

A practical toolkit with recommendations for analysing and visualising patient-reported outcomes in early phase dose-finding oncology trials: OPTIMISE-AR

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Summary

Patient-reported outcomes (PROs) are increasingly recognised for their role in assessing tolerability in dose-finding oncology trials (DFOTs). However, PRO analysis and reporting within DFOTs is often unclear and inconsistent. OPTIMISE-AR (incorporating Patient-reported outcomes in dose-finding trials–Analysis Recommendations) establishes a practical toolkit supporting the statistical analysis, visualisation, and reporting of PRO data within DFOT publications.

International, multidisciplinary, cross-sector statistical analysis and data visualisation working groups identified analytical and visualisation approaches for PROs addressing key DFOT PRO research objectives. Informed by existing literature, case studies and recommendations are provided in this policy review for analysing binary, ordinal, and continuous PRO data to assess tolerability across dose levels and timepoints, and to integrate PROs into interim and final dose-decision processes. The OPTIMISE-AR toolkit is structured around four methodological domains aligned with key DFOT PRO research objectives, providing statistical analysis and data visualisation recommendations for (1) PRO endpoints across time points, (2) PRO endpoints between time points, (3) Time-to-event PRO endpoints, and (4) PRO endpoints for formal dose-decision making in model-based dose-finding designs.

As PROs play an ever-increasing role in tolerability assessment, this work promotes analysis and data visualisation of PRO data, facilitating robust, patient-centred tolerability conclusions and supporting the broader development of tolerable and effective treatments.

Introduction

DFOTs play an essential role in drug development, and are primarily focussed upon the assessment of safety, tolerability, and preliminary efficacy for new treatments with the aim of determining recommended dose(s) for further investigation. There is growing recognition among clinicians and policy makers of the value of patient-reported outcomes (PROs) within the assessment of tolerability in early phase dose-finding oncology trials (DFOTs).¹⁻³ Whilst a treatment's safety and tolerability has typically been assessed within DFOTs using clinician-reported measures such as Common Terminology Criteria for Adverse Events (CTCAE) grading,⁴ the definition of tolerability has been further reconsidered to consider the direct measurement from the patient.⁵

The widening scientific interest in the use of PROs for tolerability assessment in DFOTs is driven by initiatives such as US FDA Project Optimus, Methodology for the Development of Innovative Cancer Therapies (MDICT) Taskforce, and Friends of Cancer Research.^{3,6-8} Whilst such interest is reflected in the increasing use of PROs within DFOTs for tolerability assessment,⁹ their adoption (and guidance to support their integration) remains scarce.

In recognition of the existing absence of well-defined PRO research objectives for DFOTs,¹⁰ the OPTIMISE-ROR (incorporating Patient-reported outcomes in dose-finding trials-Research Objective Recommendations) project^{11,12} has recently established consensus-driven PRO research objective recommendations for tolerability assessment within the DFOT setting. However, there remains little guidance to support trialists wishing to analyse and report such research objectives alongside PRO data within their trial reports.

Recommendations have been provided for the analysis and reporting of PRO data within randomised controlled trial (RCT) and single-arm trial settings, including by the SISAQOL consortium (Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data)^{13,14} and other groups including FDA,^{15,16} EMA,¹⁷ HTA Coordination Group,¹⁸ and the PROTEUS consortium (Patient-Reported Outcomes Tools: Engaging Users and Stakeholders).¹⁹ However, research indicates that when PROs are analysed and reported in DFOTs, statistical analysis approaches and data visualisation methods are commonly inconsistent and poorly reported - reducing the opportunities to provide reliable conclusions for treatment tolerability and compare study findings across trials.¹⁰

In response to this challenge, the OPTIMISE-AR project (OPTIMISE–Analysis Recommendations) was established to develop a toolkit of analysis and visualisation approaches for PRO data within DFOT reports. The project aims to support authors reporting PRO data in their DFOT publications, increasing transparency and facilitating interpretation by diverse readers, including (but not limited to) clinicians, statisticians, data ethics

committees and regulators. OPTIMISE-AR complements OPTIMISE-ROR guidance,^{11,12} providing a PRO analysis toolkit aligned with PRO research objectives crucial to DFOTs. Whilst OPTIMISE-ROR identifies critical PRO research objectives for DFOTs, it does not provide guidance to support trialists in selecting rigorous statistical analysis and data visualisation approaches to report these objectives. OPTIMISE-AR extends beyond the scope of OPTIMISE-ROR to ensure that PRO research objectives implemented in line with OPTIMISE-ROR are analysed and reported rigorously and transparently within trial reports.

Methods

The OPTIMISE-ROR and OPTIMISE-AR projects were developed and registered together²⁰ with the Enhancing Quality and Transparency of Health Research (EQUATOR) Network's methodological framework for guideline development.²¹ An international, cross-sector, multi-disciplinary team was assembled to contribute to the shaping of the OPTIMISE-AR toolkit. This team of 18 members included 6 statisticians and 5 PRO specialists from academia and industry, 4 clinicians, 2 regulators, and 1 patient partner. Based on each member's expertise, members were allocated to two working groups:

The Statistical Analysis group (primarily statisticians and PRO methodologists: ACD, AR, CY, EA, JLL, KRR, MJG, MP, and NAW) explored statistical methods for two key statistical analyses including analysis of PRO data over time and across doses, and estimation and inference using PRO data to find recommended dose(s).

The Data Visualisation group (including all stakeholder categories: ACD, AM, AR, ARH, CS, CY, EA, JL-K, JR, MJC, MJG, MP, OK, RW, SNS) discussed and refined figures and tables to be recommended for use in DFOTs to display PRO data, including descriptive summaries (e.g., boxplots and bar plots) or model-based/estimation outputs (e.g., Kaplan-Meier curves and fitted trends from mixed effects models).

Literature review of analysis and visualisation methods for PROs

A literature review was undertaken to identify relevant statistical analysis and data-visualisation techniques within published literature for the analysis of PRO data. This review informed the initial evidence base from which potential approaches for the toolkit were drawn.

Search strategy and selection criteria

Papers eligible for the literature review were English language guidelines, recommendations, or reviews providing guidance for data analysis or visualisation of tolerability data archived on PubMed between 28/02/2015 and 06/03/2025.

Literature was extracted by EA (Emily Alger) in XML format on 06/03/2025.

Eligible papers were extracted using the following search strategy: ("statistic*[Title] OR "reporting"[Title] OR "visualising"[Title] OR "analyze"[Title] OR "review"[Title] OR "recommendation*[Title] OR "guidance"[Title] OR "consensus"[Title] OR "guideline"[Title]) AND ("trial*[Title] OR "studies"[Title]) AND ("quality of life"[Title] OR "patient reported outcome*[Title] OR "patient-reported outcome*[Title] OR "CTCAE"[Title] OR "adverse events"[Title] OR "harms"[Title]) AND ("2015/02/28 00:00":"3000/01/01 05:00"[Date - Publication] AND "English"[Language])

EA and Yu Qiao both assessed each entry for eligibility. All queries that arose during data extraction were discussed and differences of opinions between reviewers were resolved through discussion. 773 papers were assessed for eligibility, and 9 papers were eligible. Figure 1 of the supplementary materials presents the associated PRISMA flow diagram, citing eligible papers.

