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BMJ Research Methods and Reporting (RMR) Article:

Recommendations for Including or Reviewing Patient-Reported Outcome Endpoints in Grant Applications

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Standfirst: *Patient-reported outcomes (PROs) are increasingly included in research studies to provide the patient perspective. Grant applicants and grant reviewers require guidance on the key information that should be included in funding applications to demonstrate rigorous PRO methods. This paper provides prioritized practical recommendations from an international consortium of PRO experts to inform grant applicants in preparing their research strategies and grant reviewers in evaluating applications.*

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INTRODUCTION

Patients, clinicians, regulators, policy makers, and clinical guideline developers value information regarding the impact of disease and treatment from the perspective of patients. Thus, patient-reported outcome (PRO) assessments that collect this information are a critical aspect of research studies.[1-8] The PRO results from research studies can only be used if they are measured appropriately and reported clearly. However, a recent review of 160 international clinical trials with PRO endpoints showed that sub-optimal reporting was frequent, and over one-third failed to report the PRO findings at all.[9]

A number of methodologic tools to improve the design, analysis, reporting, and interpretation of PROs in research studies have been developed.[10-15] These tools were developed using rigorous methods, including engaging patients and other stakeholders, to provide guidance on designing the PRO aspects of research studies, collecting and analyzing the PRO data, and interpreting and reporting the PRO findings. The PROTEUS Consortium (Patient-Reported Outcomes Tools: Engaging Users & Stakeholders) was formed to optimize the use of PROs in research studies and clinical practice, in part by promoting the use of these and other PRO resources.[16] It builds on the work of other initiatives, such as those to develop core outcome sets[17] and PRO measure selection.[18] A June 2019 PROTEUS Consortium meeting (Baltimore, MD), including both grant applicants and funders, identified publication of recommendations regarding the key PRO elements that should be included in grant applications as an important strategic initiative.

Four general methodologic areas require consideration specifically for the PRO components of proposed research studies: (1) rationale, (2) study procedures, (3) PRO measure selection, and (4) analytic approach. Detailed guidance regarding these PRO methods are available from the PRO resources described above. Specifically, the 2013 Standard Protocol Items:

Recommendations for Interventional Trials (SPIRIT) guidance identified the minimum elements required in clinical trial protocols, generally;[19] the SPIRIT-PRO extension provides specific recommendations for PRO aspects of clinical trials, including the rationale and study procedures.[10] The International Society for Quality of Life Research (ISOQOL) published minimum standards for PRO measures for use in patient-centered and comparative effectiveness research,[11] consistent with other guidance documents.[18] The Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints Data (SISAQOL) Consortium has made preliminary recommendations on analytic approaches, with further work in progress.[12] The recommendations in each of these documents were developed using rigorous, stakeholder-engaged, formal consensus development processes. However, given the space constraints in most grant applications, it is not possible to include all the recommended information from these three documents. The PROTEUS Consortium recommended identifying the key information to include in grant applications to demonstrate and evaluate the preparedness of investigators to conduct the PRO aspects of the study rigorously, and to ensure that adequate resources have been budgeted. By ensuring preparedness at the grant application phase, the hope is that investigators will be more likely to conduct the study successfully and report the PRO findings effectively.

The aim of this project was to identify the key information from existing guidelines that should be included in grant applications to ensure rigorous methods for assessing the patient's perspective using PROs. The authors, a subgroup of Consortium members, volunteered to develop these recommendations on behalf of the Consortium.

METHODS

A full description of the four-step informal consensus development process the multidisciplinary author team used to develop the recommendations can be found in the Technical Appendix.

[illegible] cover a range of career and disciplinary backgrounds. In addition, multiple authors were involved in developing the SPIRIT-PRO extension (MB, MC, DK, MK), and the ISOQOL Minimum Standards for selecting a PRO measure for use in research studies (CS, MB), and the SISAQOL analysis guidance (MC, MK); ED serves as the senior scientific director for a major funding organization. Example text was developed to illustrate how the relevant information for the final recommendations could be included in the grant application.

