SPIRIT-PRO

PROtocol Template

About this PROtocol Template

Patient-reported outcome (PRO) data from clinical trials can provide valuable evidence to inform shared decision making, labeling claims, clinical guidelines, and health policy; however, the PRO content of clinical trial protocols is often suboptimal.

To address this issue an international, consensus-based, PRO-specific protocol guidance (the SPIRIT-PRO Extension) was developed and published in 2018:

> Calvert M, Kyte D, Mercieca-Bebber R, et al. Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols: The SPIRIT-PRO Extension. *JAMA.* 2018;319(5):483–494. doi:https://doi.org/10.1001/jama.2017.21903

This PROtocol template aims to promote implementation and use of the SPIRIT-PRO Extension for trials where PROs are a primary or key secondary outcome; however content is also recommended for use where PROs are exploratory outcomes. This PROtocol template was designed as a stand-alone document which may be incorporated into any clinical trial protocol. When using this addendum please cite as:

Journal to add E&E paper reference please

Nothing in this template should be construed to represent or warrant that persons using this template have complied with all applicable laws and regulations. All individuals and organizations using this template have the responsibility for complying with the applicable laws and regulations or regulatory requirements for the relevant jurisdiction.

We recommend integration of key SPIRIT-PRO information within relevant sections of the protocol (e.g., rationale, schedule of assessments, objectives, endpoints, and statistical analysis). Additional notes from the SPIRIT-PRO group and the industry advisory group (IAG) have also been provided where necessary.

In addition we recommend a separate PRO specific section of the protocol which provides further background information, justification for selection of measures, details on psychometric properties of measures and data collection procedures. The protocol template aims to serve as a guide and sections can be moved to best fit with existing trial templates, however we recommend the use of the SPIRIT-PRO checklist to ensure all content has been covered (Page 18). Efforts should be made by protocol writers to avoid unnecessary repetition of content.

Protocol writers can confirm that they have successfully adhered to the SPIRIT-PRO guideline using the checklist available here:
https://jamanetwork.com/journals/jama/article-abstract/2671472

Protocol writers are encouraged to read and consider other relevant resources which are beyond the scope of the SPIRIT-PRO Extension as detailed below:

References and useful resources:

Evidence-based recommendations for the minimum content of a clinical trial protocol

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.

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.

Enhancing the Quality and Transparency Of health Research (EQUATOR) Network: https://www.equator-network.org/

Estimands

FDA-ASCO Public Workshop: 2019 Clinical Outcome Assessments in Cancer Clinical Trials Fourth Annual Workshop. King-Kallimanis, B. Systematically defining research objectives and framing questions using the estimand framework. https://www.fda.gov/drugs/news-events-human-drugs/fda-asco-public-workshop-2019-clinical-outcome-assessments-cancer-clinical-trials-fourth-annual [accessed 19/12/19]

E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). October 2017. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM582738.pdf

Akacha M, Bretz F, Ruberg S. Estimands in clinical trials - broadening the perspective. Stat Med. 2017;36(1):5-19.

Akacha M, Bretz F, Ohlssen D, Rosenkranz G, Schmidli H. Estimands and Their Role in Clinical Trials. Statistics in Biopharmaceutical Research. 2017;9(3):268-71.

Permutt T. A taxonomy of estimands for regulatory clinical trials with discontinuations. Statistics in Medicine. 2016;35(17):2865-75.

Bell ML, Floden L, Rabe BA, Hudgens S, Dhillon HM, Bray VJ, Vardy JL. Analytical approaches and estimands to take account of missing patient-reported data in longitudinal studies. *Patient Relat Outcome Meas*. 2019;10:129–140. Published 2019 Apr 16. doi:10.2147/PROM.S178963

Patient Reported adverse events

If the trial is assessing patient reported adverse event and symptom monitoring consider how this links to adverse reporting in the protocol.

Kluetz PG, Chingos DT, Basch EM, Mitchell SA. Patient-Reported Outcomes in Cancer Clinical Trials: Measuring Symptomatic Adverse Events With the National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *Am Soc Clin Oncol Educ Book* 2016;35:67-73. doi: 10.14694/EDBK_159514.

Tolerability

If PROs are being used to assess tolerability this should be described.

Kluetz PG, Kanapuru B, Lemery S, Johnson LL, Fiero MH, Arscott K, Barbachano Y, Basch E, Campbell M, Cappelleri JC, Cella D, Cleeland C, Coens C, Daniels S, Denlinger CS, Fairclough DL, Hillard JR, Minasian L, Mitchell SA, O'Connor D, Patel S, Rubin EH, Ryden A, Soltys K, Sridhara R, Thanarajasingam G, Velikova G, Coons SJ. Informing the Tolerability of Cancer Treatments Using Patient-Reported Outcome Measures: Summary of an FDA and Critical Path Institute Workshop. Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2018;21(6):742-7.

Analysis

The Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data (SISAQOL) Consortium aims to develop recommendations to standardize the analysis of PRO data in cancer randomized controlled trials. https://event.eortc.org/sisaqol/

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 outcome endpoints in cancer randomised controlled trials: recommendations of the SISAQOL Consortium. The Lancet Oncology 2020;21(2):e83-e96.

