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Key design and analysis principles for quality of life and patient-reported outcomes in clinical trials

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Abstract

Advances in early detection and therapy have increased the number of prostate cancer survivors, leading to a greater emphasis on examining patient-reported outcomes (PROs). PROs augment clinical outcomes, providing a more comprehensive assessment of the patient experience, including symptoms and quality of life, that may impact the overall evaluation of new therapies. The successful incorporation of PROs into clinical trials requires adherence to key design and analysis principles. We present these principles and argue that adherence to these principles is vital to ensure valid interpretation of clinical trial findings, identify meaningful differences among investigational strategies, and better translate clinical trial results to diverse stakeholders.

Keywords: Patient-reported outcomes; Quality of life; Prostate cancer

Introduction

Cancer researchers have increasingly aimed to incorporate the patient's perspective in examinations of new treatments or interventions [1]. Central to this effort is the use of patient-reported outcomes (PROs), which are designed specifically to reflect the patient's experience with respect to disease, treatment symptoms, and quality of life (QOL), as well as treatment tolerability and toxicity. PROs augment clinical outcomes through more comprehensive assessment of symptoms and side effects associated with investigational therapies and provide alternative endpoints (such as QOL) that may impact the overall evaluation of new therapies. PROs correlate strongly with typical trial outcomes, such as adverse events, and have been found to be predictive of survival outcomes in certain settings [2]. PROs are used throughout the survivorship spectrum to describe the patient experience, from adjuvant treatment settings to palliative care [3–6].

Advances in cancer treatment over many decades have transformed a cancer diagnosis into a chronic disease for many patients [7]. As the number of cancer survivors increases, research has increasingly focused on patient survivorship. There were about 15 million cancer survivors in the United States in 2016, an estimate projected to climb to 26 million by 2040 [8]. Specific to prostate cancer care, prostate cancer survivors represent about 20% of the survivorship pool in the United States [9]. Prostate cancer trials may rely heavily on PROs as part of their designs, with trial interpretations increasingly determined by the PRO results that parallel clinical endpoints. In a recent review, metastatic castration-resistant prostate cancer (mCRPC) trials with PROs better determined treatment impact by identifying toxicity vs. cancer control tradeoffs and by providing a more comprehensive evaluation of new treatments [10].

QOL in prostate cancer

In localized prostate cancer care, the various treatments for primary management of the prostate cancer have been

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known to differentially impact patient-reported QOL [11,12], an important observation given the limited accuracy of physician report of patient QOL [13]. This has been validated in clinical trials such as ProtecT, in which patients were randomized to watchful waiting vs. intervention with radical prostatectomy or radiation therapy [14]. These studies consistently demonstrate unique patterns of QOL changes for each therapy, with greater impact of surgery on urinary continence and radiation therapy on storage urinary symptoms and bowel function.

Given the sizeable population of prostate cancer survivors and the importance of assessing QOL in prostate cancer, 4 PRO domains (physical and mental well-being, fatigue, and pain) have been identified as priorities for assessment by a National Cancer Institute (NCI) working group on the inclusion of PRO measures in prostate cancer clinical trials [15]. The European Expert Consensus Panel for the Management of Metastatic CRPC recommended that PROs (pain and QOL) were appropriate as secondary outcomes in phase III trials [16]. The Prostate Cancer Clinical Trials Working Group 3 recommended the use of patient-reported assessment of adverse events (PRO-CTCAE) developed by the NCI, with a particular emphasis on physical and functional well-being and pain [17,18].