Briefly, first, we identified 40 items (37 from SPIRIT-PRO, 3 from SISAQOL) to be considered for recommendation. Second, the candidate items were rated by each of the authors using a four-point scale: (1) always include—assume there is only enough space in the grant application for one paragraph worth of content related to PROs (though this content might be described throughout the grant application); (2) always include when PRO is primary endpoint or if a second paragraph of PRO content can be included in the grant application (though this content might be described throughout the grant application); (3) helpful information if space allows; or (4) not necessary even if space allows. Third, the candidate recommendations were ranked based on average rating (for discussion purposes only -- not to be stand-alone determinants of the recommendations), and a document that provided example text to demonstrate how each item in the first two categories (i.e., always include, always include if primary endpoint or a second paragraph of PRO content can be included) could be addressed when writing the grant application. Fourth, the author team reviewed the preliminary categorizations based on the rating exercise and discussed possible changes to the item categorization and refinements to the example text. The final paper was circulated to the PROTEUS Consortium members prior to submission.

Identifying Candidate Recommendations

In the first step, an Excel spreadsheet was developed with the rows reflecting each item from SPIRIT-PRO. If the SPIRIT-PRO recommendation included multiple concepts, the recommendation was divided so that each concept could be addressed individually. For example, the SPIRIT-PRO item "Describe the PRO-specific research question and rationale for PRO assessment and summarize PRO findings in relevant studies" became three items: (a) PRO-specific research question, (b) rationale for PRO assessment, and (c) summary of PRO findings in relevant studies. There were 37 SPIRIT-PRO items included for consideration.

The ISOQOL Minimum Standards and SISAQOL recommendations are, in general, detailed elaborations on some of the items from SPIRIT-PRO related to measure selection and analysis, respectively. For example, the ISOQOL Minimum Standards items provide significantly more detail regarding four items from SPIRIT-PRO addressing justification of the PRO instrument selected; description of the PRO instrument's domains, number of items, recall period, and scaling and scoring; evidence of the PRO instrument's measurement properties; and evidence of the PRO instrument's interpretation guidelines.

The raters (i.e., the paper authors) were instructed to (a) identify any of the 37 SPIRIT-PRO items that they did not think should be considered for inclusion in grant applications and (b) identify any items from the ISOQOL Minimum Standards items or SISAQOL recommendations that should be added for consideration. For an item to be deleted from consideration, all authors had to agree that the item should not be considered. Any item that at least one author thought should be added for consideration was included.

Rating Candidate Recommendations

In step two, the candidate items were rated by each of the authors using a four-point scale: (1) always include – assume there is only enough space in the grant application for one paragraph

worth of content related to PROs (though this content might be described throughout the grant application); (2) always include when PRO is primary endpoint or if a second paragraph of PRO content can be included in the grant application (though this content might be described throughout the grant application); (3) helpful information if space allows; or (4) not necessary even if space allows. The rating categories explicitly included the amount of space available, as grant applications frequently have strict limitations regarding length, and space is at a premium. Raters also had the opportunity to include comments elaborating on their ratings.

Ranking Candidate Recommendations

In the third step, the candidate recommendations were ranked based on the compiled ratings. Specifically, an Excel workbook was developed and circulated to the authors with three spreadsheets: (a) all authors' individual ratings (de-identified); (b) collation of all comments submitted with an item's rating; and (c) a list of the candidate items ranked by average rating from more to less important. To inform the deliberations further, a Word document was included and provided example text to demonstrate how each item in the first two categories (i.e., always include, always include if primary endpoint or more space is available) could be addressed when writing the grant application. Notably, the quantitative ratings were generated for discussion purposes only and were not intended to be stand-alone determinants of the recommendations.

Refining the Recommendations

As a final step, a video conference was held during which the author team reviewed the preliminary categorizations based on the rating exercise; members who could not attend the video conference could provide their feedback via email. In addition to viewing the rankings of the candidate items by the mean rating, the author team also viewed the rankings based on the median rating. During the discussion, authors had the opportunity to recommend that the

~~categorization of any item be changed. Refinements to the example text were also discussed during the video conference.~~

~~The final paper was circulated to the PROTEUS Consortium members prior to submission.~~