Bottomley A, Pe M, Sloan J, Basch E, Bonnetain F, Calvert M, Campbell A, Cleeland C, Cocks K, Collette L, Dueck AC, Devlin N, Flechtner HH, Gotay C, Greimel E, Griebsch I, Groenvold M, Hamel JF, King M, Kluetz PG, Koller M, Malone DC, Martinelli F, Mitchell SA, Moinpour CM, Musoro J, O'Connor D, Oliver K, Piault-Louis E, Piccart M, Pimentel FL, Quinten C, Reijneveld JC, Schürmann C, Smith AW, Soltys KM, Sridhara R, Taphoorn M, Velikova G, Coens C. Moving forward toward standardizing analysis of quality of life data in randomized cancer clinical trials. Clinical trials (London, England). 2018;15(6):624-30.

Pe M, Dorme L, Coens C, Basch E, Calvert M, Campbell A, Cleeland C, Cocks K, Collette L, Dirven L, Dueck AC, Devlin N, Flechtner HH, Gotay C, Griebsch I, Groenvold M, King M, Koller M, Malone DC, Martinelli F, Mitchell SA, Musoro J, O'Connor D, Oliver K, Piault-Louis E, Piccart M, Pimentel FL, Quinten C, Reijneveld JC, Schürmann C, Sloan J, Velikova G, Bottomley. Statistical analysis of patient-reported outcome data in randomised controlled trials of locally advanced and metastatic breast cancer: a systematic review. The Lancet Oncology. 2018;19(9):e459-e69.

Bottomley A, Pe M, Sloan J, Basch E, Bonnetain F, Calvert M, Campbell A, Cleeland C, Cocks K, Collette L, Dueck AC, Devlin N, Flechtner HH, Gotay C, Greimel E, Griebsch I, Groenvold M, Hamel JF, King M, Kluetz PG, Koller M, Malone DC, Martinelli F, Mitchell SA, Moinpour CM, Musoro J, O'Connor D, Oliver K, Piault-Louis E, Piccart M, Pimentel FL, Quinten C, Reijneveld JC, Schürmann C, Smith AW, Soltys KM, Taphoorn M, Velikova G,

Coens C. Analysing data from patient-reported outcome and quality of life endpoints for cancer clinical trials: a start in setting international standards. The Lancet Oncology. 2016;17(11):e510-e4.

Other resources

Cappelleri JC, Zou KH, Bushmakin AG, Alvir JMJ, Alemayehu D, Symonds T. Patient-Reported Outcomes: Measurement, Implementation and Interpretation. Boca Raton, Florida: Chapman & Hall/CRC; 2013.

de Vet HCW, Terwee CB, Mokkink LB, Knol DL. Measurement in Medicine. Cambridge, UK: Cambridge University Press; 2011.

Fairclough DL. Design and Analysis of Quality of Life Studies in Clinical Trials. 2nd ed. Boca Raton, Florida: Chapman & Hall/CRC; 2010.

Fayers FM, Machin D. Quality of Life: The Assessment, Analysis and Interpretation of Patient-reported Outcomes. 3rd ed. Chichester, England: John Wiley & Sons Ltd.; 2016.

Streiner DL, Norman GR, Cairney J. Health Measurement Scales: A Practical Guide to Their Development and Use. 5th ed. New York, NY: Oxford University Press; 2015.

Missing Data

Mercieca-Bebber R, Palmer MJ, Brundage M, Calvert M, Stockler MR, King MT. Design, implementation and reporting strategies to reduce the instance and impact of missing patient-reported outcome (PRO) data: a systematic review. BMJ Open. 2016;6(6):e010938.

Little RJ, D'Agostino R, Cohen ML, et al. The Prevention and Treatment of Missing Data in Clinical Trials. New England Journal of Medicine 2012;367(14):1355-60.

Little RJ, Cohen ML, Dickersin K, et al. The design and conduct of clinical trials to limit missing data. Stat Med 2012;31(28):3433-43. doi: 10.1002/sim.5519

Patient Public Involvement (PPI) and Patient Experience

Kluetz PG, O'Connor DJ, Soltys K. Incorporating the patient experience into regulatory decision making in the USA, Europe, and Canada. The Lancet Oncology. 2018;19(5):e267-e74.

Table of Contents

Title page

PRO content author:

Affiliation(s), telephone:

Specify the individual(s) responsible for the PRO content of the trial protocol. (SPIRIT-5a-PRO Elaboration)

Explanation: Providing information (e.g. name, affiliation, contact details) on who wrote the PRO-specific aspects of the trial protocol promotes transparency and accountability and identifies the appropriate point of contact for resolution of any PRO specific queries. When patients have actively contributed to this process, this should be documented as per recent guidance for the reporting of patient and public involvement.[7]
Additional notes: *The PRO author should be part of the protocol writing committee. The trial study coordinator should ensure that PROs are harmonized with all the other clinical endpoints.*

1. Protocol Summary

The protocol synopsis is a short (1 to 2 pages) summary of the key points of the protocol (including PRO-specific information). This section of the protocol should be completed after the main text to ensure consistency with the main text.