Extraction of relevant PRO visualisation and statistical modelling approaches

Relevant statistical analysis and data visualisation approaches were extracted from two sources: eligible recommendation papers identified through our literature review (as described above), and published DFOT reports analysing PROs, as collated in Alger and colleagues' methodological review.¹⁰ Additional approaches

were then proposed by the two working groups (including grey literature²²). Together, these methods formed the pool of candidate approaches for potential inclusion in the toolkit.

Development of analysis toolkit

Extracted statistical analysis and data visualisation approaches were evaluated with respect to the critical PRO research objectives identified for DFOTs as part of OPTIMISE-ROR.^{11,12} With particular relevance to this toolkit, OPTIMISE-ROR identifies that (1) PRO concepts for the assessment of tolerability should include Overall Side Effect Impact, Symptomatic Adverse Events, and Overall health-related Quality of Life; (2) PROs should inform final dose-recommendations for dose-escalation and optimisation trials, regardless of trial design and be identified as exploratory/descriptive or inferential; and (3) PRO endpoints should be analysed over a defined time period and at each specific dose level.

These recommendations provided a reference for working group members to critically assess extracted analytical approaches for inclusion in the toolkit.

For (A), PRO measures used to assess PRO concepts for tolerability may include binary, ordinal, or continuous, data types and thus, analyses and visualisations for these data types are presented in this toolkit. Key PRO concepts of overall side effect impact, symptomatic adverse events, and overall health-related quality of life, can be assessed using validated instruments, such as Functional Assessment of Cancer Therapy (FACT)-GP5 item²³, PRO-CTCAE items,²⁴ and EORTC QLQ-C30 (summary scores)²⁵ respectively. More generally speaking, the PRO data type for each PRO concept within a trial depends on how the corresponding measure is scored. Furthermore, ordinal or continuous PRO data may be dichotomised and subsequently analysed as binary data using appropriate clinically relevant thresholds when applicable.

For (B), PRO analysis is important across trial design settings. Differences in typical sample sizes and number of investigated doses can shape whether PRO analyses are primarily descriptive or exploratory, or inferential in selecting the recommended dose or dose range. The clinical interpretability of inferences to guide decision making was also considered.

For (C), PRO data analysis and visualisation approaches should consider changes over time and differences at each dose level. Approaches were evaluated considering challenges in analysing DFOTs, which typically have small sample sizes, although this can vary. In two recent reviews, dose-escalation trials were typically planned for a median enrolment of 30 patients (IQR: 18-45)²⁶, whereas dose-expansion trials enrolled a median of 27 (IQR: 13-51), with the largest including 292 participants.²⁷

Working group members assessed the relevance of each approach by considering its suitability and required revisions. They assessed the ability of the extracted approach for DFOTs to accommodate critical PRO tolerability concepts, DFOT sample sizes, and PRO analysis across time and dose levels as per (A), (B), and (C). Potential modifications or improvements to each approach to enhance clarity and use were subsequently considered before identifying additional approaches that could be valuable, or any extracted approaches which should be excluded.

The Statistical analysis working group discussed statistical analysis approaches for PRO data across four meetings between February 18th and July 4th 2025. The group critically assessed the strengths and limitations of each analysis approach for DFOTs, combining their considerations with evaluations from existing literature. Methods were assessed for their relevance within an exploratory or descriptive setting and for inferential statistical analysis, where PROs may be used in conjunction with other endpoints to determine a recommended phase II dose.²⁸

The Data Visualisation working group held four meetings between February 18th and April 4th 2025, during which visualisation methods deemed unsuitable for PRO data in DFOTs were first excluded following group discussion and agreement. Visualisations deemed appropriate were standardised and modified in line with existing recommendations for PRO visualisations^{22,29} and SISAQOL-IMI¹⁴ guidance. These standardisations include highlighting directionality of PRO scores, descriptive labels (e.g., none/mild/moderate/severe) indicating score meaning, traffic light colors to indicate desirable or undesirable score ranges, and threshold lines across score bars to indicate whether scores are better or worse than threshold scores.

Visualisations were iteratively refined following each meeting and circulated to working group members for additional input. Pre-final recommendations in the OPTIMISE-AR toolkit were rigorously reviewed and refined over two rounds by all team members before full approval. Presented figures maximise interpretability for diverse stakeholders by presenting figures in familiar clinical formats (e.g., box plots, line trajectories) while maintaining methodological rigor in representing PRO change.

Role of the funding source

The funders had no role in study design, data collection, analysis, data interpretation, or writing of the report.

Results

Case study of the analysis of continuous PRO data at the final analysis

As a practical reference for the reader, we begin with a case study illustrating how a PRO research objective and its corresponding analysis can inform clinical decision-making before presenting the OPTIMISE-AR toolkit. Whilst applied to one example, this case study encourages reflection on the broader methods subsequently presented in the OPTIMISE-AR toolkit and the role they may play in the interpretation of PROs for a given trial.

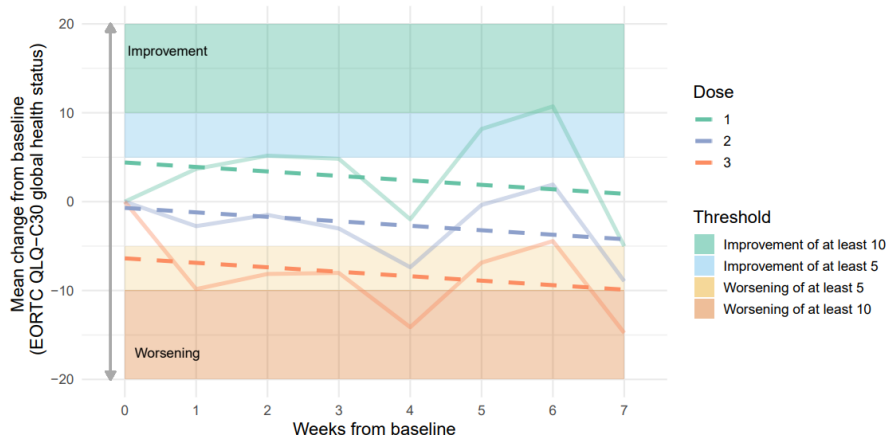
This case study illustrates the use of PROs to assess treatment tolerability based on overall health-related quality of life in a simulated DFOT with three dose levels. EORTC QLQ-C30 Global health status scores are collected over eight weeks (including baseline) for 30 patients per dose, with non-treatment related death and missing PRO data simulated.

Death-related dose discontinuation is one example of an intercurrent event – an event that occurs after treatment initiation and affects the interpretation or the existence of the outcome data.³⁰ In DFOTs, strategies to handle intercurrent events (e.g. while-on-treatment strategy) are increasingly relevant for endpoints such as PROs which are collected over extended time periods, with the analysis and reporting of PRO data under different strategies potentially influencing trial conclusions and decision-making.³¹

The objective in this study was to assess tolerability by comparing mean change from baseline in EORTC QLQ-C30 Global health status scores across three doses, using a while-on-treatment strategy up to week seven in the safety analysis set.