RESULTS

~~[redacted]~~ presented in the Technical Appendix. The final recommendations for information to "always include" or "include if the PRO is a primary endpoint or if a second paragraph of PRO content can be included~~additional space is available~~" are presented in Tables 1~~2~~ and 2~~3~~, respectively, along with example text. ~~The headings have been slightly modified from the categories used in the rating exercise to avoid the use of the word "paragraph," given that the PRO information might not all be reported in the same section.~~

~~The Word document with example text for each of the recommendations was organized by section of the grant, and there was some minimal editing and combining of the items involved in moving from the Excel spreadsheet rankings to the text version. For example, "Justify the PRO instrument to be used" and "Evidence of PRO instrument patient acceptability and burden should be provided or cited, if available, ideally in the population of interest" were combined into "Justify the PRO instrument selected and provide or cite evidence of PRO instrument measurement properties and patient acceptability/burden, ideally in the population of interest." Also, it was considered inconsistent to recommend that between-group comparison objectives always be included where relevant but within-group comparison objectives only when space allows; these recommendations, as well as the recommendation to specify the timepoint of interest, were thus combined under "always include." During the discussion, the author team made further refinements to the example text to clarify how to address the recommendations, in~~

~~some cases giving different examples based on the study design (e.g., in cases where the PRO data will or will not be monitored to inform clinical care).~~

The specific results from the first three steps of the recommendation-development process are presented in the Technical Appendix. The final recommendations for information to "always include" or "include if the PRO is a primary endpoint or if a second paragraph of PRO content can be included~~additional space is available~~" are presented in Tables 1~~2~~ and 2~~3~~, respectively, along with example text. ~~The headings have been slightly modified from the categories used in the rating exercise to avoid the use of the word "paragraph," given that the PRO information might not all be reported in the same section.~~

Based on the refinements and the combination of some items, there are now 6 topics that should always be covered: rationale, research question, outcomes of interest, timepoints for assessment, data collection plan, and analysis methods (Table 1~~2~~). An additional 10 topics should be addressed if the PRO is a primary endpoint or if additional space is available (Table 2~~3~~). These topics provide more detail regarding the PRO study's background and rationale, data collection and management, and analysis. The 15 PRO topics that may also be helpful to include in grant applications if space allows are listed in Table 3~~4~~.

DISCUSSION

This Research Methods and Reporting article provides recommendations aimed at both grant writers and grant reviewers (including researchers and patient-partners) regarding the PRO information that should be included in grant applications. As the assessment of PROs becomes more common, in part due to the increasing emphasis on patient-centered research, it is critical for grant applicants to be able to demonstrate, and for grant reviewers to be able to evaluate, the knowledge of the study team and their ability to undertake scientifically rigorous PRO

research. At the same time, recommendations need to be cognizant of the strict space constraints common in grant applications. Using guidance documents that had been developed through rigorous, stakeholder-engaged methods as the basis, we identified the key topics for inclusion in grant applications. This prioritization exercise was required because space constraints for many grant applications would not allow coverage of, for example, all of the information recommended by SPIRIT-PRO. Therefore, our goal was to identify the subset of existing recommendations relevant for grant applications using a multi-step approach. The cut-offs in categorizing the items were somewhat arbitrary and qualitative review of the recommendations informed the final decisions. To provide additional practical guidance, we also included example text demonstrating how each of the recommended topics could be addressed in a grant application.

It is important to note, however, that this paper is not a guide for how to design a PRO study. For example, the illustrative text for dealing with multiplicity in Table 2, Point 10, describes selecting a single PRO domain for hypothesis testing. Other approaches for addressing this issue would be to adjust the p-values to take account of multiple testing and retain a nominal overall p-value or to de-emphasize reporting p-values in favor of reporting confidence intervals. As another example, per Table 1, Point 4~~based on the recommendations in this paper~~, the timepoints for PRO assessment should always be addressed in grant applications, and "At baseline and every 6 weeks (maximum 6 cycles), to be done prior to the clinical assessment" is an example of how to describe the timepoints. However, the process for determining which are the most informative timepoints for a specific study (e.g. consulting with clinical experts, patient partners, and trials units) is not described here. Further, more detail regarding the timepoints for PRO assessment should be included in the study protocol, in accordance with SPIRIT-PRO with, for example, a table. The same applies for many of the other recommendations, which would require more detail in the study protocol and/or statistical analysis plan, which typically do

not have space constraints. Sufficient PRO expertise within the study team is required to implement these recommendations in practice.