1.3. Schedule of Activities (SoA)

Include a schedule of PRO assessments, providing a rationale for the time points, and justifying if the initial assessment is not pre-randomization. Specify time windows, whether PRO collection is prior to clinical assessments, and, if using multiple questionnaires, whether order of administration will be standardized (SPIRIT-13-PRO Extension).
Additional notes: *The PRO schedule of assessments should be summarised in a table alongside all other trial assessments to provide trial staff with a single point of reference. Ideally PRO assessments should appear in the table in the order which assessments will take place. If more than one PRO measure is being used, each may be specified on a separate line if they are administered at different time points.*

Procedure	Screening (up to X days before Day 1)	Intervention Period [Days or Weeks, etc.]									E/D *	Follow-up (X days after last dose)	Notes E/D = Early Discontinuation
		–1 (time window)	1 (time window)	2 (time window)	3 (time window)	4 (time window)	5 (time window)	6 (time window)	7 (time window)	8 (time window)			
List PRO assessments consistent with desired order of completion in study visits (more than one line may be necessary). Further details should be provided in Section 4.2. (SPIRIT 13 PRO Extension)													

2. Introduction

2.1. Study Rationale

2.1.1. Summary of PRO-specific rationale

Describe the PRO-specific research question and rationale for PRO assessment and summarize PRO findings in relevant studies. (SPIRIT-6a-PRO Extension)
Additional note: *As with other clinical information, the PRO-specific rationale should be summarized here and detailed information including summary of PRO findings in relevant studies should be provided in Section 4.2. Scientific Rationale for Study Design or in the PRO-specific section 8.1.*

Explanation: Inclusion of PROs in a trial requires careful consideration and planning. A clearly defined question helps with selection of measures and specification of hypotheses and analyses. When the PRO is a secondary or exploratory outcome, a brief rationale may be adequate.[6]

3. Objectives and Endpoints

State specific PRO objectives (including relevant PRO concepts/domains). (SPIRIT-7-PRO Extension)
Additional notes: *The level of detail on the PRO endpoints should also be similar to the other clinical endpoints to ensure harmonization. State whether specific PRO domains will be used for confirmatory or descriptive or exploratory purposes (SISAQOL recommendation statement (RS)1).[4] If primary or secondary objectives are confirmatory objectives (draw conclusions about treatment efficacy), there is a need to specify whether the objective is to show superiority, equivalence or non-inferiority (SISAQOL RS2).[4]*

Explanation: Pre-specification of objectives encourages identification of key PRO domains and time points, reducing the risk of multiple statistical testing and selective reporting of PROs based on statistically significant results.[8]

Specify the PRO *endpoint: the* concepts/domains used to evaluate the intervention (e.g., overall health-related quality of life, specific domain, specific symptom) and, for each one, the analysis metric (e.g., change from baseline, final value, time to event) and the principal time point or period of interest. (SPIRIT-12-PRO Extension)
Additional note: *Utility measures (e.g. EQ-5D) that inform cost-utility evaluations should also be included here.*

Explanation: The PRO concepts/domains and time points for assessment should closely align with the trial objectives and hypotheses. Because of the risk of multiple statistical testing, the domain(s) and principal time point(s) for analyses should be specified *a priori*.[8 9]

Objectives (including PRO objectives)	[Endpoints]
Primary	
1.	
Secondary	
2.	
Tertiary/Exploratory	
3.	

4. Study Design

4.1. Scientific Rationale for Study Design (PRO-specific) [Note this section could also be combined into the PRO-specific section 8.1]

Describe the PRO-specific research question and rationale for PRO assessment and summarize PRO findings in relevant studies. (SPIRIT-6a-PRO Extension)
Additional notes: *Detailed information should be provided here. Information not provided in Section 2.1.1. Summary of PRO-specific rationale should be presented here. Indicate how PRO evaluation aligns with the overall trial design, so it addresses the research objectives.*

Explanation: Inclusion of PROs in a trial requires careful consideration and planning. A clearly defined question helps with selection of measures and specification of hypotheses and analyses. When the PRO is a secondary outcome, a brief rationale may be adequate.[6]

5. Study Population

Specify any PRO-specific eligibility criteria (e.g., language/reading requirements or pre-randomization[1] completion of PRO). (SPIRIT-10-PRO Extension)
If PROs will not be collected from the entire study sample, provide a rationale and describe the method for obtaining the PRO subsample. (SPIRIT-10-PRO Extension)
Additional notes: *Efforts should be made to provide translated PRO versions where needed to promote inclusivity in PRO completion. Specify reasons if translated versions are not provided and certain populations are excluded. PRO-specific eligibility criteria should be included alongside other eligibility criteria to ensure research personnel have a single point of information.*

Explanation: Any PRO-specific eligibility criteria should be considered at the design stage of the trial and clearly specified in the protocol. In large trials, sufficient power may be achieved by collecting PROs from a representative subset of participants, while in some trials it may not be possible to collect PROs in the entire population (e.g., because of non-availability of validated questionnaires in all languages)[10]; in such instances, the rationale for the sampling method should be described.