A linear mixed effects model is utilised to analyse mean change from baseline in the continuous PRO domain, adjusting for dose, time and baseline PRO score, while accounting for repeated patient measurements. The data being simulated and the associated mathematical model are presented in the appendix.

Figure 1 presents the descriptive observed mean changes from baseline at each timepoint, alongside PRO score trends modelled using a mixed effects model across the three dose levels, with a risk table indicating patients with intercurrent events or missing data. Table 1 of the appendix presents the corresponding statistical analysis of the linear mixed-effect model.



Sample size (n = 90)	Dose 1	28	29	25	27	26	24	23	22
	Dose 2	29	29	29	24	26	27	25	25
	Dose 3	29	28	28	27	26	26	24	26
Cumulative intercurrent events	Dose 1	0	1	2	2	2	4	4	6
	Dose 2	0	0	1	2	2	2	2	2
	Dose 3	0	1	2	2	2	2	3	4
Missing data at timepoint	Dose 1	2	0	3	1	1	2	3	2
	Dose 2	1	1	0	4	2	1	3	2
	Dose 3	1	1	0	1	2	2	3	0

Figure 1 Mean change in EORTC QLQ-C30 Global health status from baseline until week 7 (score range: 0-100; higher scores indicate improved global health). Solid lines indicate the observed mean change at each timepoint. Dotted lines display the modelled trend from the linear mixed effects model, adjusting for dose, time, baseline PRO score and accounting for repeated patient measurements. Dose discontinuation is treated as an intercurrent event, with patients excluded from the analysis at subsequent timepoints after discontinuation. Missing data excludes patients with unreported scores due to incomplete patient reporting or data entry errors.

Covariate	Estimate	Standard Error	95% Confidence Interval
Intercept	-0.19	1.87	[-3.85, 3.47]
Timepoint	-0.50	0.12	[-0.73, -0.27]
Dose 2	-5.11	1.12	[-7.29, -2.92]
Dose 3	-10.8	1.11	[-13.0, -8.60]
Baseline score	0.07	0.02	[0.02, 0.11]

Table 1 Linear mixed-model analysis of mean change in EORTC QLQ-C30 Global health status from baseline until week 7 adjusted for dose, time, baseline PRO score and repeated patient measurements. Score range: 0-100, higher scores indicate improved global health. Dose discontinuation is an intercurrent event excluding patients from analysis. Missing data excludes patients with unreported scores due to incomplete patient reporting or data entry errors. Dose 1 is used as the reference category for comparisons in the analysis.

In line with SISAQOL-IMI guidelines,¹⁴ analysis inference should be accompanied alongside PRO score interpretation thresholds to indicate meaningful between-group difference of change in score across doses and, depending on the context, it may be appropriate to use thresholds of different magnitudes.¹⁴

Musoro and colleagues³² suggest a between-group PRO score interpretation threshold of 5–10 points on the EORTC QLQ-C30 Global Health Status may be considered clinically important. For illustration, primary interpretation reporting of both 5- and 10-point thresholds are utilised for dose comparisons.³²

The negative timepoint coefficient (-0.50, 95% CI: -0.73 to -0.27) indicates a statistically significant decline in global health status over time, with Dose 2 and Dose 3 showing larger reductions than Dose 1. Dose 1 vs Dose 2 shows a statistically significant difference (-5.11, 95% CI: -7.29 to -2.92), interpreted as clinically meaningful worsening only at the lower 5-point PRO score interpretation threshold. This difference suggests a potential tolerability concern that should be interpreted cautiously and evaluated alongside safety data, including dose-limiting toxicities (DLTs) and adverse events. Dose 1 vs Dose 3 difference is both statistically significant (-10.8

points. 95% CI: -13.0 to -8.60) and clinically meaningful at the 10-point threshold, indicating stronger evidence of tolerability concerns. As some studies have used lower interpretation thresholds for cancer types, careful justification of the chosen interpretation threshold is essential, as this threshold directly impacts the interpretation of results.³²

OPTIMISE-AR Toolkit

The OPTIMISE-AR toolkit supports the analysis and visualisation of PRO data across relevant data types and is structured around four objectives: (1) PRO endpoints across time points, (2) PRO endpoints between time points, (3) Time-to-event PRO endpoints, and (4) PRO endpoints for formal dose-decision making in model-based dose-finding designs. After addressing objectives (1)-(3), we outline general inferential considerations for the introduced methods in both exploratory and formal decision-making contexts before discussing objective (4).

To ensure standardisation in toolkit presentation, synthesised data were generated to illustrate analysis and visualisation approaches. Simulated PRO-CTCAE data and EORTC QLQ-C30 data, informed by Watson et al³³ and CheckMate 066³⁴ (NCT01721772) respectively, demonstrate analysis for the case study and objectives (1) – (3). These simulated datasets were designed to reflect realistic patterns of treatment tolerability observed in phase I and advanced melanoma trials. Clinician- and patient-assessed DLT data are simulated for results presented for objective (4). Technical details on data synthesis are provided in the appendix (pp 2-3).

(1) PRO endpoints across timepoints

For DFOTs, a PRO objective could look to assess tolerability across dose levels by analysing the longitudinal tolerability profile of a treatment. Such endpoints may assess whether patients at higher doses experience worse tolerability than patients at lower doses at any timepoint within the trial.

These objectives support researchers to analyse PROs at all reported timepoints, including ordinal (eg. severity of nausea or overall side effect burden) or continuous PRO measures (eg. overall health-related quality of life). Figure 2 presents exemplar visualisations of PRO scores across multiple timepoints and dose levels. Figure 2A, 2C, and 2D focus on dose-level aggregate trends whilst Figure 2B considers individual heterogeneity. Figure 2A builds on proposals for ordinal PRO-CTCAE scores in later phase trials^{35,36} to support the comparison across multiple dosages. Figures 2B-D focus on continuous PRO data, with Figure 2B showing individual patient trajectories.³⁷ Figure 2C evaluates mean change from baseline for PRO scores³⁵ with associated improvement and worsening thresholds indicated¹³ though trialists may also consider visualising mean score rather than mean change in score.^{38,39} Figure 2D summarises the distribution of PRO scores as a box plot⁴⁰ though violin plots may also be considered.³⁸

Missing data and intercurrent events can be reported by dose and timepoint in a table, as shown in Figure 2D. Similar tables can be created for other visualisations (eg. Figure 2C) to transparently report sample sizes at each timepoint to support interpretation of PRO analyses and summaries.

The modelling of PROs across timepoints leverages their longitudinal profile to enable more efficient use of the data. However, effective longitudinal modeling requires careful consideration of the dependency structure inherent for repeated measurements. Statistical modelling approaches to analyse PROs across timepoints are discussed in the appendix (pp 5-8).

