluded by a sensitivity analysis to enhance the robustness of PRO results from RCTs.

What is the implication and what should change now?

- At the time of disclosing results of PRO analyses from RCTs, investigators should pay special attention to missing PRO data handling, related sensitivity analyses, and subsequent reporting, ideally to be already included in study protocols and statistical analysis plans.

One critical and much-discussed aspect regarding precise and transparent reporting of PROs in clinical trials, from both a scientific and regulatory approach perspective, is missing data [9,10]. Missing data are defined as ''values that are not available and that would be meaningful for analysis if they were observed'' [11]. The potential for bias associated with missing data is a problem that may undermine the scientific credibility of causal conclusions from clinical trials [11]. The issue becomes even more relevant when considering the incidence of missing PRO data in randomized controlled trials (RCTs) laid bare by a review by Bell et al. (2014) [12], with 95% of RCTs published in top medical journals having missing data with a median percentage of participants with a missing outcome of 9%, ranging from zero to 70%. A recent study found that only 7.4% of trials published in six top-tier oncology journals adequately (i.e., meeting current reporting guidelines) report on missing HRQoL data [13]. Bell et al. (2019) [14] attempted to explain the frequent occurrence of missing PRO values by the potential burden of PRO data collection for cancer patients due to repeated assessments throughout a trial. Besides the potential for bias and undermining the benefits of randomization by potentially leading to imbalance between treatment arms, high rates of missing PRO data substantially reduce power and inflate standard error. Possible reasons for missing PRO data can be administrative failure, patient refusal or patients' poor health condition [14]. Especially problematic is the latter, as systematic missingness of PRO data, due to the inability to complete questionnaires, for example, due to treatment side effects in one treatment arm, may lead to erratic conclusions from the analysis of the assessed PRO data, if not handled properly.

Preventing missing data as much as possible should be considered the leading maxim in clinical trials. If even a rigorous study design fails to avoid missing PRO data, it is essential (1) to be explicit about assumptions on the mechanism of missing data, (2) to take the mechanism of missingness (defined by Little & Rubin (2002) [15]) into account when deciding on statistical approaches to deal with missing data, (3) to perform sensitivity analyses for investigating how robust the results are to the assumptions made in the primary analysis, and (4) to transparently report on (1), (2), and (3) [14]. Transparent reporting strategies allow to estimate the impact of missing PRO data and its potential to bias clinical trials [16].

The aim of this scoping review is to address the common problem of missing PRO data in RCTs by assessing the current practice of reporting missing PRO data and related aspects and sensitivity analyses in breast cancer RCTs. The choice of the exemplary patient population is justified by breast cancer being the most common cancer in females, with an estimated 2.3 million worldwide newly diagnosed cases each year [17], and therefore many RCTs being performed in this disease.

2. Methods

2.1. Study design and search strategy

This work is a scoping review, justified by the broader nature of the review question intending to identify the current reporting practice of a concept of interest, herein missing PRO data. The decision is based on recommendations by Munn et al. (2018) [18]. The manuscript was prepared in accordance with Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist [19]. The completed PRISMA-ScR checklist is provided in the appendix (Supplementary Table S1).

An electronic search of PubMed to identify RCTs published between January 2019 and February 2022 was performed.

Inclusion criteria for RCTs were:

– At least one PRO endpoint (either primary, secondary, or exploratory)

- An overall sample size of at least 50 patients
- Evaluating biomedical treatments (i.e., surgery, chemotherapy, radiotherapy, targeted therapy, hormonal therapy, and immunotherapy)
- Breast cancer patients only, requiring a homogeneous sample, strictly excluding mixed cancer populations

The term PRO is considered an umbrella term, both covering unidimensional measures (e.g., visual analog scales (VAS) for pain) and multidimensional concepts such as HRQoL [3].

2.2. Selection of sources of evidence

A team of six reviewers did the screening, as well as the data extraction, in rotating pairings. Two reviewers decided on the eligibility of publications on abstract and full-text levels. If disagreements between the duo persisted, a third reviewer resolved the remaining conflicts. An external reviewer, who was not involved in this work, performed an additional eligibility check of a random sample of included and excluded articles. Publications that referred to the same trial (shown by an identical trial registration number and/or trial acronym) were identified and linked to ensure that the charted data refer to the trial as a whole and not to single publications.