6. Study Intervention

6.1. PRO capture method involving a medical device

Notes: *Some ePRO systems may meet the requirement for a medical device (for example by providing actionable alerts). If the ePRO fulfils the definition of a medical device, then the protocol should refer to the relevant regulatory directive for that jurisdiction.*

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal from the Study

7.1. Discontinuation of Study Intervention

Describe the process of PRO assessment for participants who discontinue or deviate from the assigned intervention protocol. (SPIRIT-18b (ii)-PRO Elaboration)
Additional note: *Participants who withdraw from the study should be provided pre-paid packaging to return PRO assessments and ePRO devices if applicable.*

Explanation: A clear plan for collection of PROs for trial participants who withdraw early from a study or who discontinue the intervention helps minimize bias,[11] ensures that staff collect all required PRO data in a standardized and timely way, and may assist ethical appraisal of the study.[6]

8. Study Assessments and Procedures

8.1. Efficacy Assessments

8.1.1. Patient Reported Outcomes

Specify the PRO Hypotheses (SPIRIT-7-PRO Extension)
Additional note: *Also specify whether the objective is to support superiority, equivalence or non-inferiority.*

Explanation: Pre-specification of objectives and hypotheses encourages identification of key PRO domains and time points, reducing the risk of multiple statistical testing and selective reporting of PROs based on statistically significant results.[8]

Justify the PRO instrument to be used and describe domains, number of items, recall period, instrument scaling and scoring (e.g., range and direction of scores indicating a good or poor outcome). Evidence of PRO instrument measurement properties, interpretation guidelines, and patient acceptability and burden should be provided or cited if available, ideally in the population of interest. State whether the measure will be used in accordance with any user manual and specify and justify deviations if planned. (SPIRIT-18a (i)-PRO Extension).
Additional note: *Interpretation guidelines should include reference to pre-defined clinical relevance thresholds, preferably specific to the PRO population.*

Explanation: The selection of PROs to be used in a clinical trial requires careful consideration. Ideally, the measure should be validated in the target population.[12] Consideration should be given to the number of questionnaires to be used, acceptability of the questions, and the likely patient burden (e.g., time taken for completion, cognitive burden, emotional burden). Justification for the measures selected will help trial personnel understand why specific measures are being used.[13] Questionnaires should be used in accordance with any existing user manuals to promote data quality and ensure standardized scoring, and any deviations should be described.[6]

Include a schedule of PRO assessments, providing a rationale for the time points, and justifying if the initial assessment is not pre-randomization. Specify time windows, whether PRO collection is prior to clinical assessments, and, if using multiple questionnaires, whether order of administration will be standardized. (SPIRIT-13-PRO Extension)

Additional notes: *State the mode of administration (e.g., paper and/or electronic capture). Baseline PROs should be completed prior to randomization allocation. The windowing for the first on treatment assessment should ensure the recall period does not overlap with day 0 of the trial (e.g., if recall is 7 days the minimum window should be trial day 7). The order of PRO administration should be the same for the entire duration of the study. Specify when patients are still expected to complete a PRO assessment (e.g., whether PROs will be collected after disease progression or not). This will allow calculation of completion rates (SISAQOL recommendation statement (RS) 19-20).[4] This information can be summarised in section 1.3 with further detail provided in this PRO-specific section.*

Explanation: Provision of an easy-to-follow schedule will assist staff and may help reduce missing data.[1] Collecting PRO data prior to randomization helps ensure an unbiased baseline assessment, and if specified as an eligibility criterion, ensures data completeness. This is important because baseline PRO data are often used as a covariate in analyses and are essential to calculating change from baseline. Completion of PROs prior to clinical assessments (as these may influence patient responses) and standardization of the order of questionnaire administration are advised to help reduce measurement error.[14] Allowable time windows for each scheduled PRO assessment should be specified to ensure that PRO data collection captures the effect of the clinical event(s) of interest.[6]

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). (SPIRIT-18a (ii)-PRO Extension)

Additional notes: *Specify whether participants would be completing assessments at the site. If so, they should be completed prior to any other assessments, procedures, or discussions with their care team. Participants should also be given time and a quiet space to complete the assessments. If electronic PRO collection tools are unavailable, damaged or lost, describe procedure to follow for the collection of PROs according to the SoA.*

Explanation: It is important that both research personnel and trial participants understand how, when, and where PRO data will be collected in the study. Increasingly, electronic PRO assessment is undertaken in trials, so evidence of equivalence between different modes of administration should be considered.[15] If electronic PRO measures contain only minor modifications with respect to the paper-based versions, usability testing and cognitive debriefing may provide sufficient evidence of equivalence.[15 16] The setting for PRO data collection should be described and standardized across trial intervention groups and sites.[6]

Specify PRO data collection and management strategies for minimizing avoidable missing data. (SPIRIT-18b (i)-PRO Extension)
Additional notes: *Signpost to statistical analysis plan (SAP) as required. Collect reasons for missed PRO assessments during the trial. These could be documented in the case report forms (CRF). SISAQOL, CONSORT-PRO Extension and PROTEUS may be consulted for further guidance on missing data.*[2 4 5]