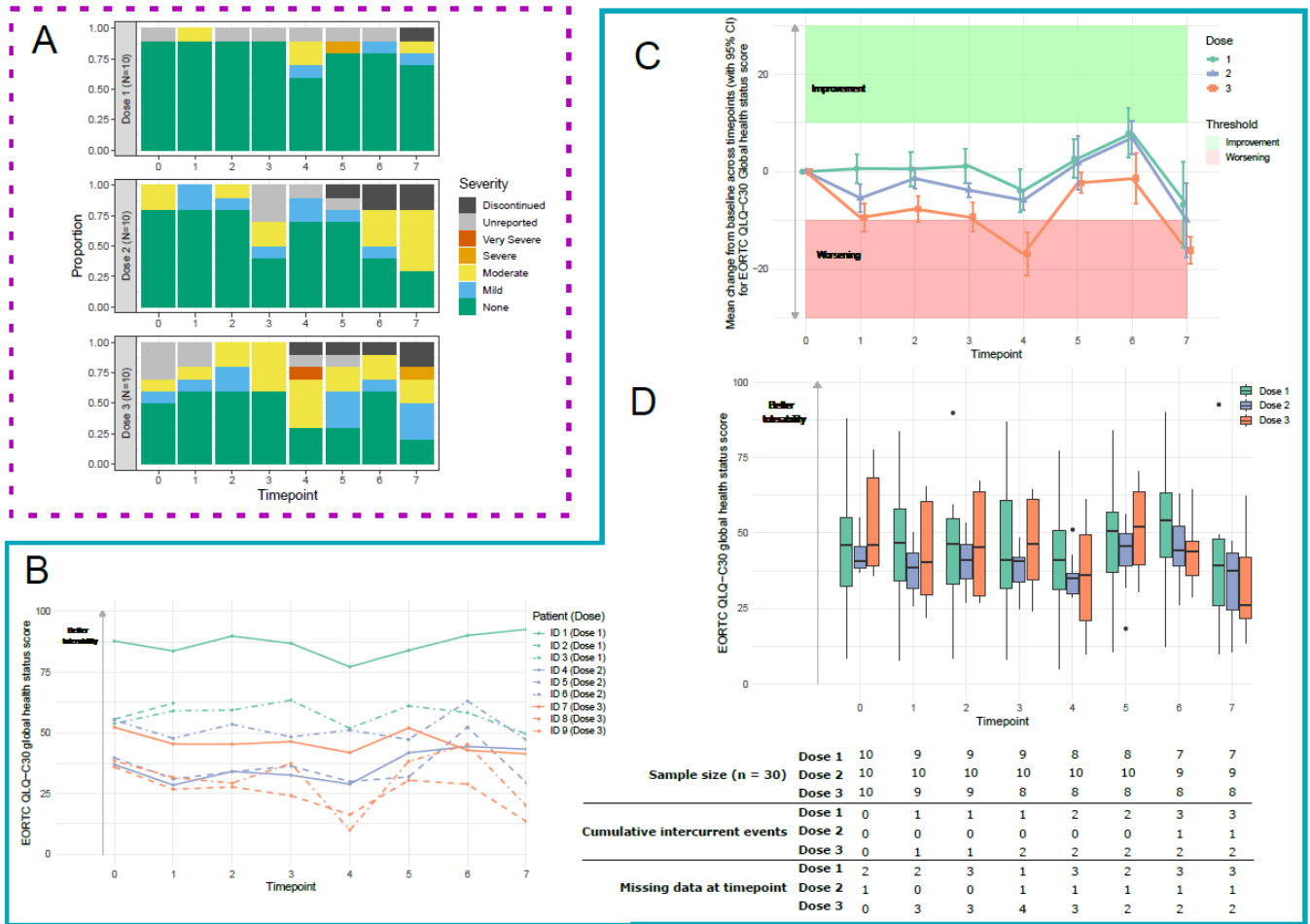


Figure 2 Exemplar data visualisations for PROs across timepoints and dose levels, partitioned by whether PRO data is ordinal (purple dotted box, Figure A) or continuous (blue solid box, Figure B-D). (A) PRO-CTCAE symptom items severity scores at each timepoint for three doses with ten patients allocated to each dose. Category "Unreported" indicates patients with no PRO-CTCAE at baseline or post-baseline timepoints. (B) Patient-level trajectories of EORTC QLQ-C30 global health status scores at each assessment timepoint for three doses with three patients allocated to each dose. (C) Mean change from baseline across 7 timepoints of EORTC-QLQ-C30 global health status for three doses with ten patients allocated to each dose, with 95% confidence intervals and clinically important worsening and improvement thresholds indicated. (D) Box plots of EORTC QLQ-C30 global health status scores at each assessment timepoint for three doses with ten patients allocated to each dose, with risk tables indicating the number of patients who receive treatment and reported PROs at each timepoint. A higher score indicates better outcomes in (B)-(D).

(2) PRO endpoints between timepoints

PRO objectives for DFOTs might analyse tolerability to treatment at two clinically meaningful timepoints across dose levels. This objective might include endpoints to assess whether patients at higher doses experience worse tolerability at the final assessment timepoint than patients at lower doses when compared to baseline.

When visualising PROs between two clinically meaningful timepoints, we may consider maximum baseline-adjusted scores and changes from baseline among others. Figure 3 presents data visualisations for differences in PROs between timepoints. Collapsing multiple timepoints into a single summary measure enables figures to display more than one PRO score, whether that be to display multiple symptomatic adverse events or various functional domains. In any case, trialists should check that such comparisons between domains are reasonable. Figures 3A and 3B present differences between ordinal PRO scores as both a magnitude of worsening or improvement⁴¹ and as a maximum baseline-adjusted difference³⁵ between baseline and a final assessment timepoint. Figure 3B can be readily extended to butterfly plots displaying clinician-reported adverse events alongside patient-reported symptoms, an example is provided within Supplemental Figure 4 in Watson et al.³³ Such figures can indicate concordance between outcomes by visualising insights for both clinician and patient reporting, providing a clear avenue to integrate PRO reporting within more traditional clinician-AE assessment. Figures 3C and 3D present visualisations for continuous PRO scores.⁴² In each case, mean change in PRO score are presented with a corresponding measure of variability (95% CI or standard

error). The data presented in Figure 3C can equivalently be presented as a radar plot.⁴³ Statistical modelling approaches to analyse PROs between timepoints are discussed in the appendix (p9).

