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Title	Patient Preference Trials in Oncology:A Scoping Review and Recommendations on Reporting
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Published in	Journal of Clinical Epidemiology
Publication Date	2025-08
Link	https://dspace.library.uu.nl/handle/1874/466300
Citation	Kamp, D, Kessels, R, Mohammad, N H, Schmitz, R S J M, IntHout, J, van Laarhoven, H W M, May, A M & Groenwold, R H H 2025, 'Patient Preference Trials in Oncology : A Scoping Review and Recommendations on Reporting', Journal of Clinical Epidemiology, vol. 184, 111837. https://doi.org/10.1016/j.jclinepi.2025.111837
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Universitair Medisch Centrum Utrecht (UMCU)	Yes

Journal of Clinical Epidemiology 184 (2025) 111837

Journal of Clinical Epidemiology

ORIGINAL RESEARCH

Patient preference trials in oncology: a scoping review and recommendations on reporting

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Accepted 17 May 2025; Published online 23 May 2025

Abstract

Objectives: The feasibility, generalizability, and validity of randomized controlled trials (RCTs) may be compromised when patients have preferences for specific trial arms. The patient preference trial (PPT) design, which assigns at least a subset of the patients based on their preference rather than randomization, has been proposed as an alternative. The aim of this review was to provide an overview of the application of the PPT design in oncological research, with a particular focus on PPTs designed to assess the effectiveness of an intervention and provide recommendations on reporting.

Study Design and Setting: We performed a scoping review including all prospective oncological studies where trial arm allocation for part or all of the patients was based on patients' preferences. Retrieved information included research objectives, motivation for the design choice, baseline covariate adjustments, and sample size calculations.

Results: We identified 44 PPTs, of which 34 (77%) aimed to investigate intervention effectiveness and were reviewed in more detail. Of these 34 effectiveness PPTs, 24 (71%) studies were completed trials, while 10 were protocols. The most frequently indicated rationale behind opting for the PPT design was the perceived infeasibility of an RCT (17 [50%] studies). Baseline covariate adjustment was performed in 18 (53%) studies. Fourteen out of 24 completed trials reported an unequal allocation ratio across trial arms not anticipated during the design.

Conclusion: This review identified several challenges for PPTs in oncology. Future PPTs should take bias due to confounding and unequal group sizes arising from the preferential allocation into account and report on these issues, as these aspects are crucial for the validity and statistical power of the study. © 2025 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Keywords: Trial; Nonrandomized; Randomized controlled trial; Preference; Oncology; Reporting guidelines

1. Introduction

Randomized controlled trials (RCTs) are the gold standard for evaluating the effect of clinical interventions [1]. Randomization is expected to create similar groups, which implies that any differences in outcomes between the groups can be attributed to the intervention. However, in research practice, patients may prefer one of the interventions. Such patient preferences can affect the feasibility of the RCT, as well as the generalizability and validity of the results.

Funding: This work was financially supported by Stichting Vrienden UMC Utrecht & Wilhelmina Kinderziekenhuis [project number 1522166]. The funder was not involved in the study design, collection, analysis and interpretation of data, writing of the report or the decision to submit the article for publication.

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https://doi.org/10.1016/j.jclinepi.2025.111837
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What is new?

Key findings

- The patient preference trial (PPT) design, which assigns at least a subset of the patients based on their preference, has been proposed as an alternative to the randomized controlled trial design in oncology.
- We identified 44 PPTs in oncology, of which 34 has a primary objective to assess the effectiveness of an intervention.

What this adds to what is known?

- This scoping review of the application of the PPT design in oncology provides a comprehensive overview and offers methodological considerations and recommendations for researchers considering a PPT design.

What is the implication and what should change now?

- Future PPTs need to consider methods to deal with bias due to confounding and unequal group sizes arising from the preferential allocation.

Patients with a specific preference may decline trial enrollment to avoid randomization to their nonpreferred arm, slowing accrual and thereby jeopardizing the feasibility of an RCT. In a worst-case scenario, the RCT could be outpaced by the emergence of new interventions, causing the trial to lose relevance before completion [2]. Additionally, declining trial enrollment due to treatment preferences can affect the generalizability of the RCT results when these preferences are related to specific patient characteristics.

Furthermore, in unblinded RCTs, patients may withdraw after randomization to an undesired arm, causing missing (outcome) data. Moreover, randomization to a patient's nonpreferred arm can also influence their adherence to the study protocol and outcome assessments, referred to as resentful demoralization [3]. In both situations, the validity of the trial results could be jeopardized.

The abovementioned consequences of patient preferences also impact RCTs in oncology, where the urgency of treatment decisions can be heightened by the aggressive nature of the disease. Possibly more than in other fields of medicine, oncological patients often do not feel comfortable leaving treatment decisions to chance, as in RCTs [4,5]. Participation in oncological clinical trials is low; 2%-5% of cancer patients participate [6,7]. Furthermore, up to 40% of oncological clinical trials remain uncompleted, in part due to slow patient accrual [8]. These figures stress the need for alternative trial designs in oncology.

The patient preference trial (PPT) design has been proposed as such an alternative [9]. In a PPT, at least a subset of the patients is assigned to a trial arm based on an individual patient's preference rather than by randomization. This could improve patient accrual when strong preferences are expected. However, trial arm allocation by preference may create groups that differ in more respects than only treatment status. The question arises whether a PPT can offer a valid alternative to an RCT in oncology. Therefore, we performed a scoping review, aiming to provide an overview of the application of the PPT design in oncological research. We focus particularly on PPTs that have as primary objective to assess the effectiveness of an intervention, as the lack of randomization may introduce bias due to confounding, complicating causal inference. We will discuss the types of interventions employed, motivations driving the adoption of the PPT design, and methodological considerations for the analysis of oncological PPTs. Finally, we will offer recommendations on reporting of PPTs.

2. Methods

No protocol was registered; however, the Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for Scoping Reviews were followed [10].

2.1. Literature search

We performed a systematic literature search up to October 2, 2024, in Medline (Ovid), Embase.com, and SCOPUS (Supplement 1). Inclusion criteria were (i) prospective studies in which trial arm allocation for part or all of the patients was based on their preferences, (ii) investigating interventions in oncology, (iii) published in peer-reviewed journals with full text available in English. No additional exclusion criteria were applied. Multiple publications of the same trial were regarded as one study, with primary analyses reviewed and supplemented as needed. If only a protocol was found, we searched for published results; if none were found, only the protocol was included. If published trial results were found, both the protocol and the report on the results were included. One author (D.K.) screened by title and abstract, followed by full-text review. A second author (R.K.) screened a random sample to assess for consistency.

