Supporting a Patient-Centric Approach to Dose Optimization in Oncology: The Essential Role of Patient-Reported Outcomes (PROs)

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Introduction

Patient experience data (PED) in the context of drug regulation is a growing part of the totality of evidence to understand the safety and efficacy of a cancer therapeutic. PED intends to provide information about patients' experiences with a disease or condition.[1] One type of PED, patient-reported outcomes (PROs), is a clinical outcome assessment based on information directly reported by the patient about the status of their own health condition. Patients are uniquely positioned to report their own quality of life, symptoms, and function, and several studies support that patients are a highly reliable reporting source of such information that adds value to the traditional clinician assessment.[2] For example, clinicians, including oncologists, may overestimate functional status and underestimate patient symptoms, supporting the clinical and scientific value of PROs for quantifying symptomatic adverse events (AEs) with the greatest impact on patient health-related quality of life while on the therapy.[3]

Recent US Food and Drug Administration (FDA) draft guidance highlights the need for benefit-risk planning when developing new oncology drug and biologic products, including collecting appropriate data to inform the dose exposure response for efficacy and safety/tolerability.[4] Oncology clinical trials commonly consider clinician-reported safety data, dose modifications, dose discontinuations, and severe AEs including hospitalizations to determine tolerability. In 2018, Friends of Cancer Research (*Friends*) gathered key stakeholders to develop a new working definition of treatment tolerability that incorporates the patient experience by collecting rigorously developed PRO data to inform symptomatic toxicity and functional information.[5] The group aligned on the position that a complete understanding of tolerability should include direct patient measurement on how they are feeling and functioning while on treatment. Integrating PROs early in drug development, alongside traditional measures, can support a more comprehensive understanding of the benefits and risks of a therapeutic, including the perception of the patient on the tolerability of the therapy and their ability or desire to adhere to the dose or intensity of therapy for prolonged periods. This can add unique data to inform dose optimization, or dose range, for new oncology drugs.

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To adequately implement this expanded definition of tolerability, drug sponsors need to select and deploy fit-for-purpose PROs using well-defined and reliable tools at an assessment frequency appropriate for the drug.[6] Several symptom libraries are available, and one tool developed specifically to capture symptomatic side effects is the National Cancer Institute (NCI)'s Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) symptom library.[7] *Friends* identified this tool in 2015 as a potential resource, and many of the earlier operational challenges delaying its commercial use have been addressed since then. The PRO-CTCAE can be used across various trial contexts in multinational settings to provide patient-reported symptomatic toxicity information that complements standard clinician-reported CTCAE safety data. In addition to individual symptom data, tolerability can be informed by other widely available PRO measurement systems to evaluate side effect impacts including patient-reported overall side effect bother, physical function, and ability to work and carry out leisure activities. Physical function can be measured in a variety of ways, including using the Patient-Reported Outcomes Measurement Information System (PROMIS)® physical function item bank or the functional scales from the European Organization for the Research and Treatment of Cancer item library (EORTC QLQ-F17).

While PRO use is common in randomized registrational trials, PRO collection in early phase trials is rare.[8–12] There is increasing interest across stakeholders involved in early phase cancer trials in using PRO data as valuable complementary information to inform tolerability and later phase trial design.[13] FDA has emphasized the need to collect PROs in cancer clinical trials by offering suggestions for core PROs and how to measure them in draft guidance.[6] Regulatory authorities in other jurisdictions are also placing increasing emphasis on the collection of PRO data in a variety of settings.[14] While there are limited examples of use of PROs in dose finding trials, there is interest in identifying feasible approaches for the collection and use of these data in early phase clinical trials, particularly to inform dose selection.[6,15]