The recommendations reported here are primarily directed at grant applicants and grant reviewers, and we would refer individuals to the foundational ISOQOL Minimum Standards,[11] SPIRIT-PRO,[10] and SISAQOL[12] guidance for other contexts. There are also guidance documents for how to report the results of PRO research studies[13,14] and for how clinicians should evaluate the PRO literature.[15] Following the above recommendations at the formative, grant application phase positions a research team to successfully report their results meaningfully at the completion of the study. It is also important to note that many of the recommendations included here are not specific to PROs and would apply to many other research study endpoints. By "beginning with the end in mind," these recommendations are intended to help both grant applicants and grant reviewers ensure the rigor and relevance of PRO research studies.

CONTRIBUTORS AND SOURCES

Dr. Snyder led the recommendation development process described here and serves as the guarantor of the article. She is a PhD outcomes and health services researcher with extensive experience in the use of PROs and is the Principal Investigator of the PROTEUS Consortium. Dr. Brundage is the PROTEUS Consortium co-Principal Investigator and partnered with Dr. Snyder in leading this project. He is a practicing radiation oncologist and senior clinical trialist. The PROTEUS Consortium recommended development of this grant writing guidance. All authors participated in the recommendation development process as described above and reviewed and approved the final version of the manuscript. They include clinicians, researchers, grant applicants, and grant reviewers with expertise in PROs, clinical trials, or both.

The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

KEY MESSAGES

- With the increasing emphasis on patient-centered research and the associated increased use of patient-reported outcomes (PROs) in research studies, guidance is needed for how grant applicants can demonstrate, and how grant reviewers can evaluate, the knowledge of the research team and their ability to conduct high-quality PRO research.
- Based on existing international guidelines that were developed using rigorous, stakeholder-engaged, formal consensus development processes, we developed practical recommendations for the information regarding PROs that should be included in grant applications, along with example text to demonstrate how to address each recommendation.
- The recommendations are sensitive to the space constraints of grant applications and prioritize (1) information that should always be included, (2) information to add when a PRO is the primary endpoint or when space allows, and (3) information that is helpful to include when space is not an issue.

CONFLICT OF INTEREST DISCLOSURES

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REFERENCES

1. U.S. Food and Drug Administration. Guidance for Industry. Patient Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. *Federal Register* 2009;74(35):65132-3.
2. Acquadro C, Berzon R, Dubois D, Leidy NK, Marquis P, Revicki D, Rothman M. Incorporating the patient's perspective into drug development and communication: an ad hoc task force report of the Patient-Reported Outcomes (PRO) Harmonization Group meeting at the Food and Drug Administration, February 16, 2001. *Value Health* 2003;6:522-531.
3. Au H-J, Ringash J, Brundage M, Palmer M, Richardson H, Meyer RM, NCIC CTG Quality of Life Committee. Added value of health-related quality of life measurement in cancer clinical trials: the experience of the NCIC CTG. *Expert Rev Pharmacoecon Outcomes Res* 2010;10(2):119-128.
4. Till JE, Osoba D, Pater JL, Young JR. Research on health-related quality of life: dissemination into practical applications. *Qual Life Res* 1994;3(4):279-283.
5. Lipscomb J, Gotay CC, Snyder C (Eds). Outcomes Assessment in Cancer: Measures, Methods, and Applications. Cambridge: Cambridge University Press, 2005.
6. Brundage M, Bass B, Ringash J, Foley K. A knowledge translation challenge: clinical use of quality of life data from cancer clinical trials. *Qual Life Res* 2011;20:979-985.
7. Bezjak A, Ng P, Skeel R, Depetrillo AD, Comis R, Taylor KM. Oncologists' use of quality of life information: results of a survey of Eastern Cooperative Oncology Group physicians. *Qual Life Res* 2001;10:1-13.
8. Kluetz PG, O'Connor DJ, Soltys K. Incorporating the patient experience into regulatory decision making in the USA, Europe, and Canada. *Lancet Oncol* 2018;19(5):e267-e274.
9. Kyte D, Retzer A, Ahmed K, Keeley T, Armes J, Brown JM, Calman L, Gavin A, Glaser AW, Greenfield DM, Lanceley A, Taylor RM, Velikova G, Brundage M, Efficace F, Mercieca-