The interpretations of several prostate cancer studies have been influenced by the examination of general and prostate cancer-specific QOL [19]. In their randomized, multicenter study comparing antiandrogen therapy with chemical castration for advanced prostate cancer patients, Chodak et al. [20] found that the antiandrogen therapy group exhibited better QOL scores through 6 months of treatment. Osoba et al. [21] found larger and longer-lasting improvements in QOL among mCRPC patients treated with mitoxantrone and prednisone. SWOG trial S9916 established docetaxel as providing superior survival outcomes for patients with mCRPC [22,23]. In SWOG S9916, patients completed the EORTC QLQ-C30 and the EORTC prostate cancer module (PR25) as well as the McGill Pain Questionnaire Short Form at study randomization, and again 10 weeks, 6 months, and 1 year later. Patients randomized to docetaxel had similar global QOL and pain scores as those randomized to mitoxantrone. Within the subdomain of the EORTC QLQ-C30 of nausea/vomiting, docetaxel patients exhibited a worsening of their symptoms compared with mitoxantrone patients in whom these symptoms subtly improved. Otherwise, the QOL instrument subdomains did not differ by treatment group. Thus, the survival advantage offered by docetaxel did not come at the expense of increased QOL burden.

PRO design principles

The inclusion of PROs in cancer trials can provide key insight into patients′ study experience, symptoms, and response to treatments. The successful incorporation of PROs into clinical trials requires adherence to several basic design

Table 1
Key design and analysis principles for studies using patient reported outcomes

Principle	Concerns	Strategies
Hypothesis-driven research questions	■ Indiscriminant use of PROs induce a higher burden of data collection and risk of false-positive findings.	■ Apply hypotheses regarding patient experience and treatment response to formulate research questions.
Validated instruments	■ Examination of QOL in clinical studies should accurately measure intended outcomes.	■ Use validated PRO instruments, translated into languages specific to the study population. ■ Avoid alterations to validated instruments.
Limited patient and site burden	■ Completion of PRO instruments could burden patients focused on treatment choice. ■ Administration of PRO instruments requires clinical resources.	■ Limit use of PROs to those supported by study hypotheses. ■ Parsimony of PRO selection will minimize time required to complete PROs.
Feasibility	■ Incorporation of PROs must not interfere with the clinical study. ■ Patient selection should not bias QOL studies.	■ Use simple eligibility criteria for QOL substudies. ■ Include all patients in QOL study unless it is a barrier to the clinical study.
Assessment design	■ QOL endpoints must be assessed for long enough to detect clinically meaningful effects. ■ Long follow-up increases risk of nonresponse and incomplete response.	■ Prespecify data collection schedules. ■ If feasible, align PRO assessment schedules with clinical follow-ups.
Statistical design	■ Analyses should be easy to interpret clinically. ■ Design should allow comparison of outcomes by study arm at specified times.	■ Select sample size to allow full power for comparisons by study arm. ■ Consider longitudinal analyses that compare QOL changes over time.
Missing data strategies	■ Missing data could occur owing to patient dropout and incomplete assessments. ■ If non-random, missing data can bias analyses.	■ Use electronic reminder systems to ensure timely and complete assessments. ■ Examine patterns in missing data. ■ Conduct sensitivity analyses if data are missing non-randomly.

principles. These principles are broadly characterized as: (1) the use of hypothesis-driven research questions, (2) use of validated PRO instruments, (3) the feasibility of PRO assessment in the context of the trial's main objective(s), (4) minimizing respondent burden on patients and sites, and (5) avoiding bias in the assessments of PRO outcomes (Table 1).

Hypothesis-driven research questions

The inclusion of PROs in clinical trials should be predicated on investigator's hypotheses regarding patient experiences and anticipated associations with the investigational therapies. This hypothesis-driven approach permits easier interpretation of clinical impact and provides a valuable patient perspective on the cancer treatment experience. In addition, by focusing only on pertinent QOL questions based on prior observations, the reliance on hypothesis-driven research questions limits the excessive use of PROs in trial settings, thereby reducing the possibility of false-positive findings and the burden of form completion for patients and data management for study sites.

Use of validated instruments

Descriptive and comparative examinations of QOL within a study setting must rely on validated instruments. The validation of a PRO is a stepwise process that assures that the instrument accurately measures what it is intended to measure, and measurably demonstrates attributes of validity, reliability, and responsiveness [1,24]. Translations into selected languages specified in eligibility must also be formally executed and responsive to the anticipated study population [25]. Validated instruments should not be altered as this may affect the survey validity. Similarly, extracting single questions from an instrument may subvert the validity of the construct being assessed.