2.3. Data extraction & data synthesis

Data extraction was also done by two independent reviewers following the procedure above. For matters of standardization, standard operating procedures (SOPs) for each item were developed and made available for the reviewers. The data extraction form was piloted on a sample of studies ($N = 15$) leading to a refinement of the a priori defined SOPs. The literature software DistillerSR [20] was used throughout the review procedure, enabling transparency and automated conflict display. The first section of the data extraction form was dedicated to obtaining an overview of the characteristics of the RCTs assessed. Information was extracted on industry or study organization involvement,

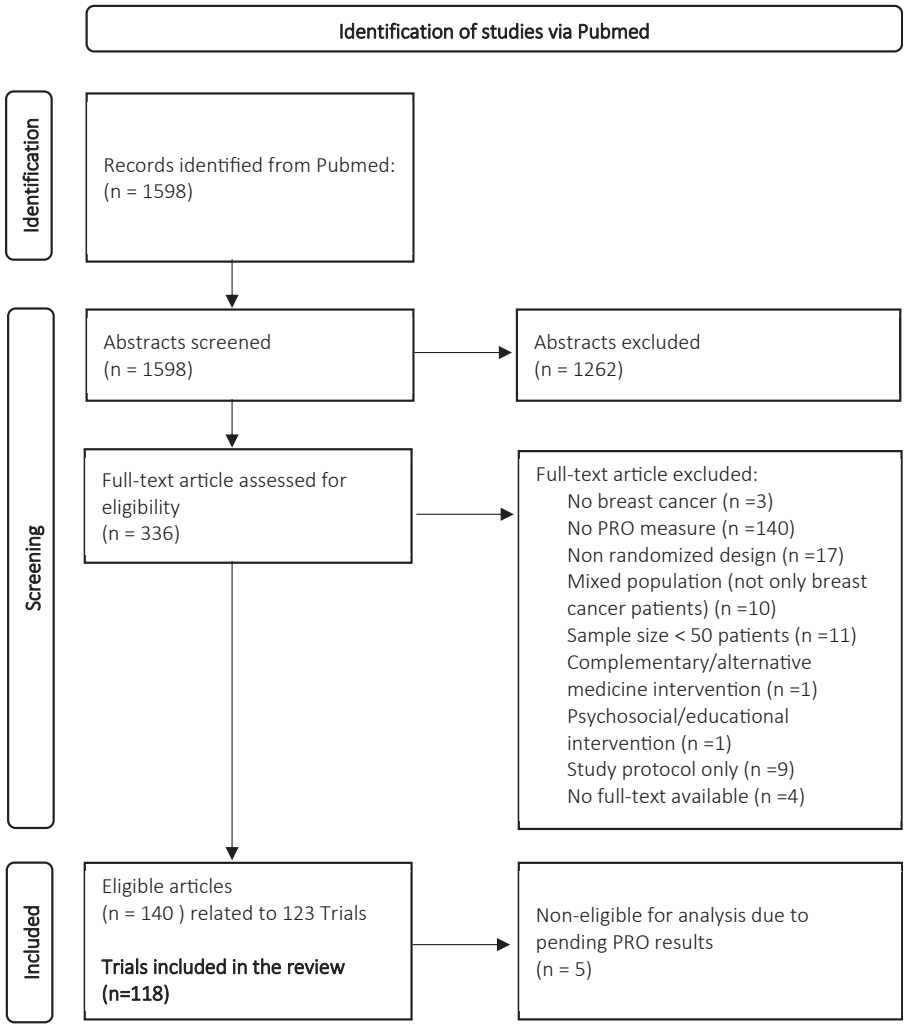

Fig. 1. PRISMA Flow chart adapted from [22].

study phase, sample size, and the biomedical treatment administered to patients in the experimental arm. This form was followed by a section on PROs, including the PRO instrument, and the assessment mode. According to the taxonomy proposed by the SISAQOL consortium, RCTs were categorized according to their PRO objective (i.e., time to event, magnitude of change, and proportion of responders) [4]. The extracted variables on the extent of missing PRO data, the statistical approach to dealing with missing PRO data, and the reasons for missing PRO data originate from established checklists [5,21]. For the full list of information extracted for each trial included, see Supplementary Table S2. For categorical variables, frequency and proportions were described using SPSS Version 27.0.0.0. For visualization purposes, a heatmap was created using R version 2022.12.0 + 353.