2.2. Data extraction and synthesis

The data extraction form (Supplement 2) was developed and piloted with all authors, then refined through group discussion after reviewing the first five articles. The form included the study design, terminology for the study design,

the type of interventions, and whether the primary objective was to assess the effectiveness of the interventions. We performed a more detailed review of PPTs which had as their primary objective to assess the effectiveness of an intervention. For those PPTs, we extracted the motivations for the design, patient-reported reasons for preferences, statistical considerations, whether the trial was completed as planned, and acknowledgment of design limitations. Data were extracted by one author (D.K.), with ambiguities checked by a second author (R.K.), and when necessary, a third author (A.M.). Data were summarized in tables, forming the basis for methodological considerations and recommendations developed through discussions with all authors.

3. Results

3.1. Overview

The literature search identified 3008 unique articles, of which 89 were selected for full-text screening (Fig 1). This resulted in 44 included PPTs, summarized in Supplement 3. Among the included studies were 11 (25%) study protocols without published trial results, three (7%) pilot studies, two (4%) reports of interim results, and 28 (64%) completed trials.

3.2. Study designs

The used study designs for PPTs are illustrated in Figures 2 and 3. We distinguished two main types of PPTs: a full PPT and a partially randomized PPT. In a full PPT, all patients are allocated to the trial arms solely based on their preferences, and this design was used in 26 (59%) included studies. In a partially randomized PPT, a subset of patients is allocated to trial arms based on their preferences, whereas another subset is allocated to trial arms by randomization. The partially randomized PPT design was used in 18 (41%) studies.

3.3. Terminology

Various terms were used to describe PPTs. Most studies (30, 68%) used the word "preference" or "choice." Six full

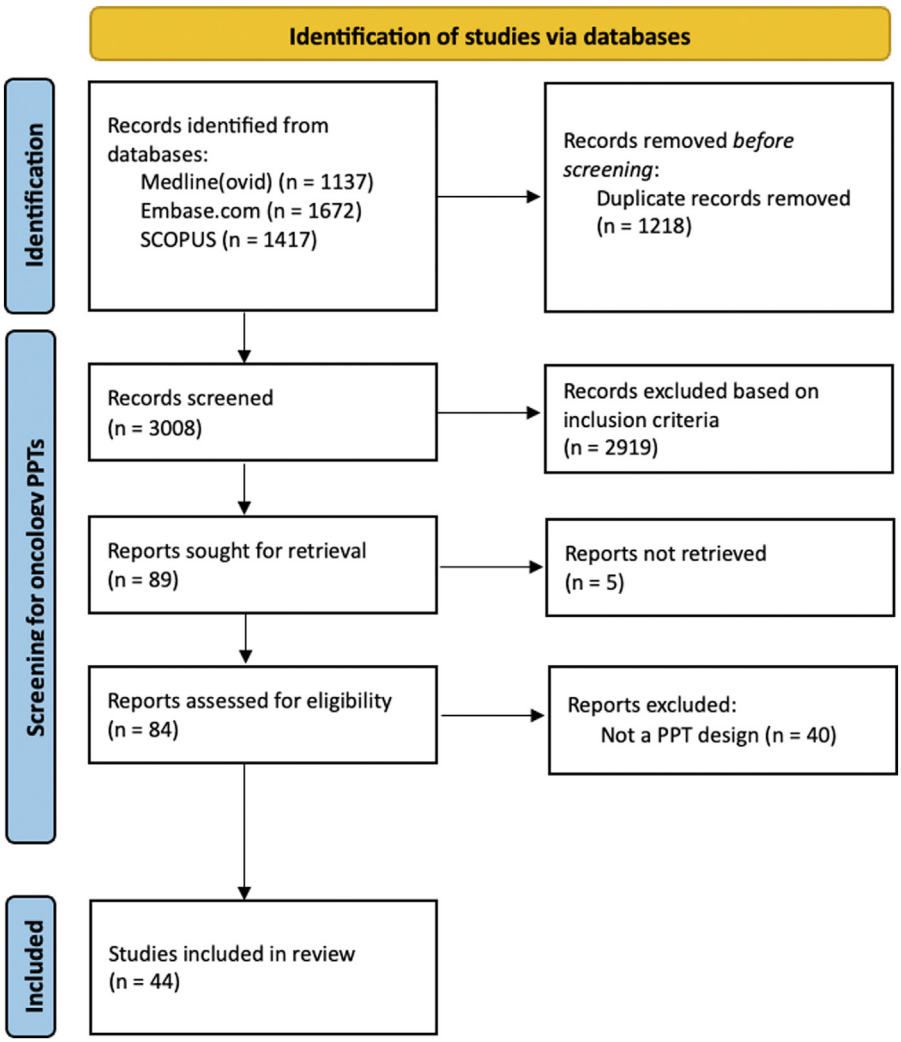


Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2020 flow diagram of the literature search results. PPT, patient preference trial.

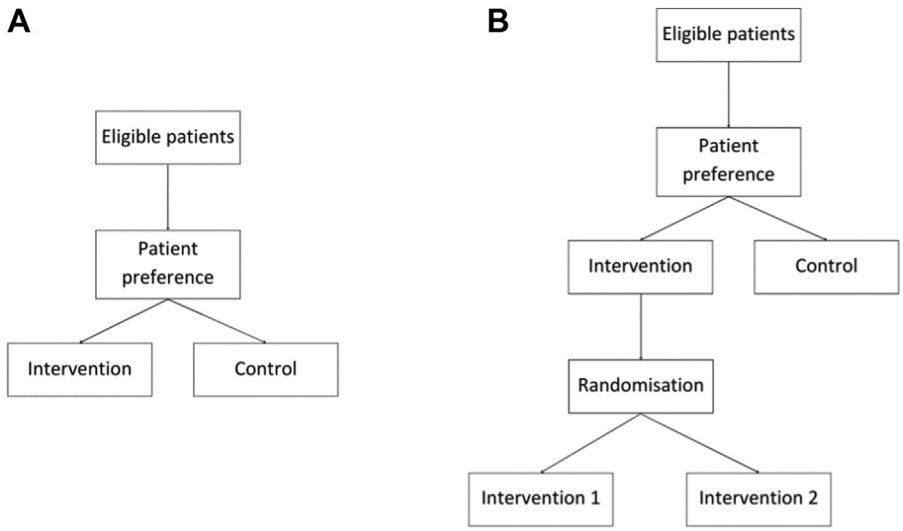


Figure 2. Full PPT study designs. A, All patients are preferentially allocated. B, All patients are preferentially allocated to the control or intervention arm. Those in the intervention arm are subsequently randomized to multiple interventions. PPT, patient preference trial.

