Scoping Review of Thresholds for Responder and Time-to-Event Analysis of Patient-Reported Outcomes in Breast Cancer Trials

MSR98

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INTRODUCTION

- Patient-reported outcomes (PROs) are key measures of clinical benefit and tolerability from the patient's perspective[1]
- In oncology trials, PRO analyses commonly include responder and time-to-event (TTE) analyses[2]
- These analyses rely on predefined thresholds to determine clinically meaningful change[2]
- There is substantial variability in how thresholds are selected, applied, and reported[2]
- The SISAQOL-IMI guidelines highlight the need for transparent, standardized, and consistent use of thresholds in PRO analyses[3]

OBJECTIVE

This scoping review, using systematic methods, aimed to explore how thresholds for responder and time-to-event analyses are defined, applied, and reported in randomised controlled trials (RCTs) involving breast cancer patients with PRO-based endpoints.

METHOD

- A systematic PubMed search was conducted to identify eligible RCTs in breast cancer published between 2020 and 2024
- Studies were included if they reported a PRO data analysis using responder or time-to-event (TTE) methods
- Two independent reviewers screened abstracts and full texts; a third reviewer resolved discrepancies
- Extracted information included:
  - Trial design and PRO measures
  - Threshold selection and application
  - Alignment with SISAQOL-IMI recommendations[3]

RESULTS

- 53 eligible RCTs identified in total
- About half (49.1%) were phase III trials
- Only 47.2% explicitly reported using thresholds
- 56.6% defined thresholds ad hoc without justification
- 39.6% cited external sources; 5.7% provided an explicit rationale
- The most frequently cited source for a threshold was Osoba et al., 1998
- Differentiation of tresholds by PRO domain or by improvement vs. deterioration was uncommon

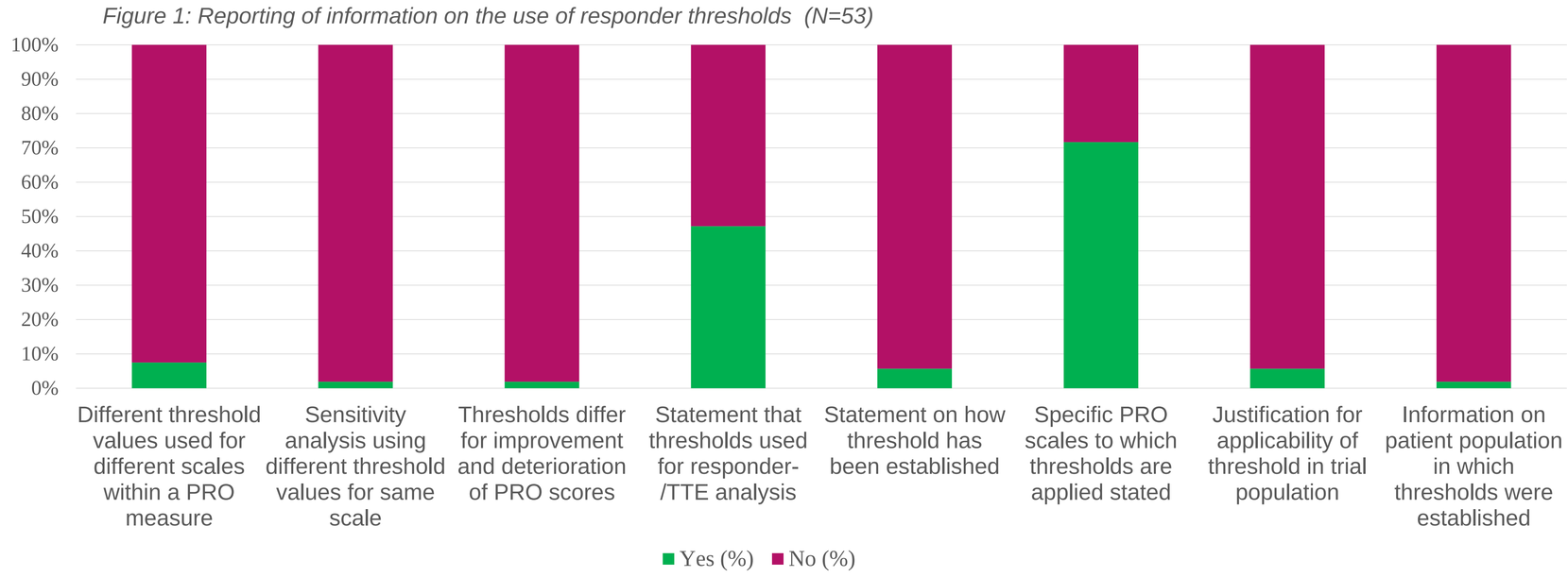
Table 1: Trial characteristics (N=53 trials)