Explanation: Missing data are a particular problem for PROs because participants with the poorest outcomes in a trial often are those who do not complete planned PRO assessments, and data cannot be obtained retrospectively beyond the time frame of interest or from medical records. This is a potentially significant source of bias and may reduce trial power.[17] It is important to note that not all missing PRO data are avoidable: participants have the right to decide not to complete questionnaires. Common reasons for avoidable missing PRO data are administrative errors, lack of explanation of the importance of PRO data, and overly burdensome questionnaires. Addressing these in the protocol should help minimize avoidable missing data. Examples of protocol content include ensuring that PRO end points and hypotheses are clearly defined and scientifically compelling, providing a rationale for PRO assessment, clearly specifying the PRO assessment time points, defining acceptable PRO assessment time windows, aligning PRO assessment time points to clinic visits (if clinically informative), minimizing participant burden, and specifying the importance of complete PRO data.[1]

Specify whether more than one language version will be used and state whether translated versions have been developed using currently recommended methods. (SPIRIT-18a (iii)-PRO Extension)

Explanation: Multinational trials, or national trials involving participants with different languages, require measures that have been translated and culturally adapted where needed using appropriate methodology.[18 19] This may influence the selection of measure to be used because inclusion of a wide range of participants can help ensure the generalizability of trial results. Plans to use translated versions should be specified in the protocol, citing references when available.[6]

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. Provide or cite evidence of the validity of proxy assessment if available. (SPIRIT-18a (iv)-PRO Extension)
Additional note: *If a proxy reporting is used, this should ideally be the same person throughout the trial.*

Explanation: In some contexts, such as trials involving young children or cognitively impaired participants, it may be necessary for someone other than a trial participant to respond on that participant's behalf. Note that proxy is different from someone assisting a person to respond to questionnaires (e.g., a nurse reads questions to a patient and writes

down their actual answers). Clear justification and specification of proxy reporting in the protocol allows external reviewers to assess potential bias and facilitates trial reporting in accordance with CONSORT-PRO.[2]

8.2. Safety Assessments

8.2.1 Monitoring of PRO data

State whether or not PRO data will be monitored during the study to inform the clinical care of individual trial participants and, if so, how this will be managed in a standardized way. Describe how this process will be explained to participants; e.g., in the participant information sheet and consent form. (SPIRIT-22-PRO Extension)
Additional note: *If PROs are used in place of or as an add-on to standard solicited AE recording (at visits/phone calls the investigators asks if there have been any problems since last visit) they should be recognised as part of the safety monitoring procedures of the trial.*

Explanation: Evidence suggests that monitoring and management of PRO alerts (psychological distress or physical symptoms evident from PRO responses that may require an immediate response) vary across and within trials.[13 18 20] To protect the interests of trial participants and minimize potential bias, it is important to specify plans for monitoring.[21] If monitoring is not planned (e.g., in a low-risk study in which alerts are not anticipated), this should also be briefly stated in the protocol, the participant information sheet, and the consent form. Alternative support mechanisms for participants should be outlined.[6]

9. Statistical considerations

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 sample size is not established based on the PRO end point, then discuss the power of the principal PRO analyses. (SPIRIT-14-PRO Elaboration)
Additional note: *Enough information on secondary, tertiary and even exploratory PRO endpoints should be provided to justify their inclusion.*

Explanation: In studies in which PROs are the primary outcome or end point, the target sample size will generally be based on an a priori sample size calculation for that end point.[9] Ideally, the criteria for clinical significance (e.g., minimal important difference, responder definition) should be specified when known.[22 23] If PROs are a secondary end point, researchers should specify whether the sample size provides sufficient power to test the principal PRO hypotheses.[9]

9.1. Statistical analyses

State PRO analysis methods, including any plans for addressing multiplicity/type I (α) error. (SPIRIT-20a-PRO Elaboration)
Additional notes: *Also state if there are no plans to address multiplicity/type I (α) error. Pre-define clinical relevance thresholds for the domains (SISAQOL recommendation statement (RS) 3-5).[4] Methods should align with specified endpoints and reflect superiority, equivalence or non-inferiority objectives (SISAQOL RS 2).[4] A power analysis can be conducted to assess whether a clinical relevant difference as specified in the objective can be detected reliably with the given sample size for the PRO population (SISAQOL RS 2).[4] If sensitivity analysis is planned, this should be pre-specified (SISAQOL RS 32).[4]*

Explanation: Many questionnaires, such as health-related quality-of-life measures, are multidimensional and therefore may yield several summary scores (e.g., multiple domains and an overall score). Furthermore, PROs are usually assessed at multiple time points. Statistical analysis of all domains and time points implies multiple hypothesis testing, which inflates the probability of false-positive results (type I error).[9] This can be contained by pre-specifying the key PRO domain(s) or overall score of interest and the principal time point(s). Any plans to address multiplicity, such as stepwise or sequential analyses, whereby multiple end points are tested in a defined sequence that contains the overall type I error to the desired level, or conventional non-hierarchical methods (e.g., Bonferroni correction), should be specified a priori.[8] The protocol should either fully address these issues or provide a summary with reference to where full details can be found (e.g., in the statistical analysis plan).[6]