PPTs used "observational," and eight used the term "nonrandom." One full PPT was described as partially randomized and one as quasi-randomized, although no randomization was reported. Five studies were described as a "prospective cohort study." In the partially randomized PPTs, the term "comprehensive cohort" was used five times.

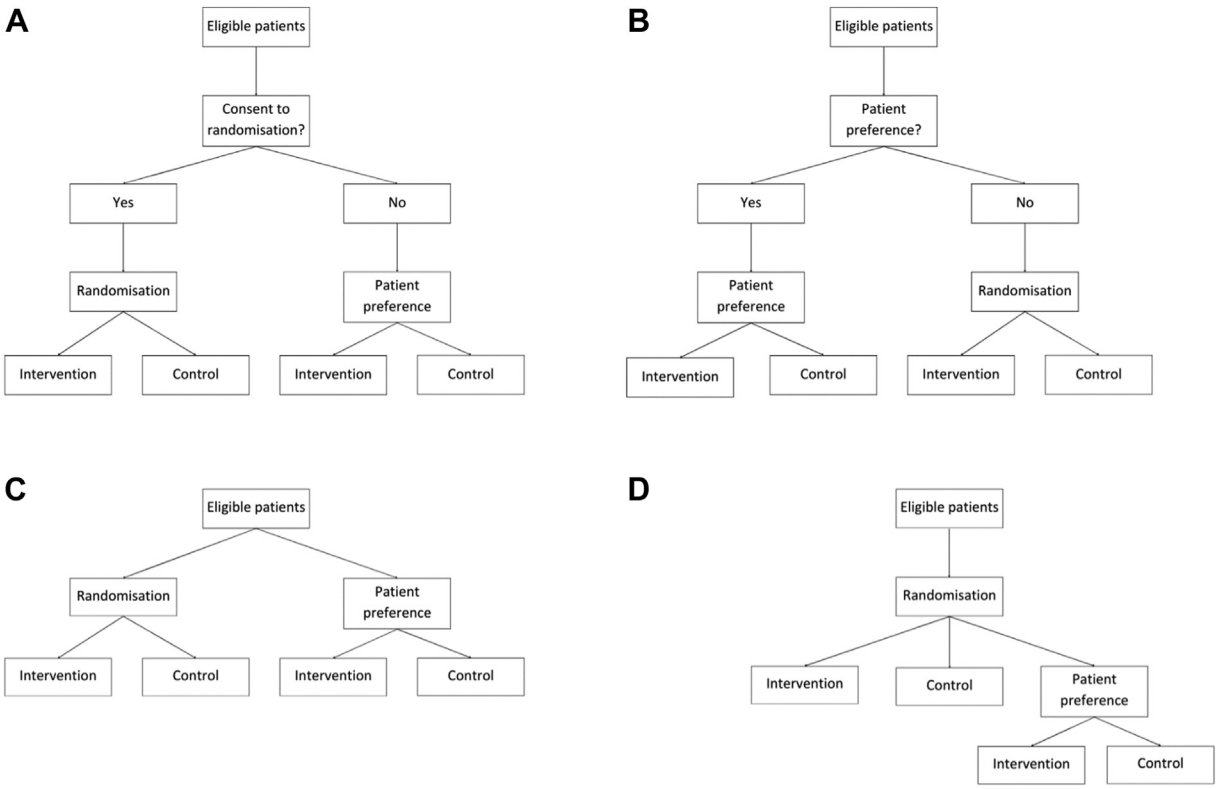


Figure 3. Partially randomized PPT study designs. A, Patients are initially asked for consent to be randomized and only those patients who decline randomization are allocated to their preferred trial arm. B, Patients are initially asked if they prefer one of the trial arms (which they are then allocated to), and only patients without a preference are randomized. C, Patients are asked if they want to be allocated to the trial arms according to their preference or by randomization. D, Patients are randomized between intervention, control or preference, and those randomized to the preference option are allowed to choose between control or intervention. PPT, patient preference trial.

3.4. Interventions and primary objectives

The investigated interventions were therapeutic treatments in 18 (41%) studies, supportive care interventions in 18 (41%) studies, screening or preventive interventions in six (14%) studies, and follow-up strategy interventions in two (4%) studies. In all PPTs, patients were unblinded to their allocated interventions.

In 34 (77%) studies, the primary objective was to assess the effectiveness of the intervention. The other studies had primary objectives concerning feasibility (5, 11%), determination of the percentage of patients that chooses intervention or control (2, 4%), assessment of the patients' attitude toward the intervention (2, 4%), or adherence (1, 2%).

3.5. Characteristics of the studies with effectiveness of the intervention as primary objective

In the remainder of the results section, we focus on the 34 studies that had as primary objective to assess the effectiveness of an intervention (Table 1). Of these 34 studies, 10 (29%) were study protocols and 24 (71%) were reports of completed trial results. Regarding study design, 15 (44%) were partially randomized PPTs and 19 (56%) were full PPTs.

3.5.1. Motivations to use a PPT design

Motivations for choosing a PPT design were reported in 25 (74%) studies. Most commonly (17 (50%) studies), the motivation concerned the unfeasibility of randomization and/or the maximization of recruitment. Additionally, three (9%) studies reported that randomization would pose ethical concerns. In five (15%) studies, the authors motivate that they chose a PPT design to minimize the effects of preferences on outcomes, whereas in three (9%) studies, the authors chose the design in order to be able to explore the effects of patient preferences on outcomes.