Feasibility

The incorporation of PROs must be feasible within the constraints of a clinical trial. To facilitate feasibility, eligibility criteria for participation in the QOL portion of the study must be clear and limited. Generally, eligibility are limited to eligibility for the clinical study and the ability to complete PRO assessments in their native language with an available language-specific validated instrument. Ideally, all patients in the clinical trial are included in the QOL study to avoid selection bias. In certain instances—such as when QOL endpoints are not vital to the inference of the clinical endpoint—participation in a QOL substudy may be optional, to remove any potential hurdles to patient participation in the clinical study.

Limited patient and site burden

The completion of PRO instruments may be burdensome to patients [26]. However, the elucidation of the patient experience of clinical trial participation is invaluable in assessing the risks and benefits of study treatments, and the use of PROs is generally accepted by patients [27,28]. Thus, we recommend cognizance of respondent burden and limiting the use of PROs to those which inform study-specific hypotheses. Some recommend a threshold of time required for completion of PROs of 20 minutes for baseline assessments and 10 to 15 minutes for follow-up assessments [29]. This also benefits research team staff, who require adequate resources for the administration and collection of PRO data. Limiting PRO burden helps ensure maximal accrual through reduction in potential hurdles to patient enrollment and follow-up.

Assessment of PROs

The amount of follow-up required for assessment of QOL outcomes must balance the need to assess meaningful differences with the risk of increasing nonresponse. Importantly, PRO data collection should start at baseline. The duration of the primary QOL endpoint must be sufficient to detect clinically important changes in QOL domains. Yet, as follow-up duration increases, nonresponse increases, with potential impact on outcome inference, especially if nonresponse patterns differ by study arm [26,30]. Furthermore, long-term QOL assessments increase the burden to sites and patients and must be justifiable in the context of the study hypotheses. Thus the PRO assessment schedule must minimize overall dropout and differential dropout by study arm. This can be achieved, in part, by aligning PRO assessments with clinical follow-up visits. Such an alignment will also facilitate interpretation of possible relationships between PROs and clinical endpoints. Automated reminder notices and the use of electronic PRO and reminder systems can further minimize missing PRO data. PRO assessments should not be linked with clinical *outcome* status (such as disease progression) to avoid inducing an artifactual statistical dependence between clinical and QOL outcomes, leading to biased study interpretations.

These key design principles are related and induce either a virtuous or a negative cycle, depending on the study design. For instance, the use of hypothesis-driven research questions to provide the foundation for QOL study designs also limits patient burden and enhances feasibility. In contrast, QOL designs without a priori hypotheses may be cumbersome for researchers and burdensome for patients in a manner that is not compensated for by the return value of the research. The Fig illustrates the interwoven relationships among the key design principles outlined above.

PRO analysis principles

PRO design principles should be incorporated alongside key analysis principles to facilitate reliable and

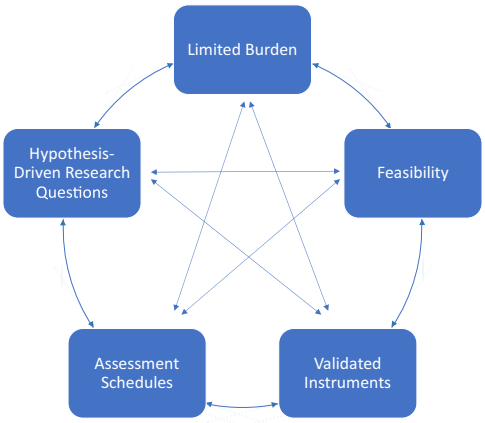

Fig. Key PRO and QOL design principles and their inter-relationships. (Color version of figure is available online.)

interpretable PRO results. Analysis principles pertain to the statistical design for testing PRO hypotheses and strategies for dealing with missing PRO data.