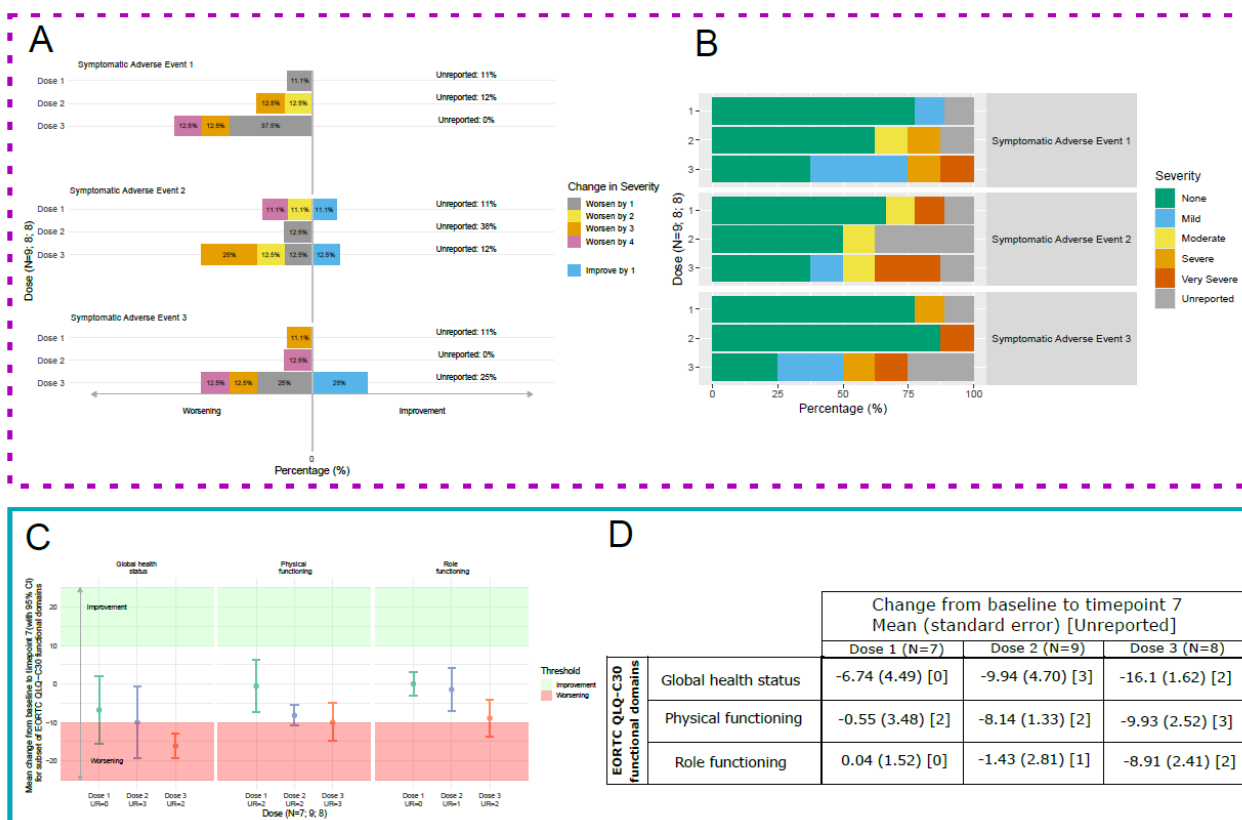


Figure 3 Exemplar data visualisations for PROs between timepoints partitioned by whether PRO data is ordinal (purple dotted box, Figures A and B) or continuous (blue solid box, Figures C and D). (A) Proportion of patients experiencing worsening or improvement for three PRO-CTCAE items between baseline and timepoint 7 for three doses with ten patients allocated to each dose. Category "Unreported" indicates patients with no PRO-CTCAE at the baseline or timepoint 7. Ten patients were allocated to each dose at baseline. At timepoint 7, nine patients in Dose 1, eight in Dose 2, and eight in Dose 3 received treatment. (B) Maximum baseline-adjusted scores for PRO-CTCAE symptom items between baseline and timepoint 7 for three doses with ten patients allocated to each dose. Category "Unreported" indicates patients with no PRO-CTCAE at the baseline or timepoint 7. At timepoint 7, nine patients in Dose 1, eight in Dose 2, and eight in Dose 3 received treatment. (C) Mean change from baseline to timepoint 7 (with 95% CI) for three EORTC QLQ-C30 functional domains for three doses with ten patients allocated to each dose. UR indicates the number of patients who did not report PROs at either timepoint. N indicates the number of patients who received treatment at that final timepoint. (D) Mean change from baseline to timepoint 7 for three EORTC QLQ-C30 functional domains for three doses with ten patients allocated to each dose, with positive change indicating improvement and negative change indicating worsening. Unreported (UR) indicates the number of patients who did not report PROs at either timepoint. N indicates the number of patients who received treatment at that timepoint. A meaningful clinical change in score is defined as an increase (improvement) or decrease (worsening) of at least 10 points.

(3) Time-to-event PRO endpoints

For DFOTs, a PRO objective could look to assess tolerability across dose levels by identifying whether patients at higher doses experience earlier undesirable PRO events (e.g., symptom worsening or dose-limiting events) compared to those at lower doses. Such objectives are typically described using time-to-event endpoints.

Time-to-event PRO endpoints can be evaluated for PRO data types including:

- (i) Binary: Time to Patient-assessed DLT,⁴⁴
- (ii) Ordinal: Time to first occurrence of baseline-adjusted deterioration or worsening in ordinal PRO scores,
- (iii) Continuous: Time to first deterioration or worsening in continuous PRO measures.⁴⁵

For time to first event, trialists might want to analyse PRO endpoints as the expected time to first event occurring or not occurring, or the probability the event (does or does not) occur by a pre-specified timepoint.

Defining a time-to-event PRO endpoint requires pre-specification of the event of interest and analysis timepoint, both of which should be clinically relevant. Trialists should carefully define the analysis population. As some patients may experience events at baseline, endpoints evaluating change from baseline may be more appropriate for survival analysis.

Figure 4 presents an illustrative example of a Kaplan-Meier graph for time-to-event endpoint: no first occurrence of a baseline-adjusted severe PRO-CTCAE score for patients reporting 15 PRO-CTCAE items. The time to first occurrence is stratified by dose and includes 95% confidence intervals for the estimator. Risk tables indicate the number of patients at risk and the cumulative number of patients who experience the event of interest for each dose level. Such tables facilitate clear reporting of intercurrent events which may be handled with patient censoring.

Time-to-event statistical modelling approaches for PRO endpoints are discussed in the appendix (pp 10-11). In settings with informative censoring and competing risks (potentially arising in light of intercurrent events), methods such as the cumulative incidence function may support analysis. Further discussion of intercurrent event handling for time-to-event PRO endpoints, alongside common strengths and limitations of methods is presented in the appendix (p 11).