3.5.2. Exploring patient preferences

Reasons why patients had a preference for one of the trial arms were reported in only three (of 24, 13%) completed trials. A minority of the studies reported the procedure of informing patients about the trial. In a study comparing surgery to chemoradiotherapy, it was reported that some patients were informed by a surgeon regarding the surgery and by a medical oncologist regarding the chemoradiotherapy, but other patients were only informed by a surgeon. The authors stated that "*the intent of the individual explaining the alternatives may have influenced the patients' choices in this study*" (Kato et al, 2021, p.1883) [11]. In one full PPT assessing a nutritional supplement during radiotherapy, all patients could try the supplement before expressing their preference for the intervention or the control group [12].

Of the 24 reports of completed trials, nine were partially randomized PPTs. In five of those studies, the majority (59%, 84%, 94%, 100%, 75%) of patients was preferentially allocated, and in the other four studies, the majority (52%, 60%, 62%, 69%) of patients was allocated by randomization (Supplement 3).

3.5.3. Analysis

3.5.3.1. Sample size calculation. In 23 (68%) studies, a formal sample size calculation was described. All of these studies approached the calculation as if it was a randomized trial. An unequal allocation ratio across the trial arms was considered in six (of 23; 26%) sample size calculations, three of which stated that this was because it was expected that patient preferences for different options would vary. One study protocol expected the allocation ratio to be between 1:1 and 2:1 and performed sample size calculations for each scenario. In four (17%) partially randomized PPTs, the sample size calculation was performed (with an equal allocation ratio) to sufficiently power the randomized part. Three of these considered data from the nonrandomized part additional data, and one specified minimum numbers of patients per nonrandomized arm. In seven (30%) studies, the allocation ratio across the trial arms was not specified; three of these calculated a minimum number of patients per arm. In the remaining five (22%) studies that performed a sample size calculation, an equal allocation ratio was considered.

3.5.3.2. Baseline comparison and adjustments. All studies (apart from the protocols) reported a comparison of baseline characteristics between patients in the different trial arms.

Baseline covariate adjustment during analysis of the primary endpoint was performed, or planned to be performed in protocols, in 18 (53%) studies. Of these 18 studies, six (33%) studies used inverse probability of treatment weighting to adjust for covariates, and in one (6%) study, the two trial arms were matched on important covariates, but the matching method was not reported. In nine (50%) studies, baseline characteristics were included as covariates in a regression model and one (6%) study used analysis of covariance. In the remaining study, the method of adjustment was unclear.

3.5.3.3. Analyses of partially randomized PPTs. Of the 15 partially randomized PPTs, eight (53%) conducted (or planned to conduct) the primary analysis separately for the randomized and preference groups. Additionally, in six (40%) partially randomized PPTs, the primary analysis was conducted (or planned) with data pooled from both the randomized and preferentially allocated patients. Finally, one partially randomized PPT included only 11 randomized patients, and it was decided to exclude those from the analysis.

3.5.4. Acknowledgment of design limitations

The authors of 15 (of 34; 44%) studies explicitly acknowledged the PPT design to have limitations compared

Table 1. Characteristics of the studies of which the primary objective was to assess the effectiveness of the intervention(s)

Reference (Full/partially randomized PPT)	Publication type	Motivation for the PPT design described?	Patient-reported reasons for preferences described? (*NA for protocols*)	Sample size calculation taking preference design into account? (If yes: how?)	Baseline characteristics comparison done? (*NA for protocols*)	Covariate adjustment performed? (Planned to perform for protocol) if yes: which method?	Completed as planned? (*NA for protocols*)	Acknowledgment of design limitations? (*Described in the terms as used by the authors*)
Alibhai et al 2022 [19] (partially randomized PPT)	Completed trial results	Yes, because preference could optimize intervention acceptance and adherence and because of poor recruitment and low generalizability of RCTs	No	Yes, calculation with unequal allocation ratio	Yes, no (relevant) differences found	No	Yes, the planned number of patients per arm was met	Yes, selection bias is mentioned as a limitation to the design
Ben-arye et al 2022 [20] (full PPT)	Completed trial results	No	No	Yes, a minimum number of patients per arm (35) was specified	Yes, some differences found	No	No, the minimum number per arm was (just) not met for the control arm (32)	Yes, the design is mentioned as a limitation (without further specification)
Brunner et al 2022 + 2023 [21,22] (full PPT)	Completed trial results	Yes, randomization was not possible as the intervention is an approved medical product proven effective in phase 4 studies. Denying it to the control group would pose ethical concerns.	Yes, preference for the control group was because of comorbidities or participation in another study	Yes, sample size calculation with unequal allocation ratio	Yes, no (relevant) differences found	No	Yes, the planned number of patients per arm was met	Yes, the lack of randomization and adjustment for confounders that may have potentially influenced the study's results are mentioned as limitations, and the study is described as an observational prospective study
Donovan et al 2018 [23] (partially randomized PPT)	Completed trial results	Yes, to provide insights about the generalizability of the randomized trial	No	No sample size calculation described	Yes, some differences found	No	Unclear, no sample size calculation and 6% chose treatment options that were not in the randomized part of the trial	Yes, the data from the preferentially allocated patients are seen as additional and only used for secondary analyses
Gall et al 2007 [24] (partially randomized PPT)	Completed trial results	Yes, to minimize bias	No	No sample size calculation described	Yes, some differences found	Yes, using ANCOVA	Yes, as far as assessable without sample size calculation	No
Grandi et al 2020 [25] (full PPT)	Completed trial results	Yes, randomization was not feasible because the intervention is an optional treatment	No	No sample size calculation described	Yes, no (relevant) differences found	No	Yes, as far as assessable without sample size calculation	Yes, the nonrandom allocation is mentioned as a limitation
Kato et al 2021 [11] (full PPT)	Completed trial results	No	No	No, calculation with equal ratio	Yes, some differences found	Yes, using inverse probability of treatment weighting using propensity scores	No, designed as a partially randomized PPT but the randomized part was discontinued due to slow accrual; only 11 participants consented to randomization	Yes, it is mentioned that because of the preferential treatment assignment, the 2 groups' backgrounds were different and confounding factors were used to adjust the comparison

(*Continued*)