9.1.1. Missing PRO data

State how missing data will be described and outline the methods for handling missing items or entire assessments (e.g., approach to imputation and sensitivity analyses). (SPIRIT-20c-PRO Elaboration)
Additional notes: *State whether PRO data is missing at the item level or at entire PRO assessment level and whether intermittent or lost to follow-up. In addition, state how missing PRO data is recorded and categorised. SISAQOL recommendations may be consulted for further guidance on missing data.[4]*

Explanation: There are 2 levels of missing PRO data: (1) patient completion of some but not all items within an instrument and (2) absence of the entire PRO assessment. Whether and how missing items should be imputed is usually specified in an instrument's scoring algorithm. When entire PRO assessments are missed, analysis requires assumptions about why those data were missing (i.e., the missing data mechanism). There are a range of statistical approaches, each with specific assumptions. Inappropriate method selection may lead to potentially biased and misleading results.[1 11] The protocol should acknowledge and summarize these issues, with full details provided in the statistical analysis plan.[6]

9.1.2. Other Analyse(s)

Note: *If psychometric analyses of the PRO measure(s) or any additional research questions are planned with the PRO data collected, this should be acknowledged in the protocol, with reference to statistical analysis plan (SAP), Calvert et al 2018 (JAMA Supplement 3).*[6]

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Publication Policy

Notes: *It is important to publish PRO data. There is evidence that this is not done enough or well. Publication of PRO data should be done according to CONSORT and CONSORT-PRO*

Note: *Whilst not a formal recommendation in the SPIRIT-PRO guidance, it is regarded as good practice to include, depending on the mode of administration, paper copies of PRO or screenshots of ePRO instruments.*
All copyrights and version information should be clearly showing in the appended PRO instruments with due acknowledgment for PROs requiring permission for use.

10.2. Appendix Copies of PROs

Glossary

Concept: "The specific measurement goal (i.e., the thing that is to be measured by a PRO instrument). In clinical trials, a PRO instrument can be used to measure the effect of a medical intervention on one or more concepts. PRO concepts represent aspects of how patients function or feel related to a health condition or its treatment."[24]
Domain: "A sub concept represented by a score of an instrument that measures a larger concept comprised of multiple domains. For example, psychological function is a larger concept with multiple domains (emotional and cognitive function) that are measured by relevant items."[24]
Endpoint*: the variable to be analysed. It is a precisely defined variable intended to reflect an outcome of interest that is statistically analysed to address a particular research question. A precise definition of an endpoint typically specifies the type of assessments made, the timing of those assessments, the assessment tools used, and possibly other details, as applicable, such as how multiple assessments within an individual are to be combined[25] (e.g. change from baseline at 6 weeks in mean fatigue score).[26]
Health-related quality of life: "a multidimensional concept that usually includes self-report of the way in which physical, emotional, social, or other domains of well-being are affected by a disease or its treatment"[27]
Important or key secondary PROs/end points: Some PRO measures (particularly health-related quality-of-life measures) are multidimensional, producing several domain-specific outcome scales; e.g., pain, fatigue, physical function, psychological distress. For any particular trial, it is likely that a particular PRO or PRO domain(s) will be more relevant than others, reflecting the expected effect(s) of the trial intervention(s) in the target patient population. These relevant PRO(s) and/or domain(s) may additionally constitute the important or key secondary PROs (identified a priori and specified as such in the trial protocol and statistical analysis plan) and will be the focus of hypothesis testing. In a regulatory environment, these outcomes may support a labelling claim. Because these outcomes are linked with hypotheses (CONSORT PRO Extension 2b),[27] they may be subject to P-value adjustment (or "α spending"). Beyond efficacy/effectiveness, PROs may also be used to capture and provide evidence of safety and tolerability (e.g. using the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™))[28]
Instrument: "A means to capture data (e.g., a questionnaire) plus all the information and documentation that supports its use. Generally, that includes clearly defined methods and instructions for administration or responding, a standard format for data collection, and well-documented methods for scoring, analysis, and interpretation of results in the target patient population."[24]
Intervention/treatment: A process or action that is the focus of a clinical study. Interventions include drugs, medical devices, procedures, vaccines, and other products that are either investigational or already available. Interventions can also include non-invasive approaches, such as education or modifying diet and exercise.[29]
Item: "an individual question, statement, or task (and its standardized response options) that is evaluated by the patient to address a particular concept"[24]
Observer-reported outcome: "a measurement based on a report of observable signs, events or behaviours related to a patient's health condition by someone other than the patient of a health care professional".[30]
Outcome*: the variable to be measured. It is the measurable characteristic that is influenced or affected by an individuals' baseline state or an intervention as in a clinical trial or other exposure[25] (e.g. a fatigue score).
Patient-reported outcome (PRO): A PRO is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else and may include patient assessments of health status, quality