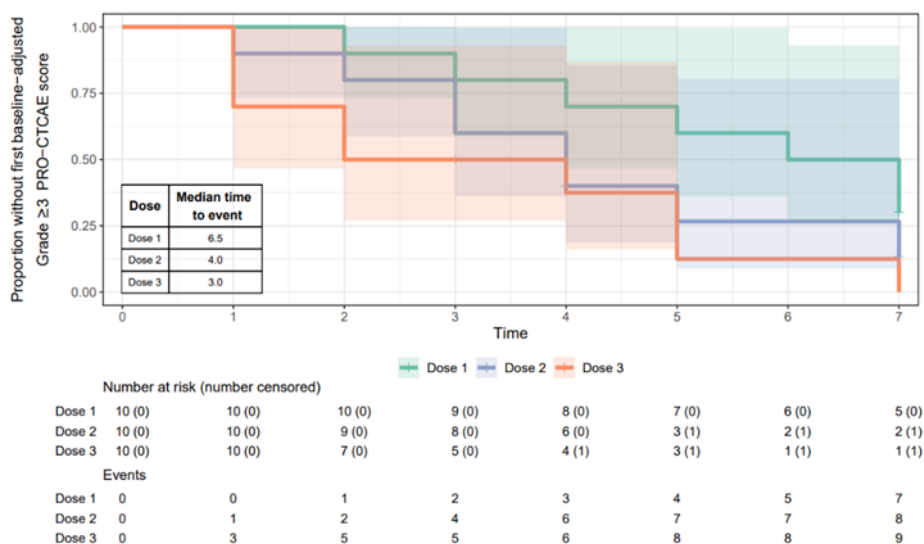


Figure 4 Kaplan-Meier survival curves of time to first occurrence of a baseline-adjusted Grade ≥ 3 PRO-CTCAE score for three doses with ten patients allocated to each dose, with 95% confidence intervals at eight timepoints.

General considerations for Statistical Inference in DFOTs

For formal decision making, the goal of PRO analysis is to support the determination of the maximum tolerated dose (MTD) or optimal biological dose (OBD) - expanding on existing decision-making to consider patient tolerability as a component to the optimal dose. Such doses may be considered the Optimal Tolerable Biological Dose or the PRO-informed tolerable MTD or OBD. A trialist should consider how PRO data is used jointly with existing data to inform decision making for the recommendation of a Phase II dose, including exploratory or descriptive analysis of PROs for clinical interpretation, or the formal embedding of PRO statistical modelling within formal decision-making.

PROs for exploratory analysis, estimation, and hypothesis testing

The use of complex, model-based approaches for the analysis of PROs may provide rigorous statistical inference on patient-assessed tolerability within DFOTs, but feasibility, sample size, and model assumptions should be carefully considered. Whilst rigorous statistical methods are essential for analysis, it is equally important that clinical teams can readily interpret results to support clinical decision-making. To achieve this balance, more complex models could be utilised to assess patient tolerability, while simpler, more interpretable models be utilised to communicate clinically actionable inferences. Exploratory analysis can summarise key trial data and estimation of MTD, OBD, and tolerability rates can provide statistical or clinical inference.

Hypothesis testing is sometimes utilised in DFOTs to analyse PROs for statistical or clinical inference.¹⁰ Trialists should consider whether a summary measure or p-value (or both) is more meaningful within their PRO reporting. While hypothesis testing may support the determination of a recommended Phase II dose, the traditionally small sample sizes in DFOTs often limit hypothesis testing to exploratory, rather than confirmatory

purposes. For each case, trialists should clearly describe where hypothesis testing is undertaken for exploratory or confirmatory purposes. A trialist should clearly identify the research objective they deem most appropriate to ensure estimation and/or hypothesis testing may contribute to the determination of a recommended Phase II dose.

Given the limited sample sizes in DFOTs, we may expect PRO statistical analysis to have wide confidence intervals. It is generally advisable to not only present p-values or point estimates, but also appropriate measures of uncertainty such as confidence intervals or credible intervals (for Bayesian approaches) in line with good reporting standards.⁴⁶⁻⁴⁸ Such measures provide valuable context on the level of uncertainty within the specific trial setting – even if imprecise.

Trials have utilised exploratory PRO analysis for final dose decision-making, both to confirm identified MTDs as tolerable^{45,49,50} and within efficacy-integrated DFOTs when two doses are equally desirable in terms of toxicity and response.⁵¹

PROs embedded within dose-finding design for formal decision-making

PROs may be utilised formally within interim or final decision-making within DFOTs. Designs such as PRO-CRM (PRO-Continual Reassessment Method),²⁸ extensions,^{44,52} and others⁵³ introduce PROs as co-primary endpoints within dose-escalation trials, whilst research also indicates PROs' potential role and strengths within dose-optimisation trials.^{54,55} In such instances PROs may be introduced alongside other endpoints within one or two-stage designs with benefit-risk trade-off approaches (such as utility frameworks) to determine optimal doses.⁵⁶⁻⁵⁸

(4) PRO endpoints for formal dose-decision making in model-based dose-finding designs

We present a simulated trial using a model-based PRO-CRM design demonstrating how PROs can be incorporated into formal interim and final dose-decision making, alongside clinician-reported DLTs.

Similarly to the single outcome CRM design,⁵⁹ the PRO-CRM model-based design identifies a clinician-MTD and patient-MTD using clinician-assessed DLTs (C-DLTs) and patient-assessed DLTs (P-DLT) respectively before recommending the minimum of both MTDs. We present statistical analyses and data visualisations for a simulated PRO-CRM trial.

This section is motivated by a phase I study of radiotherapy in endometrial cancer which utilised the PRO-CRM design.⁶⁰ A C-DLT was defined as an acute grade 3 or higher gastrointestinal or genitourinary adverse event as per CTCAE. A P-DLT was defined as a severe or very severe gastrointestinal patient-reported symptom per PRO-CTCAE across a subset of clinically relevant adverse events and attributes identified by the trial team.⁶⁰

Patients are enrolled in cohorts of three and observed for DLTs within the first month of treatment. The sample size for this case study is 15 patients, with a target clinician-DLT rate of 0.25 and patient-DLT rate of 0.35. The simulated true C-DLT and P-DLT rates for the three investigated doses are (0.10, 0.16, 0.25) and (0.20, 0.35, 0.50) respectively. The true MTD under this simulation scenario is Dose 2 as it is constrained by the patient-assessed MTD.

In Figure 5A we illustrate estimation of C-DLT and P-DLT rate at final analysis alongside the reporting of C-DLT and P-DLT observations within the trial. This figure can be presented at any interim or final analysis to illustrate PRO-CRM decision boundaries and estimates for decision making. Dose 3 has an estimated C-DLT rate closest to the C-DLT target. Dose 2 has an estimated P-DLT rate closest to the P-DLT target, thus the MTD is identified as Dose 2, the smaller of the two doses closest to each target boundary.

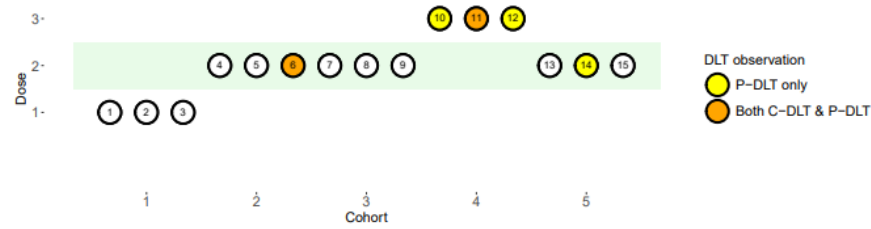
At the final analysis, C-DLT and P-DLT observations are utilised to determine the MTD recommendation. Existing tabular visualisations for DLT estimates for designs such as the CRM⁶¹ can be extended for trial designs incorporating PROs, see Figure 5B. For trialists wishing to use PROs with a benefit risk trade-off, providing tables that present PRO results alongside other key endpoints can be helpful in demonstrating how PROs contribute to the overall benefit-risk evaluation.⁵¹

Flow diagrams are recommended by CONSORT (CONsolidated Standards Of Reporting Trials) for RCTs to provide an overview of the trial to support readers' critical appraisal of trial findings.⁶² Proposals have been made to optimise the illustration of flow diagrams for DFOTs.^{47,63} Figure 5C presents a flow diagram for the PRO-CRM trial indicating the number of observed C-DLTs and P-DLTs within each cohort of patients. This figure is relevant and useful for any design which utilises PROs as a key endpoint for dose-decision making.