Table 1. Continued

Reference (Full/partially randomized PPT)	Publication type	Motivation for the PPT design described?	Patient-reported reasons for preferences described? (*NA for protocols*)	Sample size calculation taking preference design into account? (If yes: how?)	Baseline characteristics comparison done? (*NA for protocols*)	Covariate adjustment performed? (Planned to perform for protocol) if yes: which method?	Completed as planned? (*NA for protocols*)	Acknowledgment of design limitations? (*Described in the terms as used by the authors*)
Krouse et al 2023 [26] (partially randomized PPT)	Completed trial results	Yes, for a randomized study accrual would be difficult, this is not further specified	No	Yes, calculation with unequal ratio, also anticipating on more patients in the preferentially allocated groups than randomized, and added patients for anticipated loss of statistical power due to treatment selection imbalance in the preference part	Yes, some differences were found	Yes, using regression analysis	Yes, the planned number of patients per arm was met	Yes, potential residual confounding is mentioned as a limitation of the design
Kroz et al 2017 [27] (partially randomized PPT)	Completed trial results	No	No	No, calculation with unknown ratio	Yes, some differences found	Yes, using propensity scores weighting	Yes, as far as assessable without specification of minimum number of patients per arm. The total planned sample size was met	Yes, it is mentioned that the design can introduce bias and a negative interaction between allocation regime and treatment
Ma et al 2021 [28] (full PPT)	Completed trial results	No	No	No sample size calculation described	Yes, no (relevant) differences were found	No	Yes, as far as assessable without sample size calculation	No
Panwar et al 2018 [29] (full PPT)	Completed trial results	No, but it is mentioned that the intervention has financial implications	No	No sample size calculation described	Yes, no (relevant) differences were found	No	Yes, as far as assessable without sample size calculation	Yes, the study is described as a prospective cohort study
Prescott et al 2007 [30] (partially randomized PPT)	Completed trial results	Yes, because of slow accrual due to a lower acceptance of randomization than expected because of patient preferences, the design was changed from RCT to partially randomized PPT	No	No, calculation with equal allocation ratio	Yes, some differences found	No	No, designed as an RCT but changed to a partially randomized PPT.	Yes, the data from the preferentially allocated patients are seen as additional and only used for secondary analyses
Rauschecker et al 1998 [31] (partially randomized PPT)	Completed trial results	Yes, because of expected problems of getting consent to randomization (not further specified)	No	No sample size calculation described	Yes, some differences found	Yes, using multivariable Cox regression	No, designed as a partially randomized PPT but only 6.4% consented to randomization	Yes, the low rate of randomized patients is mentioned as a limitation and it is stated that the trial is analyzed as a prospective observational study because of the low percentage of randomized patients

(*Continued*)

Table 1. Continued

Reference (Full/partially randomized PPT)	Publication type	Motivation for the PPT design described?	Patient-reported reasons for preferences described? (*NA for protocols*)	Sample size calculation taking preference design into account? (If yes: how?)	Baseline characteristics comparison done? (*NA for protocols*)	Covariate adjustment performed? (Planned to perform for protocol) if yes: which method?	Completed as planned? (*NA for protocols*)	Acknowledgment of design limitations? (*Described in the terms as used by the authors*)
Rezaeetalab et al 2016 [32] (full PPT)	Completed trial results	Yes, randomization was not possible, due to lack of strong evidence about feasibility of the intervention	No	No, calculation with unknown allocation ratio	Yes, no (relevant) differences were found	Yes, using matching	Yes, as far as assessable without specification of minimum number of patients per arm, the planned sample size is met with equal ratio	Yes, it is mentioned as a limitation that participants were not randomized
Sahin et al 2022 [33] (full PPT)	Completed trial results	No	No	Yes, a minimum number of patients per arm was specified	Yes, no (relevant) differences were found	No	Yes, minimum number of patients per arm was met.	No
Sirilerttrakul et al 2021 [34] (full PPT)	Completed trial results	No	No	Yes, calculation with unequal allocation ratio	Yes, some differences found	No	Yes, planned number of patients per arm was met	Yes, the study is called a prospective nonrandomized observational study
Trachootham et al 2015 [12] (full PPT)	Completed trial results	Yes, to enhance adherence and with that increase internal validity	Yes, preference for the control was because of unsatisfaction to taste and appearance of the intervention	Yes, a minimum number of patients per arm was specified	Yes, no (relevant) differences were found	No	Yes, minimum number of patients per arm was met	No, but it is mentioned that a future randomized study should be performed
Verweij et al 2023 [35] (full PPT)	Completed trial results	Yes, because patients need motivation for the intervention, as studies show high dropout and nonresponse rates in EHealth RCTs. This leads to bias and limits the generalizability of results and random allocation would be unethical.	No	No, no calculation described (''convenience sample'')	Yes, some differences found	Unclear, it is stated that *P* values were corrected for characteristics that differed significantly between groups but not which method was used	Yes, as far as assessable without sample size calculation	Yes, it is mentioned that unknown and uncontrolled confounder could be present in this nonrandomized design
Wang et al 2017 [36] (full PPT)	Completed trial results	Yes briefly: ''due to a consideration from the standpoint of the current clinical practice''	No	No sample size calculation described	Yes, no (relevant) differences were found	No	Yes, as far as assessable without sample size calculation	Yes, it is mentioned that the preferential allocation to treatment arms suggests a possibility of selection bias
Yano et al 2022 [37] (full PPT)	Completed trial results	Yes, the benefit of the intervention might be limited to a small select group of patients	No	No sample size calculation described	Yes, no (relevant) differences were found	No	Yes, as far as assessable without sample size calculation	Yes, the design is described as an observational prospective cohort study

(*Continued*)

