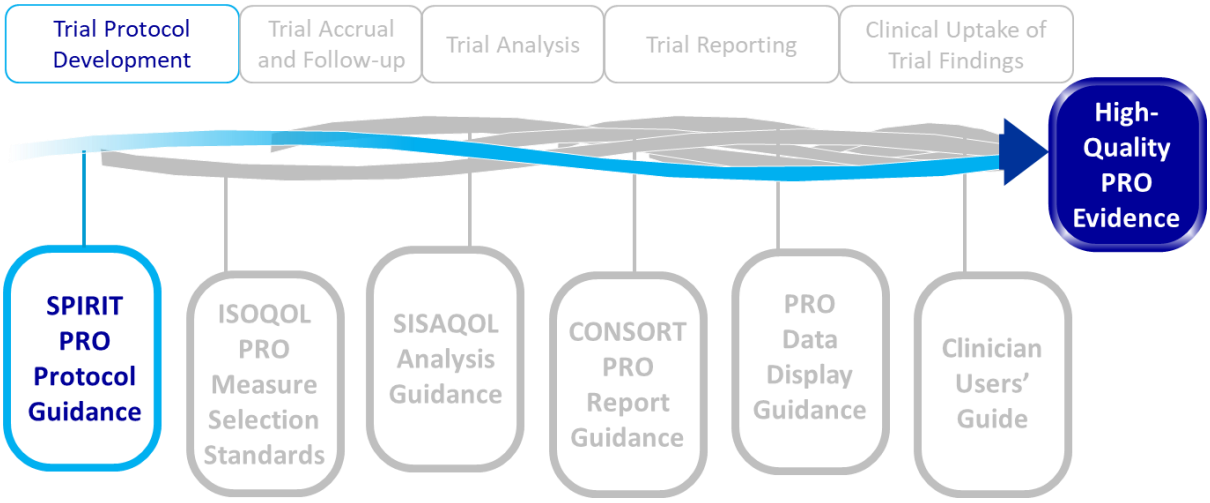
Chapter 2. Writing PRO Protocols



Standard Protocol Items: Recommendations for Interventional Trials-PRO Extension (SPIRIT-PRO)

The SPIRIT-PRO Extension recommends best practices for writing the PRO aspects of randomized controlled trial protocols. It is an extension of the general 2013 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidance that identified the minimum elements required in clinical trial protocols, generally (Chan et al., 2013). The SPIRIT-PRO Extension builds on the general SPIRIT guidance by addressing the minimum elements related to PROs that should be included in clinical trial protocols.

View SPIRIT-PRO Extension article

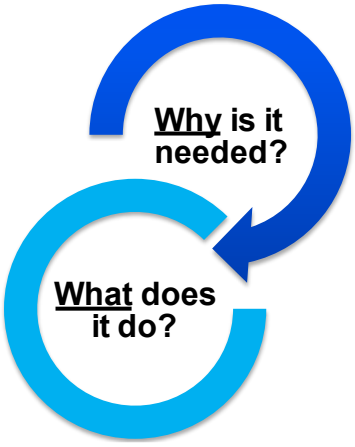
View SPIRIT-PRO Explanation and Elaboration article

View the Checklist for the SPIRIT-PRO Protocol Guidance

References

Acknowledgements

Why is This Resource Needed?



To ensure that critical aspects of the PRO study are included in the protocol for successful conduct

Recommends items to address in clinical trial protocols where PROs are primary or key secondary outcomes

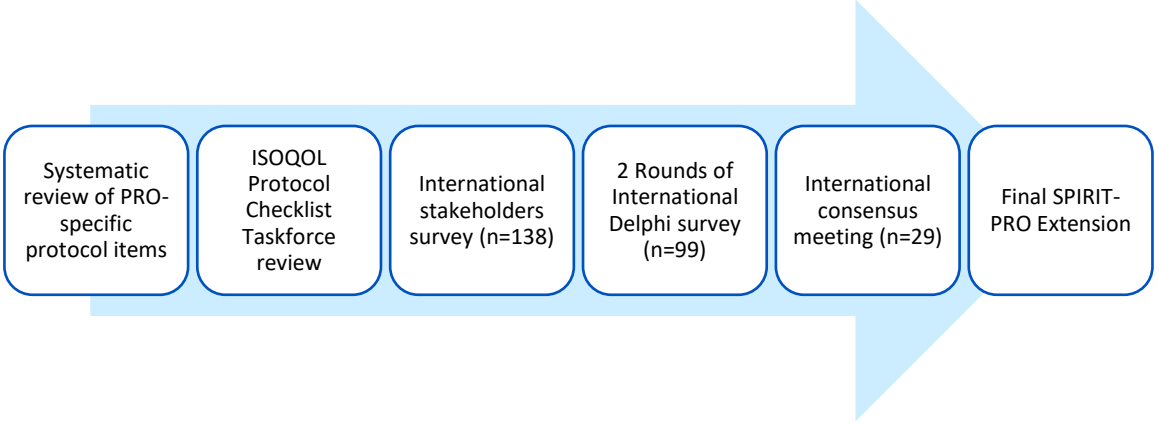
Patient-reported outcome (PRO) data from clinical trials can provide valuable evidence to inform shared decision making, labeling claims, clinical guidelines, and health policy; however, the PRO content of clinical trial protocols is often suboptimal. Although the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement was published in 2013 to improve the completeness of trial protocols by providing evidence-based recommendations for the minimum set of items to be addressed, it does not provide PRO-specific guidance.