of life, or symptoms.[24 27] PROs are assessed by self-reported questionnaires, referred to as PRO measures (PROMs) or instruments.[25]
Primary outcome: the most important outcome in a trial, pre-specified in the protocol, providing the most clinically relevant evidence directly related to the primary objective of the trial.
Proxy-reported outcome: "a measurement based on a report by someone other than the patient reporting as if he or she is the patient"[24]
Secondary outcomes: outcomes pre-specified in the protocol to assess additional effects of the intervention; some PROs may be identified as important or key secondary outcomes
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials.[31 32]
SPIRIT Elaboration item: an elaboration of an existing SPIRIT item as applied to a specific context; in this instance, as applied to clinical trials assessing PROs
SPIRIT-PRO Extension item: an additional checklist item describing PRO protocol content to address an aspect of PRO assessment that is not adequately covered by SPIRIT, as judged by available evidence and expert opinion
Time window: a predefined time frame before and after the protocol-specified PRO assessment time point whereby the result would still be deemed to be clinically relevant.[33]

* The terms outcome and endpoint are often used interchangeably, although this is not always consistent with the range of definitions available. For the definitions included in this glossary, an endpoint is defined from PRO data (i.e. the outcome) by fully specifying four components: measurement variable (e.g. fatigue "in the past week" as measured by the QLQ-C30), analysis metric (e.g., change in fatigue from baseline, final fatigue value, time to clinically important increase in fatigue (and "event"), method of aggregation (e.g., median fatigue, proportion of patients with severe fatigue, proportion of patients with clinically important change in fatigue), and time point. Note that using theses definitions, several endpoints can be defined from the same outcome source data, revealing the distinction and relationship between "outcome" and "endpoint" for PROs.

List of Abbreviations

CONSORT – Consolidated Standards of Reporting Trials

CRF – case report form

ePRO – electronic patient-reported outcome

PPI – Patient Public Involvement

PRO – patient-reported outcome

PRO-CTCAE – Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events

PROTEUS – Patient-Reported Outcomes Tools: Engaging Users & Stakeholders

RS – recommendation statement

SAP – statistical analysis plan

SISAQOL – Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data

SoA – Schedule of Activities

SPIRIT – Standard Protocol Items: Recommendations for Interventional Trials

References

1. Mercieca-Bebber R, Palmer MJ, Brundage M, et al. Design, implementation and reporting strategies to reduce the instance and impact of missing patient-reported outcome (PRO) data: a systematic review. *BMJ Open* 2016;6(6):e010938. doi: 10.1136/bmjopen-2015-010938 [published Online First: 2016/06/18]
2. Calvert M, Blazeby J, Altman DG, et al. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. *Jama* 2013;309(8):814-22. doi: 10.1001/jama.2013.879 [published Online First: 2013/02/28]
3. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Annals of internal medicine* 2013;158(3):200-7. doi: 10.7326/0003-4819-158-3-201302050-00583 [published Online First: 2013/01/09]
4. Coens C, Pe M, Dueck AC, et al. International standards for the analysis of quality-of-life and patient-reported outcome endpoints in cancer randomised controlled trials: recommendations of the SISAQOL Consortium. *The Lancet Oncology* 2020;21(2):e83-e96. doi: 10.1016/S1470-2045(19)30790-9
5. Snyder C, Smith K, Holzner B, et al. Making a picture worth a thousand numbers: recommendations for graphically displaying patient-reported outcomes data. *Quality of Life Research* 2019;28(2):345-56. doi: 10.1007/s11136-018-2020-3
6. Calvert M, Kyte D, Mercieca-Bebber R, et al. Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols: The SPIRIT-PRO Extension. *Jama* 2018;319(5):483-94. doi: 10.1001/jama.2017.21903
7. Staniszewska S, Brett J, Simera I, et al. GRIPP2 reporting checklists: tools to improve reporting of patient and public involvement in research. *BMJ* 2017;358:j3453. doi: 10.1136/bmj.j3453 [published Online First: 2017/08/05]
8. FDA. Guidance for industry. Patient-reported outcome measures: use in medicinal product development to support labeling claims. Silver Spring, MD: US Department of Health and Human Services Food and Drug Administration, 2009.
9. Sloan JA, Dueck AC, Erickson PA, et al. Analysis and interpretation of results based on patient-reported outcomes. *Value Health* 2007;10 Suppl 2:S106-15. doi: 10.1111/j.1524-4733.2007.00273.x [published Online First: 2007/11/13]
10. Kyte D, Retzer A, Ahmed K, et al. Systematic Evaluation of Patient-Reported Outcome Protocol Content and Reporting in Cancer Trials. *JNCI: Journal of the National Cancer Institute* 2019;111(11):1170-78. doi: 10.1093/jnci/djz038
11. Fairclough DL. Design and analysis of quality of life studies in clinical trials. New York: Chapman & Hall/CRC Press 2002.
12. Rothrock NE, Kaiser KA, Cella D. Developing a valid patient-reported outcome measure. *Clin Pharmacol Ther* 2011;90(5):737-42. doi: 10.1038/clpt.2011.195 [published Online First: 2011/10/05]
13. Kyte D, Ives J, Draper H, et al. Inconsistencies in quality of life data collection in clinical trials: a potential source of bias? Interviews with research nurses and trialists. *PLoS One* 2013;8(10):e76625. doi: 10.1371/journal.pone.0076625 [published Online First: 2013/10/15]
14. Leidy NK, Revicki DA, Geneste B. Recommendations for evaluating the validity of quality of life claims for labeling and promotion. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 1999;2(2):113-27. doi: 10.1046/j.1524-4733.1999.02210.x [published Online First: 2006/05/06]
15. Coons SJ, Gwaltney CJ, Hays RD, et al. Recommendations on evidence needed to support measurement equivalence between electronic and paper-based patient-reported outcome (PRO) measures: ISPOR ePRO Good Research Practices Task Force report. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2009;12(4):419-29. doi: 10.1111/j.1524-4733.2008.00470.x [published Online First: 2009/11/11]