3. Results

3.1. Literature search

Screening of 1.598 PubMed abstracts resulted in 140 eligible publications, referring to 123 unique RCTs, with 118 being analyzed, as the PRO results in five eligible trials were still pending at the time of analysis.

Fig. 1 provides an overview of the selection of sources of evidence by providing numbers of sources of evidence screened at each level, with reasons for exclusion at the full-text level and finally included publications.

3.2. Trial characteristics

Table 1 shows the trial characteristics of the 118 eligible trials. Trial organizations were involved in 24 (20.3%) of included trials, while industry involvement was present in 49 (41.5%) trials. The trial phase was not explicitly stated in more than half of the trials. Of those with a defined trial phase, phase III was the most frequent. About 70% had a sample size between 50 and 300. Thirteen RCTs (11.0%) had a sample size above 1,000. The PRO sample size was reported in the majority of trials (87.3%). In about two-thirds, the PRO sample size at the first assessment point deviated from the number of randomized patients. Interventions to reduce pain in patients were the most commonly evaluated, followed by targeted therapies, chemotherapies, hormonal therapies, as well as radiotherapies. With eight (6.8%) trials evaluating a surgical procedure, it was the least common intervention in the analyzed set of trials. Almost 70% had an active control group, while the remaining were, with one exception, placebo-controlled RCTs. A quarter of included trials had a primary PRO endpoint, while 64 (54.2%) had a predefined secondary PRO endpoint. Pain, assessed with numerical rating scales (NRS) or visual analog scales (VAS), was the most common PRO (35.6%). EORTC (European Organisation for Research and Treatment of Cancer) instruments (32.2%), that is, the QLQ-C30 [23] and the breast cancer−specific module QLQ-BR-23 [24], the FACIT (Functional Assessment of Chronic Illness Therapy) questionnaires [25], and the EQ-5D [26] were most often used validated questionnaires to assess PROs. These results are consistent with a recent review of the current practice of PRO measurement in cancer RCTs [27]. Merely 14 trials (11.9%) provided information on the assessment mode of PROs. In terms of PRO objectives, the vast majority (89.0%) analyzed mean differences between arms and/or over time, only 16 (13.6%) did a time-to-event analysis, and 14 (11.9%) analyzed the proportions of responders.

3.3. Current practice of missing PRO data handling and related aspects

Results (see Table 2) indicate a lack of reporting regarding certain aspects of missing PRO data handling. In 77 trials (65.3%) the extent of missing PRO data was reported, in 11 trials (9.3%) authors stated to not have any missing PRO data, while in 30 (25.4%) no information on missingness of PRO data assessed was provided. In 21 out of 107 (19.6%) trials with (possible) missing data, the statistical approach how they dealt with existing missing PRO data was explicitly stated, with a preference for single imputation (57.2%) over multiple imputation approaches (19.0%). In 39 out of 107 (36.4%) trials, PRO-specific reasons for missing PRO data were provided. Ten out of 107 trials (9.3%) [28−37] made assumptions on the mechanism of missingness, whereas MAR (missing at random) was the most frequently mentioned one. Six trials [28,29,35,38−40] reported a sensitivity analysis in the context of missing PRO data. Only two trials [28,34] provided information on all the aspects of missing PRO data examined in this review. Fig. 2 visualizes the density of reporting of variables (i.e., extent, PRO specific reasons, statistical approach, mechanism of missingness, sensitivity analyses) extracted across the eligible trials with darker colors indicating a higher score. The colorway indicates the score (ranging from 0 to 2), the more dark-colored fields on the map the more items scored 1 (or 2). The highest score in one row (i.e., trial), is highlighted in dark red. The relevant data for each included source of evidence can be found in Supplementary Table S3.