Objective of the Resource

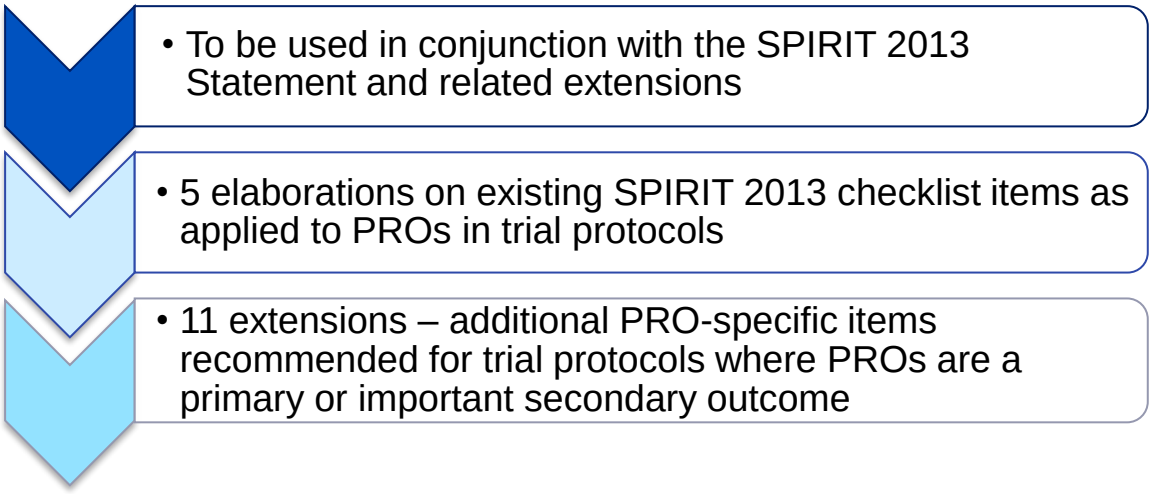
To provide international, consensus-based, PRO-specific protocol guidance: an official SPIRIT-PRO extension.

Methods for Resource Development

The SPIRIT-PRO Extension was developed through a systematic review of existing PRO-specific protocol guidance, a stakeholder survey of a group of international experts, and a Delphi exercise and consensus meeting, followed by consultation on the final SPIRIT-PRO Extension.



Overview of the SPIRIT-PRO Guidance



The SPIRIT-PRO guidance constitutes an extension to the SPIRIT 2013 statement that guides the reporting of various parts of the trial protocol sections. The key items relevant to the reporting of PROs include the following:

Introduction

- Describe PRO-specific research question, rationale, and relevant previous findings
- State PRO-specific objectives or hypotheses (including relevant PRO concepts/domains)

Methods – Participants, Interventions, Outcomes

- Specify any PRO-specific eligibility criteria
- Specify the PRO concepts/domains used to evaluate the intervention and related analysis metric

Methods – Data Collection, Management and Analysis

- Describe the PRO measure and its psychometric characteristics
- Include a data collection plan (e.g., time points, mode, setting)
- Specify language versions available
- State and justify use of proxy reporting, if relevant
- Specify strategies to minimize missing data and address missing data in analysis

Harms

- State whether PRO data will be monitored to inform clinical care

The specific elaborations and extensions are detailed below.

SPIRIT-PRO items by Protocol Sections

Administrative Information & Introduction

SPIRIT-PRO Elaboration Item 5a – Roles & Responsibilities

SPIRIT 2013:	**PRO Elaboration 2018:**
Names, affiliations, and roles of protocol contributors.	Specify the individual(s) responsible for the PRO content of the trial protocol.

Explanation:

Providing information (e.g., name, affiliation, contact details) on expert on 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.

SPIRIT-PRO Extension Item 6a – Background and Rationale

SPIRIT 2013:	**PRO Extension 2018:**
Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention.	Describe the PRO specific research question and rationale for PRO assessment, and summarize PRO findings in relevant studies.