Bebber R, King MT, Turner G, Calvert M. Systematic evaluation of patient-reported outcome protocol content and reporting in cancer trials. *J Natl Canc Inst* 2019;111:1170–1178

10. Calvert M, Kyte D, Mercieca-Bebber R, Slade A, Chan A-W, King MT; the SPIRIT-PRO Group. Guidelines for inclusion of patient-reported outcomes in clinical trial protocols: The SPIRIT-PRO Extension. *JAMA* 2018;319:483-494.
11. Reeve BB, Wyrwich KW, Wu AW, Velikova G, Terwee CB, Snyder CF, Schwartz C, Revicki D, Moinpour CM, McLeod LD, Lyons JC, Lenderking WR, Hinds PS, Hays RD, Greenhalgh J, Gerson R, Feeny D, Fayers PM, Cella D, Brundage M, Ahmed S, Aaronson NK, Butt Z. ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research. *Qual Life Res* 2013;22:1889-1905.
12. Coens C, Pe M, Dueck AC, Sloan J, Basch E, Calvert M, Campbell A, Cleeland C, Cocks K, Collette L, Devlin N, Dorme L, Flechtner HH, Gotay C, Griebsch I, Groenvold M, King M, Kluetz PG, Koller M, Malone DC, Martinelli F, Mitchell SA, Musoro J, O'Connor D, Oliver K, Piault-Louis E, Piccart M, Quinten C, Reijneveld JC, Schürmann C, Smith AW, Soltys KM, Taphoorn M, Velikova G, Bottomley A. International standards for the analysis of quality of life and patient reported outcomes endpoints in cancer randomised controlled trials: recommendations based on critical reviews of the literature and international multi-expert, multi-stakeholder collaborative process. *Lancet Oncol* 2020;21:e83-96.
13. Calvert M, Blazeby J, Altman DG, Revicki DA, Moher D, Brundage MD, CONSORT PRO Group. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. *JAMA* 2013;309:814-822.
14. Snyder C, Smith K, Holzner B, Rivera YM, Bantug E, Brundage M; PRO Data Presentation Delphi Panel. Making a picture worth a thousand numbers: recommendations for graphically displaying patient-reported outcomes data. *Qual Life Res* 2019;28:345-56.

15. Wu AW, Bradford AN, Velanovich V, Sprangers MAG, Brundage M, Snyder C. Clinician's checklist for reading and using an article about patient-reported outcomes. *Mayo Clin Proc* 2014;89:653-661.
16. The PROTEUS Consortium. Available at: www.TheProteusConsortium.org.
17. COMET Initiative. Core Outcome Measures in Effectiveness Trials. Available at: https://comet-initiative.org/.
18. Crossnohere NL, Brundage M, Calvert MJ, King M, Reeve BB, Thorner E, Wu AW, Snyder C. International guidance on the selection of patient-reported outcome measures in clinical trials: a review. *Qual Life Res* 2020 14 Sept [Epub ahead of print].
19. Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200-207.

Table 1: Candidate recommendations, ranked by mean rating, also showing median rating