FDA announced Project Optimus in 2021, which seeks to place a greater emphasis on dose optimization and dose selection in early phases of oncology drug development towards doses that maximize the efficacy, safety, and tolerability of a drug.[16] Considering the expanded definition of tolerability for all therapies, current paradigms that focus on identifying the *maximum* tolerated dose (MTD) are not appropriate with newer targeted therapies that show relevant efficacy across a range of doses, allowing for better tolerability and potential adherence at doses lower than the MTD. PROs should be included in early phase studies to provide a foundational understanding of short- and longer-term symptom and functional impacts to optimize dosing and facilitate more informed development in later phases. Better understanding of the tolerability of different doses throughout early drug development could inform selection of a dose or doses for approval that patients are more likely to be able to take following approval. Collection of PROs for dose optimization encompasses both the first in human Dose Escalation trials, as well as the Dose-Expansion trials.[17]

Friends convened industry, academic, regulatory, and patient advocate representatives to discuss opportunities and challenges for using PROs in early phase clinical trials, specifically focused on measuring tolerability to inform dosage optimization. Open questions regarding PRO inclusion in early phase trials include feasibility, trial design, impacts of sample size, optimal PRO

selection, and PROs influencing results (e.g., over/under reporting clinician AEs).[13] Including PRO assessment in early phase trials requires careful thought and consideration to fully realize the value of symptom and functional data while overcoming operational challenges.

To identify opportunities, challenges, and solutions for using PROs to inform dose optimization in cancer clinical trials, the working group focused on the following objectives:

- Highlight ways PROs can characterize tolerability and support dosage optimization
- Provide a clinical trial design framework for incorporating PROs into dosage optimization studies
- Discuss opportunities for using PRO findings from early phase studies to inform later phase study designs and to complement traditional safety data for regulatory decision-making

Using PROs to Complement Commonly Collected Data to Inform Dose Selection

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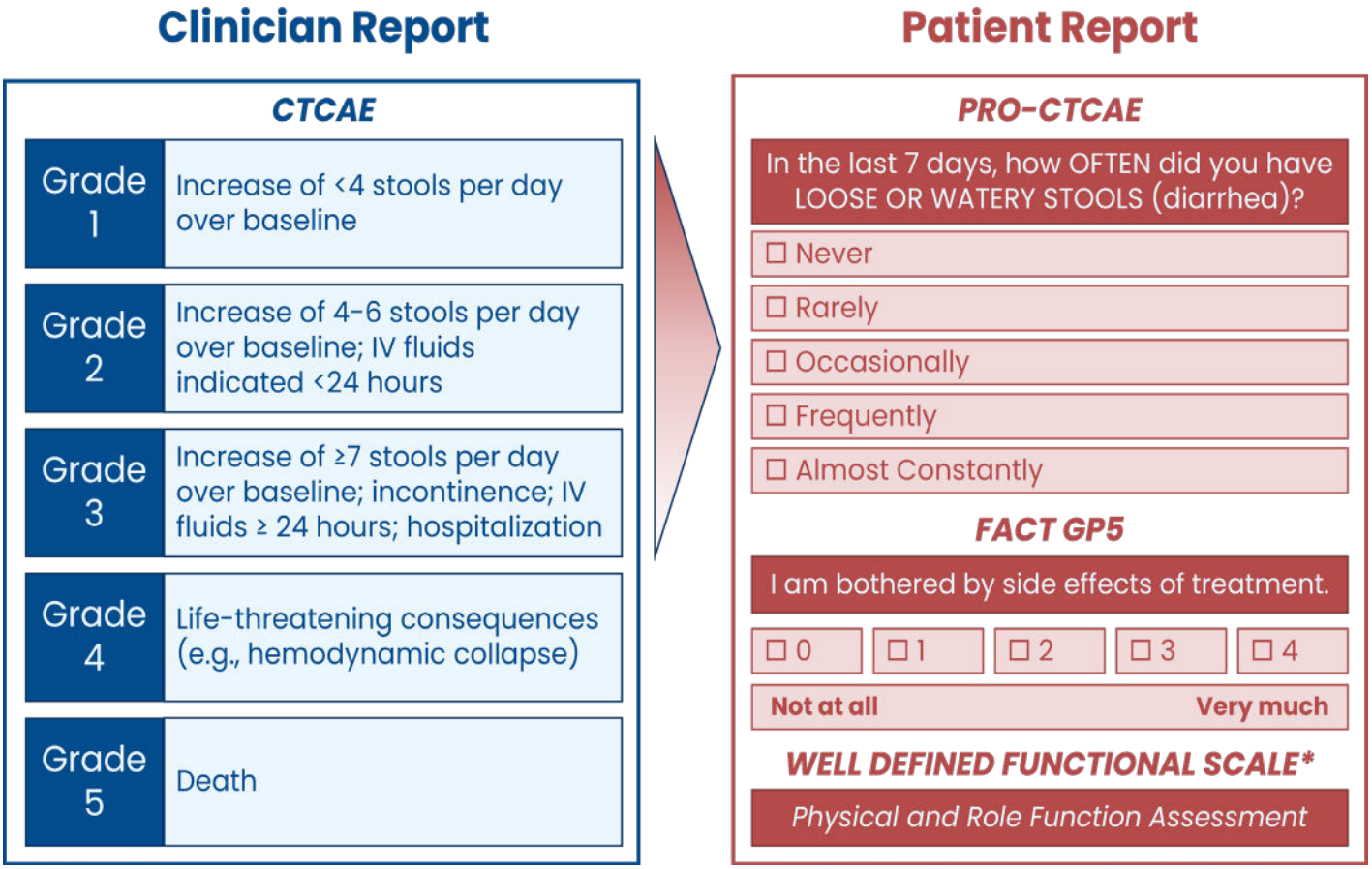
PROs provide unique information characterizing specific symptoms, overall side effect burden, and their impact on a patient's ability to function. The systematic nature of PRO collection informs onset, duration, severity, and resolution of side effects and their impacts. Many oncology drugs require long-term administration of therapy to maintain tumor response and control. As such, the tolerability of the drug may shift as patients transition from the immediate to the long-term phase of treatment. For example, even lower grade (Grades 1 and 2) symptomatic AEs may become more burdensome than infrequent Grade 3 toxicity, especially when multiple prolonged lower grade symptomatic toxicities are experienced simultaneously.[5] While standard clinician-reported AE data provide a rate of worst grade AEs experienced at any time during the clinical trial to characterize tolerability, additional granularity about the severity, frequency, duration, and impacts of side effects can be elucidated from PROs.