Variables	N (%)
Sample size of PRO analysis population	
50-100	11 (20.8)
101-500	30 (56.6)
501-999	8 (15.1)
1000+	4 (7.5)
Trial phase	
II	8 (15.1)
III	26 (49.1)
Not reported	19 (35.8
Type of treatment	
Targeted theapy	17 (53.1)
Supportive Care- pain management	9 (16.9)
Hormonal therapy	6 (11.3)
Chemotherapy	5 (9.4)
Supportive Care – antiemetics	5 (9.4)
Surgery	4 (7.6)
Radiotherapy	3 (5.7)
Supportive Care – neuropathy	3 (5.7)
Immunotherapy	2 (3.8)
Anaesthesia	2 (3.8)
Supportive Care - other	1 (1.9)

Table 2: Selection of thresholds for responder or time-to-event analyse (N=53 trials)

Justification of selected threshold	N (%)	Most frequently cited references (in N=21 trials)	N (%)
Ad-hoc threshold without justification	30 (56.6)	Osoba et al (1998)[4]	12 (57.1)
Reference to study establishing threshold, or reference to other study using this threshold	21 (39.6)	Cocks et al. (2008)[5]	2 (9.5)
Rationale provided for selected threshold	3 (5.7)	Cocks et al. (2012)[6]	2 (9.5)
		Eton et al. (2004)[7]	2 (9.5)
		Guyatt et al. (2002)[8]	2 (9.5)
		Mathias et al. (2011)[9]	2 (9.5)
		Other	10 (47.6)

Figure 1: Reporting of information on the use of responder thresholds (N=53)



CONCLUSIONS

- This review highlights considerable variability and a lack of transparency in the selection and reporting of thresholds for responder and time-to-event analysis of Patient-Reported Outcome data in breast cancer randomized controlled trials.
- To enhance the clinical relevance and interpretability of PRO data, standardized guidelines for establishing and selecting suitable thresholds, as well as thorough reporting, are needed.

REFERENCES

[1]U.S. Food and Drug Administration. FDA Patient-Focused Drug Development Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision-Making. Silver Spring, MD: U.S. Food and Drug Administration; 2025.
[2]Pe M, Alanya A, Falk RS, Amdal CD, Bjordal K, Chang J, et al. Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints in Cancer Clinical Trials-Innovative Medicines Initiative (SISAQOL-IMI): stakeholder views, objectives, and procedures. Lancet Oncol. 2023;24(6):e270-e83.
[3]Consortium S. SISAQOL: Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints Data [Available from: https://www.sisaqol-imi.org.
[4]Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol. 1998;16(1):139-44.
[5]Cocks K, King MT, Velikova G, Fayers PM, Brown JM. Quality, interpretation and presentation of European Organisation for Research and Treatment of Cancer quality of life questionnaire core 30 data in randomised controlled trials. Eur J Cancer. 2008;44(13):1793-8.
[6]Cocks K, King MT, Velikova G, de Castro G, Jr., Martyn St-James M, Fayers PM, Brown JM. Evidence-based guidelines for interpreting change scores for the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. Eur J Cancer. 2012;48(11):1713-21.
[5]Eton DT, Cella D, Yost KJ, Yount SE, Peterman AH, Neuberg DS, et al. A combination of distribution- and anchor-based approaches determined minimally important differences (MIDs) for four endpoints in a breast cancer scale. J Clin Epidemiol. 2004;57(9):898-910.
[6]Guyatt GH, Osoba D, Wu AW, Wyrwich KW, Norman GR. Methods to explain the clinical significance of health status measures. Mayo Clin Proc. 2002;77(4):371-83.
[7]Mathias SD, Crosby RD, Qian Y, Jiang Q, Dansey R, Chung K. Estimating minimally important differences for the worst pain rating of the Brief Pain Inventory-Short Form. J Support Oncol. 2011;9(2):72-8.

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