ITEM	MEAN	MEDIAN
Preliminarily Ranked: Always include		
Describe the PRO-specific research question.	1.1	1
State PRO analysis methods.	1.1	1
Specify the PRO concepts/domains used to evaluate the intervention (eg, overall health-related quality of life, specific domain, specific symptom).	1.3	1
Include a schedule of PRO assessments.	1.3	1
Describe the rationale for PRO assessment.	1.4	1
Preliminarily Ranked: Include If PRO is primary endpoint or more space is available		
When a PRO is the primary end point, state the required sample size (and how it was determined) and recruitment target (accounting for expected loss to follow-up).	1.7	2
Include a data collection plan outlining the permitted mode(s) of administration (eg, paper, telephone, electronic, other) and setting (eg, clinic, home other).	1.7	1
Summarize PRO findings in relevant studies.	1.8	2
State specific PRO objectives or hypotheses (including relevant PRO concepts/domains).	1.8	2
Clearly state the broad PRO research objectives for each PRO domain or item of interest: Treatment efficacy or clinical benefit; Exploratory or describe patient perspective	1.9	2
Clearly state the between-treatment group comparison that will be used for each PRO domain or item of interest: Superiority; Equivalence or non-inferiority	1.9	2
Evidence of PRO instrument measurement properties should be provided or cited, if available, ideally in the population of interest.	1.9	2
Specify whether more than 1 language version will be used.	1.9	2
Include PRO analysis plans for addressing multiplicity/type 1 (α) error.	1.9	2
Specify PRO data collection and management strategies to minimize missing data.	2.0	2
When the trial context requires someone other than a trial participant to answer on his or her behalf (a proxy-reported outcome), state and justify the use of a proxy respondent.	2.0	2
If PROs will not be collected from the entire study sample, provide a rationale and describe the method for obtaining the PRO subsample.	2.1	2
For each specified PRO concept/domain used to evaluate the intervention, specify the analyis metric (eg, change from baseline, final value, time to event) and the principal time point or period of interest.	2.1	2
Justify the PRO instrument to be used.	2.1	2
Outline the methods for handling missing items or entire assessments (eg., approach to imputation and sensitivity analyses).	2.1	2
Specify any PRO-specific eligibility criteria (eg, language/reading requirements or prerandomization completion of PRO).	2.2	2
Evidence of PRO instrument patient acceptability and burden should be provided or cited, if available, ideally in the population of interest.	2.2	2
State whether or not PRO data will be monitored during the study to inform the clinical care of individual trial participants.	2.2	2

Table 1 (cont.): Candidate recommendations, ranked by mean rating, also showing median rating

ITEM	MEAN	MEDIAN
Preliminarily Ranked: Helpful if space allows		
Describe PRO instrument's domains, number of items, recall period, and scaling and scoring (eg, range and direction of scores indicating good or poor outcome).	2.3	2
Evidence of PRO instrument interpretation guidelines should be provided or cited, if available, ideally in the population of interest.	2.4	3
State how missing data will be described.	2.4	2
Clearly state the within-patient or within-treatment group PRO objective. Valid within-individual or within-group PRO objectives include the following: • Improvement (Time to improvement, Magnitude of improvement at time t, Proportion of responders with improvement at time t); • Worsening (Time to worsening; Magnitude of worsening at time t; Proportion of responders with worsening at time t); • Stable state (Time to [end of] stable state; Proportion of responders with stable state at time t); • Overall effects (Overall PRO score over time; Response patterns or profiles)	2.6	3
Specify the individual(s) responsible for the PRO content of the protocol.	2.7	2
Provide a rationale for the PRO assessment time points.	2.7	3
If sample size is not established based on the PRO end point, then discuss the power of the principal PRO analyses.	2.7	3
State whether the measure will be used in accordance with any user manual and specify and justify deviations if planned.	2.7	3
Provide or cite evidence of the validity of proxy assessment if available.	2.7	3
Justify if the initial PRO assessment is not prerandomization.	2.8	3
If PRO data will be monitored to inform clinical care, how this will be managed in a standardized way.	2.8	3
Describe how PRO data monitoring for clinical care will be explained to participants; eg, in the participant information sheet and consent form.	2.9	3
Specify time windows for PRO assessment.	3.0	3
State whether translated versions have been developed using currently recommended methods.	3.0	3
Describe the process of PRO assessment for participants who discontinue or deviate from the assigned intervention protocol.	3.1	3
Specify whether PRO collection is prior to clinical assessments.	3.2	3
If using multiple questionnaires, specify whether order of administration will be standardized.	3.2	3

Table 12: Topics that should always be covered, with example text for each *

1. Describe the rationale for PRO assessment.

It is anticipated that the majority of patients in this trial will have asymptomatic metastatic disease (detected by a rise in prostate-specific antigen [PSA] or routine imaging). As such, the quality-of-life (QOL) outcomes for each treatment will be secondary outcomes reflective of the negative impact on QOL for either Treatment A or Treatment B, and the trial findings can be placed in context of the disease-related outcome benefits. The results will be used for … (examples: inform clinical practice guidelines, health technology assessment, regulatory application, describe treatment impact).