Figure 1 highlights an example of how systematically captured PRO data assessing symptoms and functional impacts can complement clinician reporting. In this example, clinician-reported Grade 1-2 diarrhea is considered "low grade," which can minimize the patient's perceived impact of the symptom and may not be considered when defining safety and tolerability of a product in a clinical trial. For diarrhea, the clinician report for lower grade AEs may obscure a wider range of symptom severity and impact on function, which is true of other symptomatic toxicities (e.g., visual, cutaneous, and mucosal side effects). The PRO-CTCAE data of the patient report of diarrhea can provide additional insight, which can be further expanded by assessing how bothered the patient is by side effects overall using an item such as the Functional Assessment of Cancer Therapy (FACT) GP5 item ("I am bothered by side effects of treatment") and by how they report their physical function and ability to work and perform leisure activities using patient-reported functional assessments. Studies have shown that patients with more frequent diarrhea also have worse physical function, which is seen consistently at time intervals over the course of treatment.[18] The additional, longitudinal information provided by PROs can

add granularity and trajectory for the individual symptom as well as potential impacts to how bothered patients are, their function, and medication adherence.[19] This information is not discernable by clinician report alone, particularly for Grade 1-2 clinician AEs.

Figure 1: Example of clinician-reported data and patient-reported data. Patient-reported data can add information to expand on lower grade clinician rated CTCAE side effects (i.e., Grade 1-3). For instance, a CTCAE grade 2 diarrhea event could be considered by a patient as almost constant diarrhea that results in high side effect bother and adverse impacts on physical function and role function (i.e., ability to work or carry out leisure activities).