Table 1. Continued

Reference (Full/partially randomized PPT)	Publication type	Motivation for the PPT design described?	Patient-reported reasons for preferences described? (*NA for protocols*)	Sample size calculation taking preference design into account? (If yes: how?)	Baseline characteristics comparison done? (*NA for protocols*)	Covariate adjustment performed? (Planned to perform for protocol) if yes: which method?	Completed as planned? (*NA for protocols*)	Acknowledgment of design limitations? (*Described in the terms as used by the authors*)		
Harmsen et al 2015 [38] + Steenbeek et al 2021 [39] (full PPT)	Protocol + completed trial results	Yes, randomization was a barrier for participation based on a previous feasibility study under eligible patients and health care participants	No	Yes, calculation with unequal allocation ratio	Yes, some differences found	Yes, using mixed-model analysis	Yes, planned number of patients per arm was met	Yes, the nonrandomized design is mentioned as a limitation because it might introduce confounding by individual patient preference		
Moergel et al 2009 [40] & Kammerer et al 2023 [41] (partially randomized PPT)	Protocol + completed trial results	Yes, the preference part (''observational study'') is added as a backup if randomization (challenged because of a rare condition and substantially different treatment arms) of patients fails due to a strong preference effect.	No	No, calculation with equal allocation ratio	Yes, no (relevant) differences found	Yes, using multivariable Cox regression	No, the protocol aimed at a sample size of 560 to be met in 4 years, but accrual was stopped after 7 years at a samples size of 209. In addition, only 16% consented to randomization	Yes, the risk of selection bias and systematic differences is mentioned, and the results are interpreted as observational due to the high number of patients allocated preferentially		
Zopf et al 2012 [42] + Zopf et al 2015 [43] (partially randomized PPT)	Protocol + completed trial results	Yes, ethical reasons, the fact that the intervention is accessible for all cancer patients and that recruitment and adherence would be challenging due to long intervention period	No	No, calculation with equal allocation ratio	Yes, no (relevant) differences were found	Yes, using propensity scores	No, all participants had a preference for one of the groups so none were randomized, and the planned sample size of 182 was not met; there were only 85 participants included when the study had to be discontinued after 5 years due to financial reasons	Yes, the design and the possibility that it has introduced bias is mentioned as a limitation		
Russo et al 2021 [44] (full PPT)	Interim trial results	No, but it is mentioned that the design reflects real-world practice	Yes, preference for the intervention: more convenience, less time commitment, no wait time. Preference for the control: ability to ask questions to a genetics provider, ability to do the visit from home	No sample size calculation described	Yes, no (relevant) differences were found	No	Study still ongoing, article concerns analysis of first 127 patients	Yes, it is mentioned as a limitation that it is not a randomized trial		
Augustinus et al 2023 [45]	Protocol	Yes, because of slow accrual due	NA	Yes, a minimum number of patients per arm was	NA	Yes, using inverse probability of	NA	Yes, the possible introduction of selection	184 (100%) 1: 92	NA

(*Continued*)

Table 1. Continued

Reference (Full/partially randomized PPT)	Publication type	Motivation for the PPT design described?	Patient-reported reasons for preferences described? (*NA for protocols*)	Sample size calculation taking preference design into account? (If yes: how?)	Baseline characteristics comparison done? (*NA for protocols*)	Covariate adjustment performed? (Planned to perform for protocol) if yes: which method?	Completed as planned? (*NA for protocols*)	Acknowledgment of design limitations? (*Described in the terms as used by the authors*)	
		to strong patient preferences, the design was changed from RCT to full PPT to minimize selection bias and improve feasibility		specified		treatment weighting using propensity scores		bias and the impossibility of correcting for unknown confounders are mentioned as limitations of the design	(50%) 2: 92 (50%)
Bach et al 2022 [46] (full PPT)	Protocol	Yes, feedback (not further specified) from participants in a phase II randomized trial, patient and public consultation endorsed patient choice	NA	Yes, calculation with unequal allocation ratio	NA	Yes, using Bayesian logistic regression analysis	NA	Yes, the data from the preferentially allocated patients are seen as additional and only used for secondary analyses	
Brock et al 2024 [47] (partially randomized PPT)	Protocol	Yes, the possibility to include all potential study participants including those who refuse randomization and a lower drop-out rate in the control arm	NA	Yes, a minimum number of patients per arm was specified	NA	Yes, using ANCOVA	NA	Yes, the primary analysis will include only the randomized patients. The difficulty in predicting the willingness of participants to be randomized is mentioned as a limitation and it is stated that if the number of randomized study participants is too small, the data must be analyzed as a prospective cohort study	
Carlson et al 2017 [48] (partially randomized PPT)	Protocol	Yes, to maximize recruitment and explore the effects of preferences on outcomes	NA	Yes, calculation with equal ratio for randomized part. The preference part was added to the sample	NA	Yes, using linear mixed models	NA	Yes, it is described that the design may introduce biases caused by preference and it is described as a challenge that the proportion of people who will have a preference is unknown	
Hansson et al 2024 [49] (partially randomized PPT)	Protocol	Yes, because recruitment and achieving unbiased and generalizable results would be a challenge in an RCT (not further specified)	NA	Yes, calculation with equal ratio for randomized part. In the preference part, patients will be included until the calculated minimum number of patients per arm is reached in both arms	NA	Yes, using regression analyses	NA	No	

(*Continued*)

Table 1. Continued

Reference (Full/partially randomized PPT)	Publication type	Motivation for the PPT design described?	Patient-reported reasons for preferences described? (*NA for protocols*)	Sample size calculation taking preference design into account? (If yes: how?)	Baseline characteristics comparison done? (*NA for protocols*)	Covariate adjustment performed? (Planned to perform for protocol) if yes: which method?	Completed as planned? (*NA for protocols*)	Acknowledgment of design limitations? (*Described in the terms as used by the authors*)
Ikoma et al 2023 [50] (full PPT)	Protocol	Yes, randomization was considered infeasible because patients often have strong preferences regarding the intervention and the control	NA	No, calculation with equal ratio	NA	Yes, using inverse probability of treatment weighting using propensity scores	NA	Yes, the study is described as a prospective cohort study
Klafke et al 2015 [51] (partially randomized PPT)	Protocol[a]	Yes, to recruit more patients, thus increasing external validity and generalizability of the results, to minimize measurement bias due to patient being disappointed by their treatment allocation, and to compare patients with and without a preference and explore characteristics associated with preference	NA	Yes, calculation with equal ratio for randomized part. The preference part was added to the sample and was assumed to be 60% of the total	NA	No	NA	Yes, the data from the preferentially allocated patients are described as observational and will only be analyzed descriptively and used to assess external validity of the randomized part
Philipps et al 2023 [52] (partially randomized PPT)	Protocol	Yes, to prevent exclusion of patients with a strong preference for one of the arms	NA	Yes, calculation with equal ratio for randomized part. The preference part will be added to the sample and is assumed to be 33% of the total.	NA	Yes, using regression analyses	NA	Yes, the randomized and preferentially allocated patients will be analyzed separately. It is stated that it is possible that most participants opt to select their preferred arm which would lead to failure to reach the required randomized sample size and this would necessitate a change in study design and analysis plan.