4. Discussion

This scoping review addresses the current practice of missing PRO data handling in publications of RCTs in patients with breast cancer. The results indicate nontransparency when taking different levels into account and noncompliance with recommendations in the field. Although 74.6% reported the quantity of missing data, only 36.4% provided PRO specific reasons for missing data and the majority (80.4%) did not offer any clear statement on how missing data were handled from a statistical point of

Table 1. Trial characteristics ($N = 118$)

Variables	N	%
Trial organisation(s) involved		
No	94	79.7
Yes	24	20.3
Industry involvement		
No	69	58.5
Yes	49	41.5
Trial phase		
II	15	12.7
III	37	31.4
IV	1	0.8
Not reported	65	55.1
Sample size (patients randomized)		
50–100	39	33.1
101–300	44	37.3
301–999	22	18.6
1,000+	13	11.0
PRO sample size (at first assessment point) reported		
Yes	103	87.3
Deviating from sample size (patients randomized)	69	67.0
No	15	12.7
Experimental arm (multiple options possible)		
Pain intervention	36	30.5
Targeted therapy	21	17.8
Chemotherapy	16	13.6
Hormonal therapy	10	8.5
Radiotherapy	10	8.5
Surgery	8	6.8
Antiemetic intervention	7	5.9
Intervention for neuropathy	3	2.5
Other	11	9.3
Control arm		
Active comparator	82	69.5
Placebo-controlled	35	29.7
No intervention	1	0.8
Patient-reported outcome endpoint		
Primary	29	24.6
Secondary	64	54.2
Exploratory (including not defined)	25	21.2
PRO instruments[a] (multiple options possible)		
Pain (numerical rating or visual analog scales)	42	35.6
EORTC QLQ-C30 and/or disease-specific modules	38	32.2
FACIT questionnaires	15	12.7
BPI	13	11.0
EQ-5D	13	11.0
QoR-40 questionnaire	8	6.8
HADS	6	5.1
FLIE	4	3.4
SF-12/SF-36	2	1.7
Other	46	39.0
Patient-reported outcome assessment mode (multiple options possible)		
Not reported	104	88.1
Interview (face-to-face or telephone)	8	6.8
Paper pencil	7	5.9
Electronic	5	4.2
Patient-reported outcome objective[b] (multiple options possible)		
Magnitude of change at time t & mean change/difference	105	89.0
Time to event	16	13.6
Proportion of responders at time t	14	11.9
Descriptive statistics only	4	3.4
Overall PRO score over time	2	1.7
Response patterns or profiles	2	1.7
General linear model	1	0.8

[a] EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; FACIT: Functional Assessment of Chronic Illness Therapy; BPI: Brief Pain Inventory; EQ-5D: European Quality of Life five Dimensions; QoR-40: Quality of Recovery; HADS: Hospital Anxiety and Depression Scale; FLIE: Functional Living Index-Emesis; SF: Short Form.
[b] According to Coens et al. (2020) [4].

view. The results resemble those from previous work, although the latter was not limited to breast cancer RCTs [41]. The analysis of RCTs published between 2004 and 2019 [41], indicates a slight improvement in the reporting of the extent of missing PRO data (from 69.7% to 75.6%) and the reasons for missing PRO data (from 31.4% to 36.4%), but a decrease in reporting of statistical approaches (from 28.2% to 19.6%). Sensitivity analyses to test the robustness of results under different assumptions regarding missing data, as previously highly recommended from different academic and regulatory sources [3,14,16] were only reported in six of the 118 eligible trials.

Accurate reporting is a matter of shared terminology, resulting in equal use and understanding. In the field of missing data, there are some key terms suggested by Little & Rubin (2002) [15], also referred to in this review. Although missing PRO data are considered as a primary statistical issue being the statistician's responsibility, Mercieca-Bebber et al. (2016) [16] emphasize the importance of the broader interdisciplinary research team understanding the issues associated with missing PRO data. Persisting PRO compliance problems [14] and limited reporting as shown in this review and related work [12,13,41] may reflect the sporadic attention the issue has received in the literature over

Table 2. Reporting of Missing PRO Data and Sensitivity Analyses ($N = 118$)