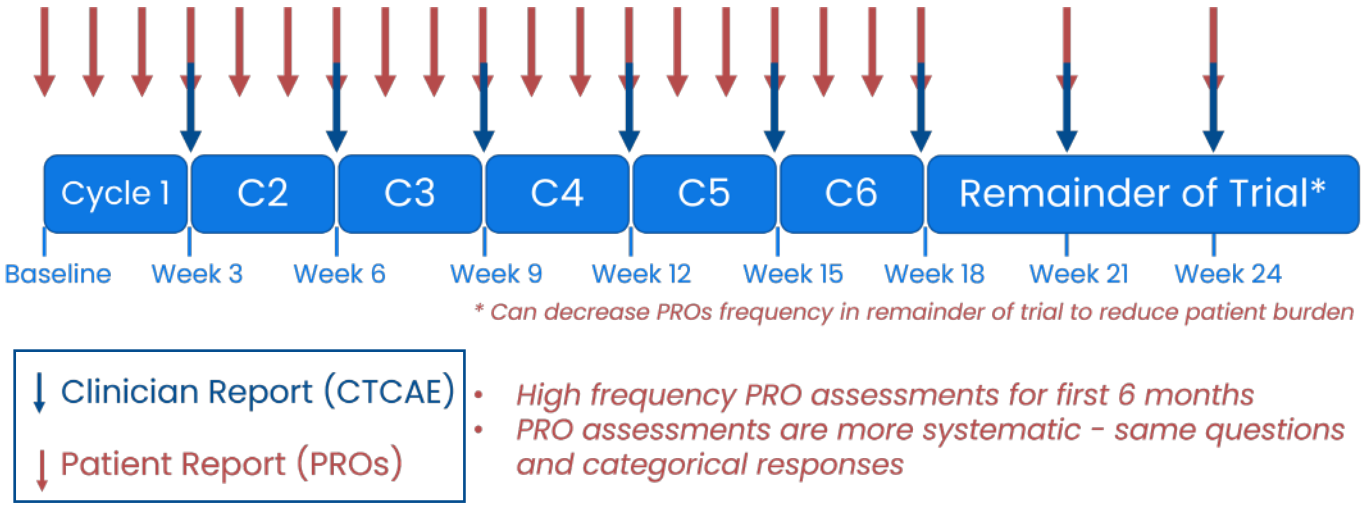


*Two examples of well-defined PRO scales for physical and/or role function are available from EORTC and PROMIS® measurement systems.

In addition to providing data on outcomes not currently assessed (i.e., side effect bother and functional outcomes), the frequency and systematic assessment of PRO data can reveal smaller but potentially important differences in a symptomatic side effect. Several studies note patients report a higher incidence and severity of symptomatic side effects than clinicians' CTCAE evaluation.[3,20,21] The added ability for PROs to inform safety and tolerability is most clear for unobservable symptoms such as neuropathy, headache, pruritis, nausea, and constipation, where assessments most differ when a patient reports their experience compared with their provider.[22] Additionally, providers measure side effects only during clinic visits, which may lead a patient to provide an assessment that does not represent their full experience of side effect

intensity over the course of the 3-4 week cycle (**Figure 2**).[23] This is particularly problematic for intermittently administered therapies, like chemotherapies administered once every 3 weeks, where maximal side effect intensity typically occurs between clinic visits. In these situations, an investigational oral drug administered daily may appear to be tolerated worse than a once every 3 week chemotherapy if assessments are being performed only once per cycle/ office visit where chemotherapy side effects have begun to resolve. More frequent systematic assessment can be valuable for exposure-response analyses related to a cardinal toxicity, and this added power becomes particularly important with the smaller cohorts evaluated in Dose Escalation trials.