(*Continued*)

Table 1. Continued

Reference (Full/partially randomized PPT)	Publication type	Motivation for the PPT design described?	Patient-reported reasons for preferences described? (*NA for protocols*)	Sample size calculation taking preference design into account? (If yes: how?)	Baseline characteristics comparison done? (*NA for protocols*)	Covariate adjustment performed? (Planned to perform for protocol) if yes: which method?	Completed as planned? (*NA for protocols*)	Acknowledgment of design limitations? (*Described in the terms as used by the authors*)
Steenbeek 2023 [53] (full PPT)	Protocol	Yes, previous (feasibility) studies have demonstrated that potential participants are not willing to be randomized	NA	Yes, the allocation ratio is expected to be between 1:1 and 2:1 and sample size calculations are made for each scenario	NA	Yes, using stabilized inverse probability of treatment weighting	NA	No
Zimmer et al 2013 [54] (partially randomized PPT)	Protocol	No	NA	No sample size calculation described	NA	No	NA	No

PPT, patient preference trial; RCT, randomized controlled trial; ANCOVA, analysis of covariance.

[a] Published trial results were found ([55]) but this article only reports on the randomized trial arms, so this is not used for this review.

Table 2. Methodological considerations and recommendations on reporting of a patient preference trial of which the primary objective is to assess the effectiveness of the intervention(s)

Design aspect	Methodological considerations	Recommendations on reporting
General	If a PPT is designed and conducted as any other (randomized) trial, thereby clearly specifying and aligning the moment when the eligibility criteria are met, treatment assignment, and start of follow-up for each patient, sources of bias like immortal time bias and selection bias can be prevented [13].	- Perform and report the PPT according to CONSORT 2010 guidelines and explain when and why deviations were necessary [56]. - Clearly describe the trial objective, research question and treatment effect (including the definition and handling of estimands) to align planning, design, conduct, analysis, and interpretation of the trial (CONSORT 2010 items 2a + b, 6a + b).
Study design	- Different PPT designs have been proposed, either with preferential allocation for all participants (full PPT) or combining preferential and randomized allocation (partially randomized PPT). - A partially randomized PPT enables the possibility to compare randomized with preferentially allocated patients to assess validity and generalizability of the results.	Clearly explain the design, preferably with a flowchart (CONSORT 2010 items 3a + b, 13a).
Motivation for the study design	A PPT design can be considered if it is expected that patients could have a preference for a particular trial arm, leading to an increased risk of either refusal of randomization or to effects on outcomes in an RCT.	Clearly motivate the design choice; e.g., in case of infeasibility of randomization: clearly outline why an RCT is considered infeasible and if this is substantiated by any prior studies.
Exploring patient preferences	- The reasons why patients have preferences for a specific trial arm can help in determining the impact of the preferential allocation on the results. - A patient's preference may be influenced by the procedure on how patients are informed about the interventions. Lack of a (standardized) procedure for informing patients might lead to bias.	- Report the patient-reported reasons for their preferences. - Report the (standardized) procedure(s) for informing a potential participant about the trial, including who provides which information and when, up until they express their preference; and if there was a standardization training performed.
Sample size calculation	Preferential allocation often creates an unequal distribution of patients among trial arms and can result in an insufficient number of patients in a trial arm.	Minimally report the (standard) sample size calculation, while accounting for an expected unequal distribution among trial arms if appropriate. This also holds for partially randomized PPTs in case the sets of preferentially allocated patients and randomized patients are both required to achieve sufficient power. A strategy could be determining the required sample size per arm based on a realistic allocation ratio and recruit until all treatment arms have reached at least that number (CONSORT 2010 item 7a).
Statistical analyses	Lack of randomization may lead to incomparable groups, thereby complicating causal inference. Casual inference in a (full) PPT depends on successful adjusting for confounding, but also relies on unverifiable assumptions regarding unmeasured confounding. The understanding and proper collection and modeling of key covariates is imperative.	- Identify, measure, and report potential key prognostic factors and confounders at the start of the study, as described in the STROBE guidelines, items 7, 9, 12, 14 [57]. - In case of a partially randomized PPT, (also) report the findings separately for the randomized and the preferential parts. - Report a comparison of the key prognostic factors and other baseline characteristics/covariates and describe if this shows any signs of relevant differences between trial arms (STROBE item 14). - Clearly report how adjustments for confounding were done. Methods that could be considered include inverse probability of treatment weighting, matching on important covariates, or a multivariable regression model. If no adjustment for confounding was performed, explain why (STROBE item 16).

(*Continued*)

Table 2. Continued

Design aspect	Methodological considerations	Recommendations on reporting
Design limitations	A PPT design will not yield the same level of (causal) evidence as an RCT.	Acknowledge and describe the limitations of the PPT design, how the design may have influenced the results and what this means for the interpretation and generalizability of the results (CONSORT 2010 item 20, STROBE item 19).

PPT, patient preference trial; RCT, randomized controlled trial; CONSORT, consolidated standards for reporting trials; STROBE, strengthening the reporting of observational studies in epidemiology.

to an RCT, stating that the PPT design could have introduced bias when comparing the interventions. Six (18%) partially randomized PPTs primarily focused on the randomized comparison and regarded the data of the preferentially allocated patients as complementary to the data of the randomized patients, thereby identifying no limitations of their trial concerning potential bias in the comparison. Furthermore, eight (24%) studies were described as an observational and/or prospective cohort study rather than a trial, which can be considered an acknowledgment of limitations, as the authors did not interpret the results as having the same level of evidence as those derived from an RCT.

3.5.5. *Completion of the study as planned*

For the 24 (of 34; 71%) reports of completed trial results, we assessed whether the study was completed as planned. We considered completed as planned as no change in the design and meeting the minimum planned sample size (per arm). If the allocation ratio was not specified, we assumed that an equal allocation ratio was planned. Overall, eight (two partially randomized PPTs and six full PPTs of 24 completed trials; 33%) studies were completed as planned. Additionally, eight (33%) studies were completed as planned as far as assessable, despite a lack of information on the minimum planned sample size per arm. Three (13%) studies reported an adjustment to the design during the trial; one full PPT started as a partially randomized PPT but was changed to a full PPT due to a low randomization rate, and two partially randomized PPTs started as an RCT. In addition, in one partially randomized PPT none of the patients consented to randomization, resulting in a full PPT without explicitly changing the design. In two (8%) studies, the planned sample size was not reached because of early trial termination due to financial reasons. While in only five (21%) studies an unequal allocation ratio was anticipated in the sample size calculation, in 19 (79%) studies the actual allocation ratio turned out to be unequal ($>10\%$ difference). In these cases, the majority of patients received the experimental intervention in 13 of the 19 studies (68%) (Supplement 3). None of the studies reported whether accrual was completed on time or if extensions were needed.