Explanation:

A clearly defined question helps with selection of measures and specification of hypotheses and analyses. Many trials include PROs without specifying the PRO-specific research question and a rationale or any reference to PROs in related studies. Staff and patients may not understand why PROs are being assessed, and missing data may result. When the PRO is a secondary outcome, a brief rationale may be adequate.

SPIRIT-PRO Extension Item 7 – Objectives

SPIRIT 2013:	PRO Extension 2018:
Specific objectives or hypotheses.	State specific PRO objectives or hypotheses (including relevant PRO concepts/domains).

Explanation:

PRO measures may be multidimensional (e.g., health-related quality of life) or unidimensional (e.g., specific symptoms such as pain). 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.

Methods: Participants, Interventions, and Outcomes

SPIRIT-PRO Extension Item 10 – Eligibility Criteria

SPIRIT 2013:	PRO Extension 2018:
Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centers and individuals who will perform the interventions (e.g., surgeons, psychotherapists).	Specify any PRO-specific eligibility criteria (e.g., language/reading requirements or pre-randomization completion of PRO). If PROs will not be collected in the entire study sample, provide a rationale and describe the method for obtaining the PRO subsample.

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 validated questionnaires may not be available in all languages); in such instances, the rationale for the sampling method should be described.

SPIRIT-PRO Extension Item 12 – Outcomes

SPIRIT 2013:	PRO Extension 2018:
Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended.	Specify the PRO 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.

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*.

SPIRIT-PRO Extension Item 13 – Participant Timeline

SPIRIT 2013:	PRO Extension 2018:
Time schedule of enrollment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended.	Include a schedule of PRO assessments, and rationale for the time points. Justify if the initial assessment is not pre-randomization. Specify time windows and whether PROs collected prior to clinical assessments. If using multiple questionnaires, whether order of administration standardized.

Explanation:

Provision of an easy-to-follow schedule will assist staff and may help reduce missing data. 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. 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.

SPIRIT-PRO Extension Item 14 – Sample Size

SPIRIT 2013:	**PRO Elaboration 2018:**
Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations.	Where a PRO is the primary endpoint, 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 PRO endpoint, then discuss the power of the principal PRO analyses.

Explanation:

The target sample size will generally be based on an *a priori* sample size calculation for the PRO end point. Ideally, the criteria for clinical significance (e.g., minimal important difference) should be specified if known. If PROs are a secondary end point, researchers should specify whether the sample size provides sufficient power to test the principal PRO hypotheses.

Methods: Data Collection, Management, and Analysis

SPIRIT 2013 Item 18a - Data Collection Methods

SPIRIT 2013:	**Four PRO Extensions 2018 (each explained below)**
Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol.	

SPIRIT-PRO Extension Item 18a (i) – Data Collection Methods

PRO Extension (i) 2018:

Justify the PRO instrument, describe domains, number of items, recall period, instrument scaling/scoring (e.g., range and direction of scores indicating a good/poor outcome).

Evidence of PRO instrument measurement properties, interpretation guidelines, and patient acceptability/burden should be 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.

Explanation:

The selection of PRO questionnaires requires careful consideration, particularly patient burden and acceptability. 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.

SPIRIT-PRO Extension Item 18a (ii) – Data Collection Methods

PRO Extension (ii) 2018:

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).

Explanation:

It is important that both research personnel and trial participants understand how, when, and where PRO data will be collected in the study. 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. The setting for PRO data collection should be described and standardized across trial intervention groups and sites.

SPIRIT-PRO Extension Item 18a (iii) – Data Collection Methods

PRO Extension (iii) 2018:

Specify whether more than one language version will be used.

State whether translated versions have been developed using currently recommended methods.

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. 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.

SPIRIT-PRO Extension Item 18a (iv) – Data Collection Methods

PRO Extension (iv) 2018:

When the trial context requires someone other than the trial participant to answer on their behalf (a proxy reported outcome), state and justify this.

Provide/cite evidence of the validity of proxy assessment if available.

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. 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. Evidence of the size and direction of proxy bias is a key aspect of the validity of proxy versions of PRO measures, informing valid interpretation, and comparison of results. The European Medicines Agency states that "in general proxy reporting should be avoided, unless the use of such proxy raters may be the only effective means of obtaining information that might otherwise be lost." The US Food and Drug Administration also discourages the use of proxy reported outcomes to inform labeling claims, recommending observer reports instead.

SPIRIT 2013 Item 18b - Data Collection Methods

SPIRIT 2013:	One PRO Extension & One PRO Elaboration 2018
Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	**(see below)**

PRO Extension Item 18b (i) - Data Collection Methods

PRO Extension (i) 2018:

Specify PRO data collection and management strategies for minimizing *avoidable* missing data.