Variables	N	%
Extent of missing PRO data stated		
Yes, extent of missing PRO data stated	77	65.3
No missing PRO data	11	9.3
No	30	25.4
Reasons for missing PRO data explained[a]		
No	68	63.6
Yes	39	36.4
Reasons for trial withdrawal/ discontinuation (not PRO specific) reported[a]		
Yes	91	85.0
No	16	15.0
Statistical approach for dealing with missing PRO data explicitly stated[a]		
No	86	80.4
YES (multiple options possible)	21	19.6
No imputation	5	23.8
Last observation carried forward	4	19.0
Multiple imputation	4	19.0
Listwise deletion (complete-case analysis)	2	9.5
Mean imputation	2	9.5
Pairwise deletion (available-case analysis)	1	4.8
Stochastic regression imputation	1	4.8
Similar response pattern imputation	1	4.8
Averaging the available items	1	4.8
Other	3	14.3
Mechanism of Missingness of missing PRO data explicitly stated[a] (multiple options possible)		
No	97	90.7
Yes, MAR (missingness at random)	5	4.7
Yes, MCAR (missingness completely at random)	3	2.8
Yes, MNAR (missingness not at random)	3	2.8
Any sensitivity analysis on missing PRO data reported[a]		
No	101	94.4
Yes	6	5.6

[a] $N = 107$ as item not relevant for trials without missing PRO data

the past 2 decades. Most of the existing work is targeted to statisticians handling missing PRO data, not reaching out to other professions involved in the design, conduct and analysis of clinical trials incorporating PRO endpoints [16]. Therefore, the handling of missing PRO data should start with study design to ideally minimize (as much as possible) the extent of missing PRO data beforehand and extend throughout the life cycle of a clinical trial, finishing off with transparent reporting in publications.

Besides shared terminology, traceability may be another key construct in the missing PRO data debate. Detailed information beyond the amount of missing PRO data, including the reasons, assumptions about the mechanism of missingness, and being explicit about the statistical approach applied, allows the reader to evaluate the procedure. Here, it is important to mention that there is no one-size-fits-it-all solution for what the best approach to deal with missing PRO data is, as it strongly depends on the above-stated circumstances. Although there are suggestions on the issues associated with ignoring missing data (i.e., relying results exclusively on complete cases), there may be scenarios where missing PRO data is ignorable [42]. A sensitivity analysis is the tool of choice to justify this approach. Even being transparent over not imputing missing PRO data enhances the credibility of reported trial results.

Reasons for and assumptions on missingness provide the basis for the distinction between ignorable and nonignorable missing PRO data. The underlying concept determining the bias potential of missing PRO data is randomness. Randomness is a critical concept in clinical trials, as randomization is the tool of choice to adjust for selection bias. In some circumstances, missing PRO data has the power to jeopardize randomization. An example of nonrandom, therefore nonignorable missing PRO data is if patients randomized to trial arm A are experiencing worse side effects than trial arm B and are therefore unable to complete the questionnaires. If complete cases would be analyzed in this scenario only, it would not provide a comprehensive picture of patients' experience. Moreover, it would lead to underestimating patients' self-reported side effects. While if administrative failure leads to missing data, for example, if the tablet for the electronic assessment is not working at one appointment, one can assume randomness, and therefore the missing PRO data could be considered ignorable. However, the loss of data, causing reduced statistical power, should be avoided. These simple examples should highlight the importance of assessing the reasons for missing data, as it is decisive for the assumptions on the mechanism of missingness, liable for the choice of an appropriate statistical approach.

4.1. Limitations

The results of this review are exclusively relying on what was reported in the publication, as information from study protocols or statistical analysis plans was not considered. However, the scope of this work is to provide information on missing PRO data in study publications.

In addition, the search was limited to one database. However, a recent study found that PubMed covered 82.8% of studies from 2012 to 2016, with a coverage rate of 90% for breast cancer studies [43]. Due to the scoping nature of the review, it was decided to search PubMed exclusively.