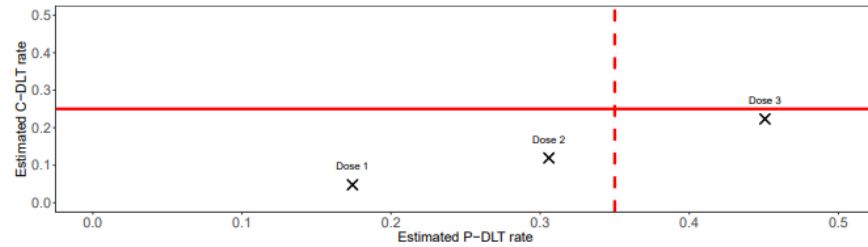
Swimmer plots have been used to illustrate individual patient trajectories on trial and can include key information including dosage, efficacy⁶⁴ and DLT information⁶⁵. Figure 5D presents an exemplar swimmer plot for the PRO-CRM trial, with the time of C-DLTs and P-DLTs indicated during each patient's follow-up. Trialists may wish to include other patient outcomes to their swimmer plot, including response indicators.

In this example, PRO-CRM identifies Dose 2 as the MTD. Utilising C-DLT data alone would identify Dose 3 as the MTD, however this dose is associated with a P-DLT rate above the pre-specified target. The inclusion of P-DLT ensures that the MTD is determined considering patient tolerability, ensuring the MTD is both safe and tolerable. Further scenarios demonstrating the role of C-DLT data and P-DLT data within decision making for the PRO-CRM design are presented in more detail in Lee et al.²⁸

A



(a) Patient dose assignment in PRO-CRM trial case study with observed Clinician-DLT and Patient-DLT outcomes.

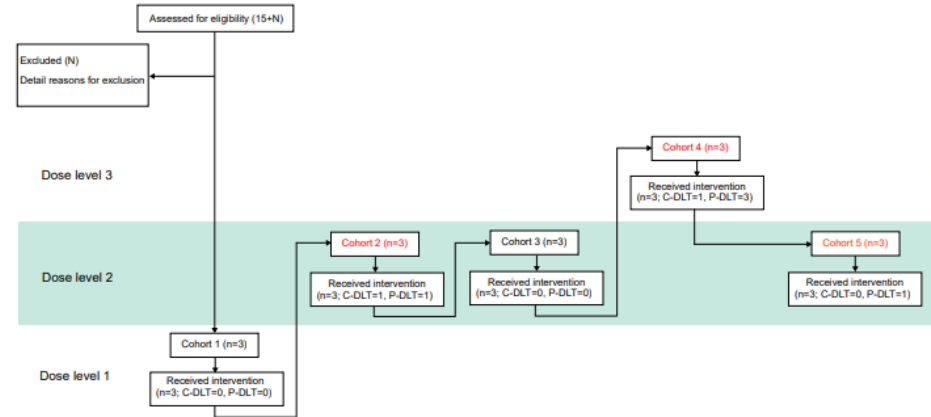


(b) Estimated P-DLT and C-DLT rate at final analysis.

B

Dose	Clinician-DLTs				Patient-DLTs			
	Prior C-DLT Rate	No. of Evaluable Patients	No. of C-DLTs	Estimated DLT rate (90% probability interval)	Prior P-DLT Rate	No. of Evaluable Patients	No. of P-DLTs	Estimated DLT rate (90% probability interval)
Dose 1	0.06	3	0	0.05 (0.01, 0.18)	0.10	3	0	0.17 (0.04, 0.39)
Dose 2	0.14	9	1	0.12 (0.02, 0.30)	0.21	9	2	0.31 (0.11, 0.53)
Dose 3	0.25	3	1	0.22 (0.07, 0.43)	0.35	3	3	0.45 (0.22, 0.65)

C



D

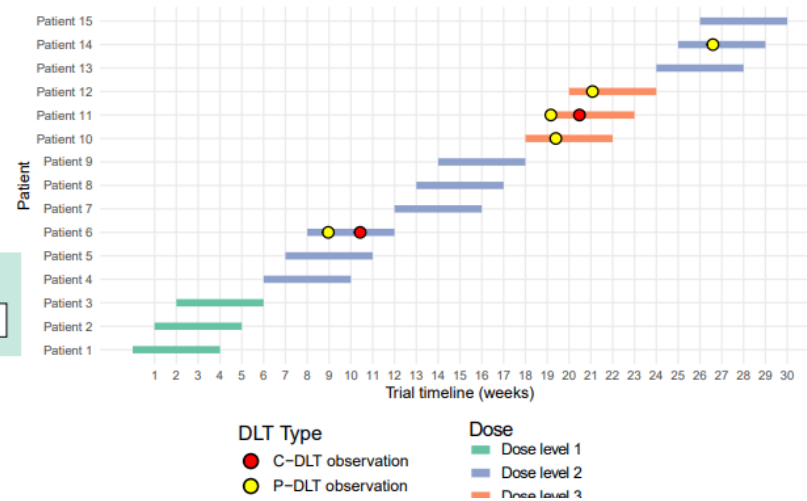


Figure 5 **A**: Exemplar figure detailing (a) observed C-DLTs and P-DLTs and (b) estimation of Clinician-reported DLTs (C-DLTs) and Patient-reported DLTs (P-DLTs) at final analysis using PRO-CRM trial design. The sample size for this case study is 15 patients, with a target clinician-DLT rate of 0.25 (red solid line) and patient-DLT rate of 0.35 (red dotted line). **B**: Prior and estimated probability of Clinician-DLT and Patient-DLT rate for each dose level at the end of the trial using the PRO-CRM trial design. The final estimated Maximum tolerated dose highlighted in bold. The sample size for this case study is 15 patients, with a target clinician-DLT rate of 0.25 and patient-DLT rate of 0.35. C-DLTs are defined as an acute grade 3 or higher gastrointestinal or genitourinary severity per CTCAE and P-DLTs are defined as a severe or very severe gastrointestinal side effect as per PRO-CTCAE. **C**: Flow diagram of dose escalation trial design using PRO-CRM. Cohorts where either clinician-reported DLTs (C-DLTs) or patient-reported DLTs (P-DLTs) occur are highlighted in red. The recommended maximum tolerated dose is indicated in green. The sample size for this case study is 15 patients, with a target C-DLT rate of 0.25 and P-DLT rate of 0.35. **D**: Swimmer plot by dose level for 15 patients enrolled in cohorts of 3 across doses with a dose-escalation study using PRO-CRM.