2. State the PRO-specific research question(s).

The objective of the QOL sub-study is to compare health-related QOL for four specific domains in men treated with Treatment A versus Treatment B in the post Androgen Receptor (AR)-targeted therapy setting.

3. Specify the PRO concepts/domains used to evaluate the research question(s) (e.g., overall health-related quality of life, specific domain, specific symptom), and the PRO questionnaire(s) selected to assess them.

QOL will be assessed with the Functional Assessment of Cancer Therapy-Prostate (FACT-P)[ref], which consists of the FACT-G (general), a 27-item self-report questionnaire that measures general QOL in cancer patients, and a 12-item prostate cancer-specific subscale. The primary QOL outcome is the FACT-P Treatment Outcome Index (TOI), which combines the physical and functional wellbeing items of the FACT-G with the 12 prostate-specific items. The null hypothesis is that Treatment A will have no negative impact on QOL compared to Treatment B for the treatment outcome index derived score.

4. Describe the timepoints for PRO assessment.

At baseline and every 6 weeks (maximum 6 cycles), to be done prior to the clinical assessment.

5. Include a data collection plan outlining the permitted mode(s) of administration (e.g., paper, telephone, electronic, other) and setting (e.g., clinic, home, other).

Data will be collected at clinic visits using paper records completed in the clinic prior to the clinic visit.

6. State the PRO analysis method(s), in relation to the objective(s). State the broad PRO objectives, specifying if they are exploratory/descriptive or aim to evaluate treatment efficacy/clinical benefit. If the latter, state specific hypotheses (including relevant PRO concepts/domains) and include whether the between-treatment group comparison tests for superiority, equivalence, or non-inferiority. If the broad PRO objectives include within-patient or within-treatment group comparisons, clearly state the assumption (i.e., improvement, worsening, stable state, overall effect), the specific objective (e.g. proportion of responders, time to PRO-event, magnitude of improvement/worsening), and the principal timepoint of interest.

The overall objective is to compare mean FACT-P Treatment Outcome Index scores between groups. The primary analyses will use GLM regression to test the hypothesis that TOI scores are, on average, higher in patients receiving the intervention compared to standard of care over the duration of the study (24 weeks). The FACT-P sub-scales will also be calculated and compared between arms in exploratory analyses. To determine clinical significance of any

observed TOI differences between arms, a 7-point change will be considered clinically meaningful [ref]. Also as an exploratory analysis, the proportion of patients improved at 12 weeks will be calculated (i.e. individual TOI score improved compared to baseline by 7 points [ref] or more) and compared between arms using unadjusted Chi-squared comparisons.

*This content might be included in a dedicated section or may be described throughout the grant application.

Table 2~~3~~: Topics that should be included if a PRO is a primary endpoint or if a second paragraph of PRO content can be included, ~~additional PRO content can be included in the grant application,~~ with example text for each*

Background & Rationale for PRO Assessment

1. Summarize PRO findings in relevant studies.

The quality of life associated with various treatments in metastatic castrate resistant prostate cancer (mCRPC) in patients undergoing therapy such as docetaxel, abiraterone and enzalutamide has previously been described (refs). However, the quality of life in patients receiving Treatment A has not been well studied or described. Treatment B has been shown to impact on patients' quality of life in a number of domains (physical functioning, emotional functioning, and specific symptoms such as fatigue, gastrointestinal and other systems) [refs].

Data Collection and Management

2. Justify the PRO instrument selected and provide or cite evidence of PRO instrument measurement properties and patient acceptability/burden, ideally in the population of interest.

The FACT-P was chosen because Treatment B has been shown to impact a number of QOL domains including physical functioning, emotional functioning, and numerous specific symptoms, and the FACT-P is validated and has been used successfully in multiple studies in this patient population [ref].

3. If PROs will not be collected from the entire study sample, provide a rationale and describe the PRO-specific eligibility criteria (e.g., PRO substudy, language/reading requirements or pre-randomization completion of PRO).

The sample size for the primary trial endpoint is 780 patients. Since this sample size would result in an over-powered PRO analysis, only the first xxx patients enrolled will participate in the PRO substudy.

