ADOPTION OF PROs IN EARLY CLINICAL TRIALS FOR ONCOLOGY DRUGS: CHALLENGES AND OPPORTUNITIES

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Despite changes in regulatory expectations, adoption of PROs in early-phase oncology trials remains very low (6%). We recommend inclusion of safety-related PROs, such as PRO-CTCAE, in these studies to supplement traditional safety data. While initial analysis can be qualitative, as development proceeds, exposure-response analyses with PROs and/or statistical approaches could be considered to aid dose optimization.

Background & Objectives

For oncology therapeutics, it has become critical to understand adverse events impact on patient function and quality of life (QoL). Consequently, there is currently a shift in the regulatory expectations for inclusion of Patient Reported Outcomes (PROs) in early-stage oncology trials and in dose optimization, consistent with the FDA Project Optimus. The need for PROs inclusion at early-stage was reiterated in recent FDA guidances[1].

However, the adoption of PROs in oncology early-phase trials remains low. The objective of this work was to:

(1) review the current landscape for PROs inclusion in oncology early-phase clinical trials
(2) review pharmacometrics and statistical analysis methods of PROs in early clinical trials and
(3) provide recommendations for incorporation and interpretation of PROs in dose selection decision-making.

Methods

Database search strategy

Searches were conducted in ClinicalTrials.gov. Oncology early-phase studies were identified using the following search strategy in the "advanced search" function: condition or disease – cancer; study type – interventional (clinical trial); study results – all studies; study phase – early phase 1, phase 1; date restriction (study start from 01/01/2022 to 31/03/2023). The search was then repeated to identify studies with a PRO endpoint by adding outcome measures – 'patient-reported outcome' OR 'PRO' OR 'quality of life' OR 'QOL' OR 'PRO-CTCAE' OR 'PRO CTCAE' OR 'patient satisfaction' in order to evaluate the adoption of PROs in recent oncology phase 1 trials. A partial QC (10%) was performed on the list of all oncology early-phase studies and a 100% QC was performed on the list of studies with a PRO endpoint.

Statistical and pharmacometrics analyses

Literature was reviewed to identify the most common pharmacometrics (PMx) and statistical methods used for PROs analysis across oncology phase 1 to phase 3, since the data base of phase 1 studies that evaluated PROs was very limited.

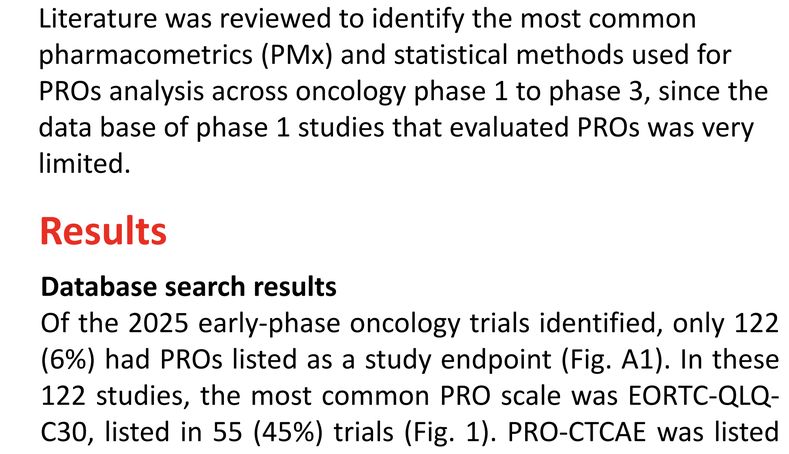
Results

Database search results

Of the 2025 early-phase oncology trials identified, only 122 (6%) had PROs listed as a study endpoint (Fig. A1). In these 122 studies, the most common PRO scale was EORTC-QLQ-C30, listed in 55 (45%) trials (Fig. 1). PRO-CTCAE was listed in only 4 (3%) trials.

Interestingly, most of the trials incorporating a PRO endpoint were life-cycle management studies sponsored by hospitals and universities (~75%). Very few trials were classical first-in-human (FiH) studies sponsored by pharma or biotech companies.

Figure 1. Most common PROs scales used in oncology early-phase trials



Pharmacometrics and statistical approaches

Pharmacometrics can be used to quantify the relationship between PROs and drug exposure and other covariates and allows for accounting for PK and PD variability by using mixed-effects modeling.