Statistical Design: PRO statistical designs typically aim to identify a minimally important difference (MID) between arms in a specified PRO instrument. MIDs for validated PRO instruments are available in the literature, and are usually derived from anchor-based (i.e., use of a reference point that is correlated with a QOL domain score) or distribution-based (i.e., use of the standard deviation of observed QOL domain scores) methods. If an MID has not been specified for an instrument, effect size estimates can be used instead. The effect size represents the ratio between the absolute difference in mean PRO scale scores by study arm and the standard deviation of that difference. Cohen has previously suggested that effect sizes can be categorized as small (0.2), medium (0.5), and large (0.8) [31]. Effect sizes from 1/3 to 1/2 a standard deviation are common [32].

MIDs or effect sizes should be assessed at selected follow-up times after trial registration (e.g., 6 mo). Power calculations account for the sample size, the MID, and the anticipated standard deviation at a given timepoint. Sample sizes should be large enough to allow comparisons by treatment arm with full power (i.e., >80%). Consistent with such a design, and to aid in interpretation, the main statistical method used for data analysis will often emphasize the difference by arm in specified PRO scale scores at a single assessment time, using linear or logistic regression approaches. However, multiple follow-up assessments are common, and longitudinal analyses should also be included where possible to examine changes in QOL over time between study arms. The use of longitudinal modeling with linear mixed models—with the patient participant as the random effect—can better account for the spectrum of assessments with increased power, although the potential for informative missing data by study arm to influence the interpretation may be increased [33,34]. In either case, covariate adjustment will account for any stratification factors used to balance the randomization assignment and —unless the change in QOL score between baseline and follow-up assessments is the primary endpoint—should also include the baseline PRO score. Other important demographic or clinical factors thought to be associated with the relationship between the intervention and the PRO, such as patient age, can be used in covariate adjustment, preferably prespecified in the protocol.

Missing data

Missing PRO data can occur owing to patient dropout as well as submission of incomplete PRO forms. Missing data will influence the interpretation of PRO data. The influence of missing data on the results can be reduced, though not wholly eliminated, if appropriately accounted for in the analysis.

To minimize the amount of missing data, a system of automated prospective reminder notifications to sites encouraging timely and complete submission of PRO forms will enable sites to better anticipate follow-up assessments and plan for communication with patients to facilitate data collection. Retrospective queries to sites for missing data are generally inadequate owing to the inevitability that patients will already have completed their clinic visit. The developing use of electronic PRO platforms, allowing patients to complete PROs on mobile devices or through web pages should enhance data collection long-term [35].

Even the best quality control practices will not prevent missing PRO data. Patterns of missing PRO data should be routinely monitored to detect potential problems. To identify whether missing data patterns are related to known prognostic factors for the study outcome, the relationship between intervention assignment and important baseline stratification variables between those with and without endpoint data can be examined using interaction tests to assess whether missing PRO data are potentially informative. Missing data patterns can also be analyzed using cohort plots [36]. Mean scores for different cohorts of patients are plotted based on the number of assessments they contributed; if, for instance, missingness depends on the variable itself at the time of dropout (i.e., worse scores at dropout are correlated with fewer assessments), then patterns of missing data are consistent with a nonignorable mechanism, or nonrandom missing data [37]. In this case, sensitivity analyses can be conducted using methods such as pattern mixture models, which enable modeling of the observed missing data patterns through covariate adjustment [38–40].