Figure 2: Frequency of PRO assessments. PRO symptom data provides more consistent data capture by asking the same question with categorical response options at a higher frequency. This data source can add power to exposure-response analyses during Dose Escalation study. High frequency PRO assessment can be reduced later in trial by asking a comprehensive PRO assessment at several longer-term cross-sectional time points (e.g., 1 year, 2 year, etc.). *Adapted from figure courtesy of Zirkelbach, Bhatnagar, and Kluetz.*



A Framework to Incorporate PROs into Dose Optimization Studies

PRO data should be collected with approaches that reduce bias, with well-defined and reliable measures, and in ways that the results can be easily interpreted to complement findings from clinician-reported outcomes. FDA's draft guidance recommends collecting and analyzing five core PROs: disease-related symptoms, symptomatic adverse events, overall side effect impact summary measure, physical function, and role function.[6] Because there are differing expected toxicities across therapeutic drug classes, individualized symptom item lists should be selected from an item library rather than using an off-the-shelf static questionnaire. For example, NCI's PRO-CTCAE is a robust item library that contains pertinent patient-reported symptoms. Other item libraries exist including both the EORTC item library and Functional Assessment of Chronic Illness Therapy (FACIT) item library.[24,25] Single item and summary measures such as overall side effect burden (e.g., FACT GP5) can complement patient-reported symptomatic AEs and

have the advantage of capturing the impact of multiple different toxicities in a single score comparable across groups of patients and different treatments. Functional impacts can be assessed by EORTC or PROMIS®.[26]

Dose Escalation Trials

Identification of an appropriate dose starts with first in human trials, often called Dose Escalation trials. PROs should be incorporated into Dose Escalation trials to gather a holistic understanding of the patient's toxicity profile. Dose Escalation trials often include a single agent, allowing for analysis of the PROs from the effect of the new agent, rather than impacts from combination therapies in later trials impacting interpretation. Descriptive trends in the severity and duration of symptomatic AEs should be evaluated among patients in these trials to help sponsors understand whether symptomatic toxicities increase with increased doses, new symptoms emerge at higher doses, or if the frequency of lower grade symptoms increases. This information can be used to inform the Dose Expansion study, including the potential of moving forward with a recommended dosage range.

Given sample size is lowest in Dose Escalation trials, high frequency systematic assessment of PRO symptom data can add power to pharmacokinetic exposure-response analyses conducted during dose-escalation. In addition, comprehensive knowledge of the patient population can clarify which PROs support an understanding of the impacts of the treatment to inform later phase PRO selection. Because many of the patients have disease that is refractory, baseline PROs should be taken before treatment initiation to normalize for symptoms of disease or side effects from prior treatments. Selecting a series of PROs related to expected AEs when there are fewer patients included in Dose Escalation studies can help narrow in on key PROs to measure in subsequent studies.

When selecting PROs for Dose Escalation studies, sponsors should consider data from pre-clinical studies, as well as side effect evidence from other drugs in the same drug class when available. A free text PRO item could be included in Dose Escalation trials when the potential treatment related symptoms are not fully known and can inform which PROs to include in subsequent trials. A single item side effect impact question like FACT GP5 can add additional information with little additional patient burden. While some of these measures, including overall side effect burden, function, and key expected symptomatic AEs, should be measured in all patients, trial designs that adapt PRO measures in later cohorts based on symptoms identified in early cohorts could be considered.

Dose Expansion Studies

The Dose Expansion study has historically focused on whether the efficacy signal warrants an additional study by using a single-arm trial with a single dose (often the MTD).[27] It is increasingly important to use Dose Expansion trials to optimize the dose, ideally by conducting a randomized evaluation of two or more doses. These early randomized evaluations of dose would not need to strongly control Type 1 error, but rather be sufficiently sized to make assessments regarding the activity/efficacy, safety, and tolerability of the different doses.[17,28] Inclusion of PROs would be instrumental in the assessment of tolerability and describing differences in tolerability among the candidate doses. To support dosing decisions in these studies, PRO data including

descriptive trends in severity and duration of symptomatic side effects should be evaluated. Systematic high frequency PRO data adds unique clinical outcome data and additional evidence to describe differences in candidate doses being compared.