16. Rutherford C, Costa D, Mercieca-Bebber R, et al. Mode of administration does not cause bias in patient-reported outcome results: a meta-analysis. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation* 2016;25(3):559-74. doi: 10.1007/s11136-015-1110-8 [published Online First: 2015/09/04]
17. Bernhard J, Cella DF, Coates AS, et al. Missing quality of life data in cancer clinical trials: serious problems and challenges. *Statistics in Medicine* 1998;17(5-7):517-32. doi: 10.1002/(sici)1097-0258(19980315/15)17:5/7<517::Aid-sim799>3.0.Co;2-s
18. Mercieca-Bebber R, Calvert M, Kyte D, et al. The administration of patient-reported outcome questionnaires in cancer trials: Interviews with trial coordinators regarding their roles, experiences, challenges and training. *Contemp Clin Trials Commun* 2018;9:23-32. doi: 10.1016/j.conctc.2017.11.009 [published Online First: 2018/04/27]
19. Wild D, Grove A, Martin M, et al. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2005;8(2):94-104. doi: 10.1111/j.1524-4733.2005.04054.x [published Online First: 2005/04/05]
20. Kyte D, Ives J, Draper H, et al. Management of Patient-Reported Outcome (PRO) Alerts in Clinical Trials: A Cross Sectional Survey. *PloS one* 2016;11(1):e0144658. doi: 10.1371/journal.pone.0144658 [published Online First: 2016/01/20]
21. Kyte D, Draper H, Calvert M. Patient-reported outcome alerts: ethical and logistical considerations in clinical trials. *Jama* 2013;310(12):1229-30. doi: 10.1001/jama.2013.277222 [published Online First: 2013/09/26]
22. Revicki D, Hays RD, Cella D, et al. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. *Journal of clinical epidemiology* 2008;61(2):102-9. doi: 10.1016/j.jclinepi.2007.03.012 [published Online First: 2008/01/08]
23. King MT. A point of minimal important difference (MID): a critique of terminology and methods. *Expert Rev Pharmacoecon Outcomes Res* 2011;11(2):171-84. doi: 10.1586/erp.11.9 [published Online First: 2011/04/12]
24. FDA. Guidance for Industry, Patient-Reported Outcome Measures: Use in Medical Product Development to Suport Labeling Claims 2009 [Available from: https://www.fda.gov/media/77832/download accessed 25/11/2019.
25. FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource 2016 [Available from: https://www.ncbi.nlm.nih.gov/books/NBK326791/.
26. Curtis L HA, Weinfurt K. Choosing and Specifying Endpoints and Outcomes: Introduction. In: Rethinking Clinical Trials: A Living Textbook of Pragmatic Clinical Trials. 2019 [Available from: DOI: 10.28929/009 accessed 12/03/2020.
27. Calvert M, Blazeby J, Altman DG, et al. Reporting of Patient-Reported Outcomes in Randomized Trials: The CONSORT PRO Extension. *JAMA* 2013;309(8):814-22. doi: 10.1001/jama.2013.879
28. Kluetz PG, Chingos DT, Basch EM, et al. Patient-Reported Outcomes in Cancer Clinical Trials: Measuring Symptomatic Adverse Events With the National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *Am Soc Clin Oncol Educ Book* 2016;35:67-73. doi: 10.14694/edbk_159514 [published Online First: 2016/06/02]
29. ClinicalTrials.gov. Glossary of Common Site Terms [Available from: https://clinicaltrials.gov/ct2/about-studies/glossary accessed 12/03/2020 2020.
30. FDA. Drug Development Tool Glossary [updated 08/15/2017. Available from: https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/ddt-glossary accessed 03/07/2020 2020.
31. Chan A-W, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials. *Annals of Internal Medicine* 2013;158(3):200-07. doi: 10.7326/0003-4819-158-3-201302050-00583

32. Chan A-W, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;8(346) doi: 10.1136/bmj.e7586
33. Fayers PM, Hopwood P, Harvey A, et al. Quality of life assessment in clinical trials—guidelines and a checklist for protocol writers: the U.K. Medical Research Council experience. *European Journal of Cancer* 1997;33(1):20-28. doi: https://doi.org/10.1016/S0959-8049(96)00412-1