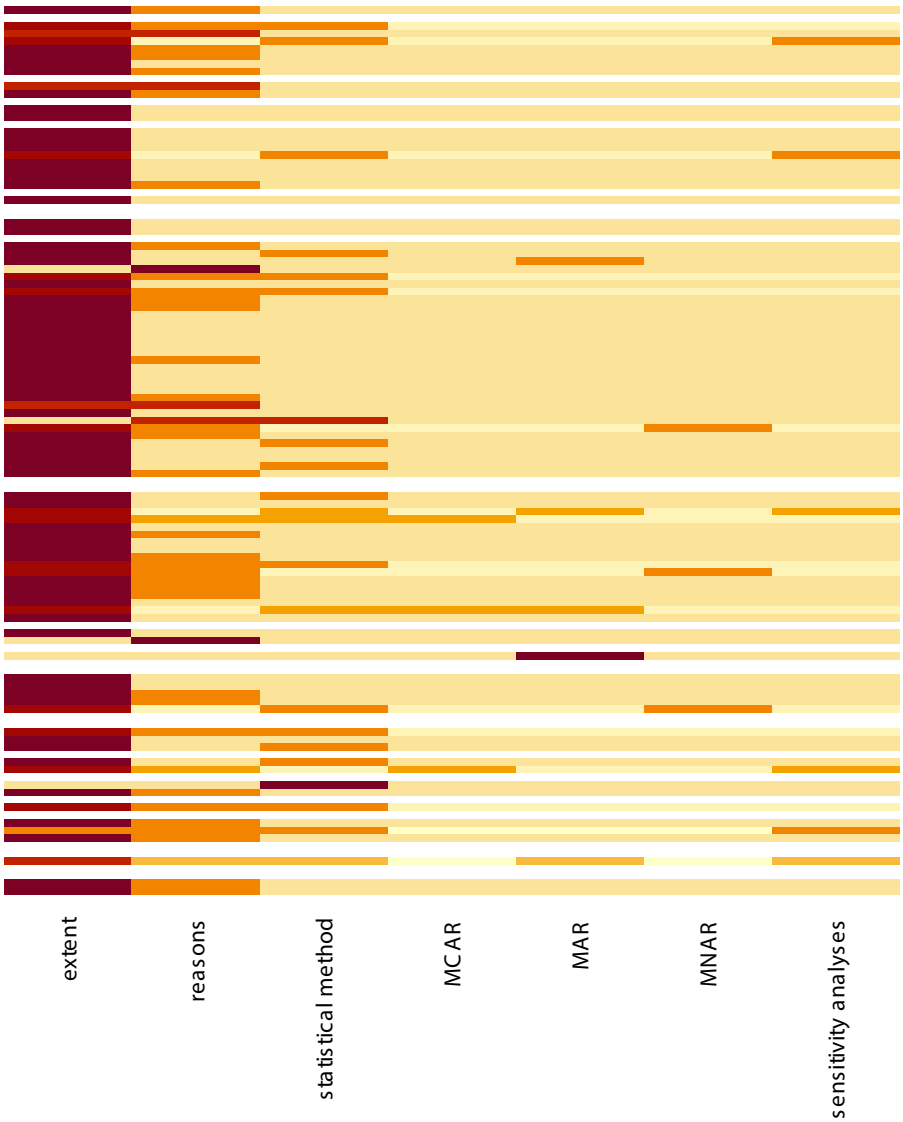

Fig. 2. Visual heatmap with detailed findings for missing PRO data reporting for each of the 118 trials. Each trial represents a row. Darker colors indicate a higher score (1–2). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

The focus on a single diagnosis, albeit the most prevalent one [17], may compromise the generalizability of the results. These concerns can be mitigated by the results of previous work including other cancers in addition to breast cancer, which are consistent with the results of the present study [41].

5. Conclusions

This review provides an overview of the current state of the art of missing PRO data reporting in breast cancer RCTs. The demonstrated lack of transparency in reporting missing PRO data handling, showing noncompliance with recommendations, hinders an informed appraisal of the potential bias evolving from eventually differing patients with complete and incomplete data in a systematic way.

Mapping the current practice of missing PRO data reporting in this level of detail—from the extent to the assumption on mechanisms leading to the choice of the statistical approach, (ideally) concluded by a sensitivity analysis—allowed to identify gaps in breast cancer RCTs. Especially in terms of being explicit about statistical approaches, and underlying assumptions, there is potential for advancement.

Author contributions

DK, JMG, and MS contributed to the conception of the review, the analysis and interpretation of the results. LD, FE, and FG contributed to the conception of the review. DK, AMMT, CM, and IA contributed to screening of references and data extraction. DK wrote the first draft of the

manuscript and all authors reviewed and revised the manuscript. All authors provided final approval of the manuscript.

Declaration of competing interest

FE had a consultancy or advisory role for AbbVie, Incyte, Janssen, and Syros outside the submitted work. The other authors have no conflicts of interest to disclose.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jclinepi.2023.07.012.

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