Sponsors should be thoughtful when designing Dose Expansion studies and consider PRO question selection that ensures relevance and minimizes duplication. It is generally recommended to focus on relevant treatment-related symptoms. The core outcomes recommended by FDA, including symptoms, overall side effect impact, and physical and role function, should be assessed with available tools in 30 or less questions, and ideally patients should not spend significant time to complete PROs at each assessment (e.g., no more than 10 minutes per assessment timepoint).[29] Sponsors should consider including a free text item in Dose Expansion studies to allow additional patient feedback on side effects and support an understanding of optimal PRO selection for subsequent trials.[30] Per FDA draft guidance, assessments made more frequently in the first few treatment cycles would be suitable across most drug development programs but this should be tailored to the treatment schedule.[6] It is recommended to consult with appropriate regulatory authorities early for advice on the PRO strategy including assessment frequency for a specific drug development context.

Additional Considerations for Early Phase Dose Optimization Studies

The patient population and the treatment regimen should be considered when deciding about PRO inclusion in Dose Escalation and Dose Expansion studies. In situations when a randomized approach will not be used but safety and tolerability remain important objectives (e.g., a Dose Escalation or Dose Expansion Trial), PROs should be thoughtfully included.[31]

An important trial design decision will be whether to allow clinicians access to PRO data during the trial. While use of PROs to inform clinical care is an active area of research, their incorporation into clinical workflow is challenging and there is no regulatory requirement that PRO data be reviewed during the trial to inform patient care. Therefore, PROs collected during dose optimization studies as part of the study protocol to inform trial results may not be shared with the trial clinician in real-time to impact care. This should be clearly explained to patients and strategies should be identified to share study-level PRO data with the community once the trial is complete. In addition, there is no requirement to compare clinician and patient reports for the same or similar side effect. Patient-reported symptom data is assessed and quantified differently than CTCAE data, and differences are expected between patient and clinician report. These and other regulatory considerations for use of PROs to inform tolerability have been previously described.[32] Currently, Project Patient Voice has focused on presenting data from registrational trials comparing two trial arms, but analysis and visualization techniques from the approach provide suggestions of how to do so for dose optimization studies and other trial designs to provide patients and providers with information about tolerability of different doses.[33]

Conclusions

PROs should be included in early phase clinical trials to better understand tolerability and to inform dose selection for future clinical trials and clinical use as well as aiding with the selection of most appropriate PRO instruments for the late phase trials with registration intent. The use of PROs in Dose Escalation and Dose Expansion studies is a newer concept and sponsors should continue to refine approaches for incorporating PROs as methodologies and analyses are improved over time. It will be critical to educate stakeholders about the value of and approach to including PROs. Additionally, careful consideration should be given to which PROs to include based on tumor type, stage of disease, evidence from similar treatments, previously collected data, and trial goals.

While major progress over the last decade has provided the necessary tools to measure PROs in clinical trials, there are still some limitations to using PRO data in clinical trials. For instance, many clinical trials are multinational, and it is critical to ensure culturally validated translations are available. This may not be a significant challenge given many early phase trials are conducted in the US and almost all widely used PRO measures have English and Spanish translations. Additionally, item libraries are being iteratively improved and may not include or have optimized all novel symptomatic side effects of interest. For instance, some of the side effects included in the PRO-CTCAE do not have measures for more than one attribute (i.e., severity, frequency, and interference), and the PRO-CTCAE does not include an overall side effect bother item. This makes it likely that multiple PRO measurement systems may need to be deployed within a single trial.

PRO results should be considered in the context of other data to establish a totality of evidence alongside clinician reports of safety and efficacy, pharmacokinetics, pharmacodynamics, and biomarker studies. PROs can be of particular value as a high-quality data stream to support exposure response relationships in dose optimization decision-making. It is acknowledged that addition of PROs in early drug development is new and will add some cost to early development. However, PRO data are uniquely positioned to add value to the characterization of tolerability which is a critical study objective in dose escalation and optimization. Additional information to better optimize dose may lead to a more tolerable marketed drug with an optimum benefit-risk profile, with better patient-reported information on side effects and positive impacts that can have advantages in adherence and provide important information for decision making by the patient and treating clinician.

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