Discussion

Building upon OPTIMISE-ROR guidance for critical PRO research objectives,^{11,12} OPTIMISE-AR provides an analytical toolkit to support trialists wanting to analyse and visualise PRO data for published DFOTs reports together with setting-specific implementation considerations for DFOTs.

Designed for a multidisciplinary readership, OPTIMISE-AR balances statistical rigor with clarity, with methods offering insights at both patient and dose level whilst remaining accessible and consistent with existing PRO guidance.

As the role of PROs in DFOTs continues to grow, OPTIMISE-AR offers a practical, fit-for-purpose resource that promotes transparent and rigorous PRO analysis and reporting. Drawing on existing evidence in DFOTs and other trial settings, OPTIMISE-AR provides foundational recommendations designed to be adaptable rather than exhaustive. Further consensus-driven guidance may be needed to support trialists as DFOT designs and PRO integration evolve.

Building upon case studies demonstrating PRO analysis and reporting, the OPTIMISE-AR toolkit is positioned for application to additional real-world case studies to further refine its recommendations. To support practical implementation, the toolkit is accompanied by R code (<https://github.com/alemily100/optimise-ar>). A user-friendly Shiny app is in development to support multidisciplinary trialists apply recommended methods. Although designed primarily to support PRO data analysis in publications, future developments could broaden OPTIMISE-AR scope to facilitate PRO reporting at other critical stages, including interim decision-making and review by safety and dose-decision oversight committees, whilst ensuring analyses are accessible and meaningful for patient advocates.²⁹

Though not deemed critical by OPTIMISE-ROR,^{11,12} the application of statistical analysis in the estimand framework is gaining increasing relevance for DFOTs. For trialists wishing to utilise the estimand framework, existing literature outlines the attributes of estimands relevant to many analysis methods discussed in this paper.⁶⁶ In the presence of intercurrent events, trialists may wish to utilise more complex statistical analysis approaches including weighted average survival and inverse probability of censoring weighting for time-to-event endpoints.⁶⁷ Joint-modelling approaches may also be considered for the longitudinal analysis of PROs in the presence of censoring.⁶⁸ The utility of such advanced statistical methods remains dependent on sample size, with methods adapted to small samples particularly relevant. The figures presented in OPTIMISE-AR use a while-on-treatment approach.³¹ To utilise other strategies for the handling of intercurrent events, demonstrated approaches suggested here can be adjusted appropriately.

Trialists analysing PROs in DFOTs can utilise OPTIMISE-AR alongside other resources developed for PRO integration in other trial settings including SISAQOL-IMI,¹⁴ providing guidance for handling missing data and applications to the estimand framework. Further recommendations are provided by the PROTEUS Consortium,¹⁹ and SPIRIT-PRO (Standard Protocol Items: Recommendations for Interventional Trials-PRO)⁶⁹ and CONSORT-PRO⁷⁰ reporting guidelines for trial protocols and RCT reports. However, such guidance is not designed specifically for the DFOT setting. Trialists should carefully assess its relevance considering DFOT-specific challenges such as the presentation of analysis across doses, typically small sample sizes, and the need to support both clinical and statistical assessment of tolerability and dose recommendations.

Conclusion

By supporting trialists analyse PRO data within DFOTs, OPTIMISE-AR facilitates the adoption of transparent, rigorous analytic and reporting practices, thereby enabling patient-centred tolerability conclusions to inform dose-decision making. This work strengthens the methodological rigour applied to PRO data, facilitating robust inferences and conclusions, and the development of both tolerable and effective treatments. OPTIMISE-AR promotes interdisciplinary collaboration among statisticians, clinicians, and patient representatives, promoting shared understanding and communication to integrate PRO findings meaningfully in DFOTs. Together, these efforts aim to advance the development of more patient-focused and scientifically robust trial outcomes.

Authors' contributions

EA: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualisation, Writing – original draft, Writing – review & editing. **AR:** Investigation, Methodology, Writing – review & editing. **ACD:** Investigation, Methodology, Writing – review & editing. **MP:** Investigation, Methodology, Writing – review & editing. **MJG:** Investigation, Methodology, Writing – review & editing. **MJC:** Investigation, Methodology, Writing – review & editing. **ARH:** Investigation, Methodology, Writing – review & editing. **OK:** Investigation, Methodology, Writing – review & editing. **JLK:** Investigation, Methodology, Writing – review & editing. **JLL:** Investigation, Methodology, Writing – review & editing. **AM:** Investigation, Methodology, Writing – review & editing. **YQ:** Data curation, Investigation, Methodology, Software, Validation, Writing – review & editing. **KRR:** Investigation, Methodology, Writing – review & editing. **JR:** Investigation, Methodology, Writing – review & editing. **CS:** Investigation, Methodology, Writing – review & editing. **SNS:** Investigation, Methodology, Writing – review & editing. **NAW:** Investigation, Methodology, Writing – review & editing. **RW:** Investigation, Methodology, Writing – review & editing. **CY:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

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Declaration of interests

AR is an employee of Modus Outcomes, a patient-centered research consultancy providing services to multiple pharmaceutical industry companies. **MJC** is Director of the Centre for Patient Reported Outcomes Research, Deputy Director of the Birmingham Health Partners Centre for Regulatory Science and Innovation and is a National Institute for Health and Care Research (NIHR) Senior Investigator. Grants: NIHR Applied Research Collaboration, Health Data Research UK, Innovate UK, Macmillan Cancer Support, GSK, Research England, European Commission and EFPIA, Brain Tumour Charity, Gilead, Janssen, Merck, NIHR, UKRI. Licenses: Symptom Burden Questionnaire-Long COVID. Consulting fees: Aparito Ltd, Boehringer Ingelheim, CIS Oncology, Merck, Genentech, GSK, Pfizer, Vertex Pharmaceuticals, ICON, Halfloop, University of Michigan, Northwestern University, EuroQoL, Shionogi, Cell and Gene Therapy Catapult outside the submitted work. Payment or honoraria for lectures: University of Maastricht, South-Eastern Norway Regional Health Authority, Cochrane Portugal, Singapore National Medical Research Council. Leadership: PROTEUS consortium. Stock: Family member has stock in GSK. **ARH** Grants or contracts: Advancell, Aveo, BMS, Full-Life, Fusion, Janssen, MacroGenics, MSD, Roche, Seagen, Tyra Biosciences, MOMA Therapeutics, Astellas, Bayer, Eisai. Consulting fees: Astellas, Bayer, Full-Life Technologies, Eisai, Janssen and MSD. Honoraria for lectures: Astellas, Janssen and MSD. Support for meeting attendance: Astellas, Bayer. **AM** grants: Astex, Merck, MSD. Consulting fees: Merck, Janssen, Pfizer, AstraZeneca, Immutep, MSD. Speaker: AstraZeneca, Janssen, Takeda, Seagen, Merck, GSK, Faron. Support for meeting attendance: Janssen. **JR** is an Editor-in-Chief of

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