3.6. *Recommendations on reporting*

Based on the limitations and challenges of PPTs identified in our review, we provided methodological considerations and accompanying recommendations on reporting for researchers who consider using a PPT design, which are listed in Table 2.

4. Discussion

We identified 44 oncological PPTs, with over one-third (16, 36%) published in the past 2 years, highlighting growing interest. The main reasons for choosing a PPT design were infeasibility of randomization and maximizing recruitment, reflecting challenges in accrual when patients have strong preferences.

This review focused on PPTs that had as primary objective to assess the effectiveness of an intervention. Most PPTs acknowledged that the design does not yield the same level of evidence as an RCT (29/34, 85%), as the lack of randomization introduces the risk of bias due to confounding. While this is true, a well-designed PPT holds great potential, provided a PPT is designed, conducted, and analyzed as any other trial, where meeting the eligibility criteria, the assigned treatment group, and the start of follow-up for each patient are clearly specified and aligned. This can prevent other sources of bias, such as selection bias and immortal time bias, leaving confounding as the only difference in bias between an RCT and a PPT [13]. However, only 18/34 (53%) studies applied any adjustment for confounding. For future PPTs, we believe it is essential to identify and assess confounders and to report whether and how adjustments are made.

We identified six different PPT designs, with patient allocation either fully based on preference or partially randomized. Partially randomized PPTs allow for a (randomized) comparison of the interventions and a (nonrandomized) comparison between patients who were randomized vs. those who received preferential treatment, which provides insights into the (face)validity and generalizability of the results, as was done in three studies. In fact, a meta-analysis on partially randomized PPTs across various clinical fields found no significant differences in primary outcomes between preferentially allocated and randomized patients, which suggests that selective participation might be limited and/or treatment effects could be similar supporting the face validity of the preference design [14]. The ability to compare both cohorts makes a partially randomized PPT preferable to

a full PPT design. However, their advantage diminishes if few patients consent to randomization. In our review, one partially randomized PPT was changed into a full PPT due to a low randomization rate, while another resulted in a full PPT after no patients consented to randomization. Thus, when planning a partially randomized PPT, the expected ratio of randomized to preferentially allocated patients must be carefully considered.

Furthermore, another challenge when designing a PPT is to set a realistic allocation ratio upfront. Although most trials (18 out of 24 effectiveness trials with completed trial results, 75%) expected an equal allocation ratio, we noted that preferential allocation rarely creates equal trial arms (only 5/24, 21%, Supplement 3). Therefore, unequal allocation ratios in PPTs are to be expected and should be accounted for in the sample size calculation. A strategy could be determining the required sample size per arm based on a realistic allocation ratio and recruit until all arms have reached at least that number.

This study identified several challenges of a PPT, including varying patient preferences, treatment allocation, and confounding. These factors can impact the treatment effect, highlighting the importance to define the targeted treatment effect upfront in an estimand [15]. We recommend researchers clearly define estimands in order to align trial design, outcome collection, and analysis [16,17].

To our knowledge, this is the first literature review of the application of the PPT design in oncology, providing a comprehensive overview and offering recommendations. These recommendations can be readily applied by researchers considering the use of a PPT design both within and outside the field of oncology, helping to strengthen the quality, methodology, and robustness of future PPTs.

Our study has several limitations, including the lack of a preregistered protocol. The study methods were discussed in preparatory meetings with all authors and continuously refined, an approach that was chosen given the limited evidence on the topic. Furthermore, screening was primarily performed by one author. However, this approach was deemed appropriate for the purpose of a scoping review, and random sample checking revealed no issues [18]. Lastly, the recommendations on reporting were formulated based on group discussions and should be considered evidence-informed suggestions rather than systematically derived guidelines.

In conclusion, the PPT design has mostly been applied when an RCT was considered infeasible, offering an alternative design that takes patient preferences into account and acknowledges the complexity and often life-altering nature of oncological care. However, future PPTs need to consider methods to deal with bias due to confounding and unequal group sizes arising from the preferential allocation. These aspects are critical for the validity and the statistical power of the results of a PPT and should therefore be explicitly reported on.

CRediT authorship contribution statement

Denice Kamp: Writing − review & editing, Writing − original draft, Methodology, Investigation, Formal analysis. **Rob. Kessels:** Writing − review & editing, Writing − original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Nadia Haj Mohammad:** Writing − review & editing, Supervision, Methodology, Investigation, Funding acquisition. **Renee S.J.M. Schmitz:** Writing − review & editing, Methodology. **Joanna IntHout:** Writing − review & editing, Methodology. **Hanneke W.M. van Laarhoven:** Writing − review & editing, Supervision, Methodology. **Anne M. May:** Writing − review & editing, Supervision, Methodology, Conceptualization. **Rolf H.H. Groenwold:** Writing − review & editing, Methodology, Conceptualization.

Declaration of competing interest

N.H.M. reports receiving research funding, medication supply, or both from Servier, having speaker roles for Servier, and being a consultant or having an advisory role for BMS, Merck, Lilly, and AstraZeneca. H.W.M.*v*.L. reports receiving research funding, medication supply, or both from Auristone, Incyte, Merck, ORCA Therapeutics, and Servier, having speaker roles for Astellas Pharma, BeiGene, Benecke, BMS, Daiichi Sankyo, JAAP, Medtalks, Novartis, Springer, and Travel Congress Management BV, and being a consultant or having an advisory role for Amphera, Anocca, Astellas Pharma, AstraZeneca, BeiGene, Boehringer Ingelheim, Daiichi Sankyo, Dragonfly, MSD, Myeloid Therapeutics, and Servier. There are no competing interests for any other authors.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jclinepi.2025.111837.

Data availability

Data will be made available on request.

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