Example: The use of PROs in a metastatic prostate cancer trial

As an example of the PRO design and analysis principles described above, we present the QOL substudy of a SWOG trial comparing standard systemic therapy (SST) with SST plus definitive treatment of the primary tumor in metastatic

Table 2
Application of PRO design and analysis principles to SWOG trial 1802

Principle	Application to S1802
Hypothesis-driven research questions	■ PRO assessment and analysis designed to test hypothesis that patients treated with SST have worse urinary function and bother scores than those on SST plus definitive treatment.
Validated instruments	■ Expanded Prostate Cancer Index Composite-26 (EPIC-26) selected for use as QOL instrument.
Limited patient and site burden	■ PRO assessment schedule to occur alongside clinical follow-up. ■ Low burden of completing EPIC-26 (approximately 10 min).
Feasibility	■ Simple QOL substudy requirements • Eligibility for clinical study • Ability to complete forms in English or Spanish.
Assessment design	■ Pre-specified PRO assessment schedule comprised of baseline and 4 other time points (6 mo, and years 1, 2, and 3).
Statistical design	■ Choice of target score differences for urinary function (5 points) and bother (6 points) based on published MIDs. ■ Alpha (0.025) chosen to account for 2 comparisons in primary objective. ■ Sample size (1,000) allows comparisons by study arm with full power. ■ Use of linear mixed models to examine QOL changes over time.
Missing data strategies	■ Analyze patterns of patient dropout and missing information. ■ Perform sensitivity analysis in case of non-random missing data.

prostate cancer (SWOG S1802). As background, men with metastatic prostate cancer have extended expected survival time and may require substantial palliative care for local progression of the primary tumor. This necessitates the implementation of PROs in the studies of new therapeutic strategies for the management of metastatic prostate cancer. Our goal was to compare patient-reported urinary function and bother scores over time by treatment arm. Key design and analysis principles for the study are outlined in Table 2. We hypothesize that men randomized to SST will have worse urinary function and bother scores over time than men receiving SST and definitive treatment. The primary PRO questionnaire is the Expanded Prostate Cancer Index Composite-26 (EPIC-26), a validated instrument that measures urinary, sexual, and bowel symptoms in function and bother domains [41] and was selected by the International Consortium for Health Outcomes Measurement (ICHOM) as the preferred prostate cancer-specific QOL instrument for the assessment of men with localized and advanced prostate cancer [42]. The EPIC-26 is estimated to take 10 minutes to complete and will be administered at baseline and 4 additional follow-up timepoints through 3 years, limiting patient and site burden. Eligible patients for the QOL study must only be eligible for the clinical study, and be able to complete the EPIC-26 in English or Spanish. The assessment schedule is designed to limit the burden of data collection on sites and patients as well as to minimize missing data. The PRO assessments are scheduled to occur alongside clinical follow-ups, allowing the clinical assessments and PROs to be linked. The assessments are scheduled to occur at initial registration, at randomization (i.e., 6 mo after initial registration), and again 1, 2, and 3 years after randomization. Since the primary objectives are to test the difference in EPIC urinary function and bother scores by treatment arm, we set alpha to 0.025 to account for multiple comparisons. The target difference for urinary function scores is 5 points and for urinary bother scores is 6 points based on published MIDs [43]. Based on these parameters and 1,000-patient total planned accrual for the clinical study, we achieve full power for comparing urinary function (97%) and bother (90%) scores by treatment arm. The 12-month urinary function and bother scores will be analyzed using multiple linear regression with stratification factors and baseline PRO scores as covariates. In addition, linear mixed models will examine changes in QOL over time. Finally, the S1,802 statistical design will include analyses of dropout and missing data patterns to assess if data are missing at random, and will incorporate sensitivity analyses if data are systematically missing.

Conclusion

PROs that assess symptoms and QOL are critical to newly planned clinical trials. The value of PROs is recognized by the NCI through its support of QOL scientific committees, its promulgation of an electronic PRO platform, and its development of patient-reported toxicity ratings [35,44,45]. As even advanced cancer patients live longer, a patient-centered approach to evaluating investigational treatments with PROs has become increasingly important, to such an extent that a PRO extension for the CONSORT (Consolidated Standards of Reporting Trials) guidelines has been proposed to allow for a more comprehensive interpretation of PROs [46]. Adherence to key PRO design and analysis principles is therefore vital, in order to ensure valid interpretation of clinical trial findings, identify meaningful differences among investigational strategies, and better translate clinical trial results to diverse stakeholders.

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