4. When the study context requires someone other than a study participant to answer on his or her behalf (a proxy-reported outcome), state and justify the use of a proxy respondent.

In general, proxy assessments are discouraged; however, there may be circumstances where proxy reporting is necessary. If proxies are going to be used and the PRO measure has been validated for proxy assessment: *The use of proxy reports is discouraged; however, proxies may be used for study participants who are cognitively impaired and unable to complete the assessment themselves. To be eligible to provide proxy data about a participant, the proxy must live with the participant, be willing to provide data at scheduled assessments, and have sufficient proficiency in English.*

5. Specify PRO data collection and management strategies to minimize missing data.

To minimize missing data, we will train staff regarding procedures for collecting PROs before clinical assessment, checking the completed forms for missing items, and submitting the data. A written manual will be provided for reference. Compliance rates (proportion of submitted forms of those expected) will be monitored in real-time, allowing for mitigation if compliance falls below that expected in specific participating centers.

6. State whether PRO data will be monitored during the study to inform the clinical care of individual study participants.

If the data will not be monitored: *To maintain blinding, patients' clinicians will not have access to the PRO data to inform clinical care.*

If the data will be monitored: *The research team will review completed PRO questionnaires. If, through this review, the research team becomes concerned for the wellbeing of the participant, they will discuss these concerns with the participant directly and may also consult with the PI and/or treating clinician if the concerns involve the patient's safety.*

Analysis

7. When a PRO is the primary end point, state the required sample size (and how it was determined) and recruitment target (accounting for expected loss to follow-up).

If the PRO had been a primary endpoint, text such as the following could have been included: *A sample size of xxx will provide 90% power to test the hypothesis that mean TOI scores are at least 7-points greater for patients randomized to Treatment B compared to Treatment A with a significance level of 5% based on an assumed SD of xx in this patient population. Seven points is considered clinically meaningful [ref]. The PRO sample size will be adjusted upwards to allow for a 15% non-compliance rate, resulting in a final sample size of yyy patients (yyy/2 in each arm).*

8. Outline the methods for handling missing items or entire assessments (e.g., approach to imputation and sensitivity analyses).

Compliance (received vs expected forms with appropriate windows) will be described. GLM regression…will, in part, account for missing data. If missing data exceeds 10% of expected measures, sensitivity analyses will be conducted.

9. Specify whether more than 1 language version will be used.

All validated languages of the FACT-P will be used.

10. Include PRO analysis plans for addressing multiplicity/type 1 (α) error.

Because we have identified a single PRO domain, the TOI, for our primary analysis comparing Treatment A and Treatment B, there is no need to adjust the alpha, and P<.05 will be used~~; for our primary analysis; all other~~ p-values for all other domains will be descriptive.

*This content is in addition to the content described in Table 1~~2~~. It might be included in a dedicated section or may be described throughout the grant application.

Table 34: Helpful information if space allows

Background and Rationale for PRO Assessment

- Describe PRO instrument's domains, number of items, recall period, and scaling and scoring (e.g., range and direction of scores indicating good or poor outcome).
- Evidence of PRO instrument interpretation guidelines should be provided or cited, if available, ideally in the population of interest.
- Specify the individual(s) responsible for the PRO content of the protocol.
- State whether the measure will be used in accordance with any user manual and specify and justify deviations if planned.
- Provide or cite evidence of the validity of proxy assessment, if available and relevant.

Data Collection and Management

- Justify if the initial PRO assessment is not pre-randomization, where applicable.
- Specify whether PRO collection is prior to clinical assessments.
- If using multiple questionnaires, specify whether order of administration will be standardized.
- Provide a rationale for the PRO assessment time points and specify time windows for PRO assessment.
- State whether translated versions have been developed using currently recommended methods.
- Describe the process of PRO assessment for participants who discontinue or deviate from the assigned intervention protocol, where applicable.
- If PRO data will be monitored to inform clinical care, how this will be managed in a standardized way.
- Describe how PRO data monitoring for clinical care will be explained to participants; e.g., in the participant information sheet and consent form.

Analysis

- If sample size is not established based on the PRO end point, then discuss the power of the principal PRO analyses.
- State how missing data will be described.