The PMx approach will depend on the nature of the PRO data, data collection schedule, and sample size. PMx approaches used for other therapeutic areas and non-PRO data can also be applied to PRO data in the oncology space. These include:

Table 1. Pharmacometrics approaches applicable to PROs

Model	Notes
Continuous data: PROs with wide range of possible scores	
Linear model	Do not account for the bounded nature of scores
Emax model	
Beta regression models	
Dichotomized data	
Logistic regression	Used for binary outcomes
Count data	
Poisson models	Can be used for data with a moderate range of scores
Negative binomial models	
Longitudinal single-item ordinal data, e.g., PRO-CTCAE	
Proportional odds model[2]*	Relatively simple to implement but does not capture correlations between consecutive measurements (i.e., Markov features)
Markov models*	Including discrete time[2], continuous time[2], and minimal continuous-time Markov-models[3]
*Implemented in analysis datasets containing >70 subjects to date	

For composite scores computed from PRO questionnaires with multiple items, using item response theory (IRT) PMx models is superior to analysis of total scores, which results in loss of information[4] (see Fig. A2). IRT models have increased statistical power to detect the drug effect. However, in the literature, IRT models have been applied to later stage studies with a large number of subjects in the analysis datasets (typically N >300).

The challenges with statistical analysis of PRO data, especially from early studies, currently include:

- Lack of standardization in data collection and analysis.
- Violation of the assumptions of linearity underlying linear models e.g., if data is too sparse.
- Lack of alignment between statistical testing approaches and the available data.
- Lack of consensus on how to handle missing data, especially as patients discontinue participation in PRO collection over time[5].

In literature, the most common statistical analysis methods for PROs included linear regression and analysis of covariance, linear mixed effects models, logistic regression for binary and original outcomes, and repeated measures analysis. Most of these were applied to phase 3 studies, with very limited use of formal statistical analysis for Phase 1 study PRO data[6].

Additionally, methods such as beta-binomial-related regression methods are being introduced to address violation of linearity assumptions related to linear models[7].

Discussion

Despite changes in regulatory expectations, adoption of PROs in early-phase oncology studies remains very low. PROs provide more granular, longitudinal and reliable information on the tolerability profile of a drug, as well as information that is not captured by traditional safety data collection, such as long-term patient acceptance of a dosing regimen. This information can be leveraged to better inform dose optimization. We recommend:

Data collection:

- Consider incorporating PROs evaluating individual, clinically symptomatic AEs, such as PRO-CTCAE, across all dose arms, as early as the FIH study, to supplement traditional safety data, when such AEs are expected.
- Choose the PRO instrument or selected items from item libraries based on typical class-related toxicities or on non-clinical toxicities. In early development, focus on minimizing patient burden while identifying notable trends; limiting the number of questions (e.g., to key AEs or attributes) may also minimize missing data.
- Plan assessments more frequently (e.g., QW) in the early treatment cycles (e.g., first 3-6 cycles), with a subsequent decrease in frequency, and should be tailored to the treatment schedule and anticipated toxicity pattern.
- Include clinical pharmacologists, pharmacometricians, and statisticians during PRO data collection planning for efficient incorporation of PRO data in dose optimization, including modeling and simulation.

Data analysis:

- Approaches like variations of the continual reassessment method (CRM), PRO-CRM[8] have been proposed that incorporate PRO-CTCAE data in dose escalation decision-making. However, PRO data in early studies could be analyzed qualitatively or in an exploratory manner like other safety data for dose-response trends in incidence and severity. Examples of informative PRO data presentation formats are available in literature and are being improved.
- As development proceeds and sample sizes increase, exposure-response analyses with PROs and/or statistical approaches could be applied. PMx methods already exist that lend themselves to analysis of PRO data as described in the results.
- Early oncology dose-finding trials typically lack power to detect statistically significant differences between dosage levels, and this is not expected from a regulatory perspective. Nevertheless, PRO data collection approaches that generate data suitable for statistical analysis is an evolving area. Having sufficient sample size for PRO data even on a limited number of endpoints could greatly assists this iterative process. Understanding which attribute of the PRO (frequency, severity, etc.) is of major clinical interest, and statistician input into data collection will help to align data collection and statistical analysis.

Collaboration is needed to build a collective body of PRO data and analysis experience to aid with iterative development and assessment of improved PMx and statistical approaches. This will also aid with evaluating the utility of PROs in early oncology studies.

Additional Figures

Figure A1. Clinical trials selection

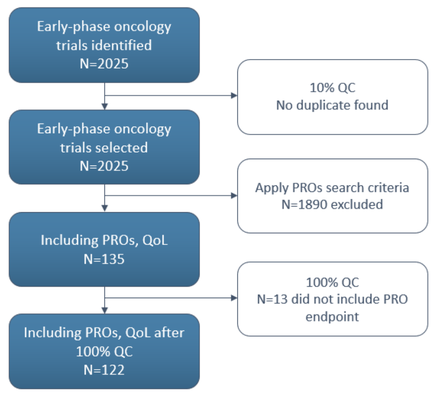


Figure A2. IRT model-predicted probabilities and expected scores between the two arms of the EMILIA trial

Source: Figure 5 [4]

Typical steady-state probabilities (circles) and expected scores (cross symbols) for each FACT-B item, as predicted by the longitudinal IRT model.FACT-B: Functional assessment of cancer therapy - breast; T-DM1: ado-trastuzumab emtansine.

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