Explanation:

Missing data are a particular problem for PROs for 3 reasons: 1) unlike some other trial outcomes, data cannot be obtained retrospectively beyond the time frame of interest or from medical records; 2) missing data reduce the effective sample size hence power for PRO analyses; 3) importantly – they are a potentially significant source of bias. Why? Because participants with the poorest outcomes in a trial often are those who do not complete planned PRO assessments.

It is important to note that not all missing PRO data are avoidable: patients have the right to decide not to complete questionnaires, which may happen if they feel too unwell. 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.

A key part of a management strategy for minimizing avoidable missing data is a plan to collect reasons for missed assessments and to review these reasons during trial conduct. Information about the rates of and reasons for missing data are also valuable during analysis and write-up, as explained in chapters 4 and 5.

A recent systematic review provides a range of design, implementation, and reporting strategies to help minimize and address missing PRO 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 patient burden, and specifying the importance of complete PRO data.

SPIRIT-PRO Elaboration Item 18b (ii) – Data Collection Methods

PRO Elaboration (ii) 2018:

Describe the process of PRO assessment for participants who discontinue or deviate from their assigned intervention protocol.

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, ensures that staff collect all required PRO data in a standardized and timely way, and may assist ethical appraisal of the study.

SPIRIT-PRO Elaboration Item 20a – Statistical Methods

SPIRIT 2013:

Statistical methods for analyzing primary and secondary outcomes.

Reference to where other details of the statistical analysis plan (SAP) can be found, if not in the protocol.

PRO Elaboration 2018:

State PRO analysis methods including any plans for addressing multiplicity/type 1 (α) error.

Explanation:

Statistical analysis of all domains and time points implies multiple hypothesis testing, which inflates the probability of false-positive results (type I error). This can be contained by prespecifying 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 or conventional non-hierarchical methods (e.g., Bonferroni correction), should be specified *a priori*. 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).

SPIRIT-PRO Elaboration Item 20c – Statistical Methods

SPIRIT 2013:

Definition of analysis population relating to protocol non-adherence (e.g., as randomized analysis), and any statistical methods to handle missing data (e.g., multiple imputation).

PRO Elaboration 2018:

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).

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. Common methods include complete case analysis, imputation (various approaches), a range of maximum likelihood modeling approaches, and sensitivity analysis. Inappropriate method selection may lead to potentially biased and misleading results. The protocol should acknowledge and summarize these issues, with full details provided in the statistical analysis plan.

Methods: Monitoring

SPIRIT-PRO Extension Item 22 – Harms

SPIRIT 2013:

Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct.

PRO Extension 2018:

State whether or not PRO data will be monitored during the study to inform the clinical care of trial participants.

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.

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. To protect the interests of trial participants and minimize potential bias, it is important to specify plans for monitoring. If monitoring is not planned (for example, 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 patients should be outlined.

Implications of Using SPIRIT-PRO Guidance

Inclusion of PRO-specific protocol content will have multiple benefits:

- Protocol writers: Encourage and facilitate careful planning of PRO components of trials, hence improve PRO trial design
- Protocol reviewers: Help research ethics committees and patient partners assess the PRO elements
- Trial staff and participants: Help staff and patients understand the rationale for PRO assessment, improve PRO data completeness and quality

➢ This in turn will facilitate high-quality analysis and reporting, and ultimately improve the quality of the global PRO evidence base

Checklist for the SPIRIT-PRO Protocol Guidance

Protocol Section	SPIRIT-PRO Item	Recommended Content	Page Addressed
Administrative Information			
Roles and responsibilities	SPIRIT-5a-PRO Elaboration	Specify the individual(s) responsible for the PRO content of the trial protocol.	
Introduction			
Background and rationale	SPIRIT-6a-PRO Extension	Describe the PRO-specific research question and rationale for PRO assessment and summarize PRO findings in relevant studies.	
Objectives	SPIRIT-7-PRO Extension	State specific PRO objectives or hypotheses (including relevant PRO concepts/domains).	
Methods: Participants, Interventions, and Outcomes			
Eligibility criteria	SPIRIT-10-PRO Extension	Specify any PRO-specific eligibility criteria (e.g., language/reading requirements or prerandomization completion of PRO). If PROs will not be collected from the entire study sample, provide a rationale and describe the method for obtaining the PRO subsample.	
Outcomes	SPIRIT-12-PRO Extension	Specify the PRO 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.	
Participant timeline	SPIRIT-13-PRO Extension	Include a schedule of PRO assessments, providing a rationale for the time points, and justifying if the initial assessment is not prerandomization. Specify time windows, whether PRO collection is prior to clinical assessments, and, if using multiple questionnaires, whether order of administration will be standardized.	
Sample size	SPIRIT-14-PRO Elaboration	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.	

Protocol Section	SPIRIT-PRO Item	Recommended Content	Page Addressed
Methods: Data Collection, Management, and Analysis			
Data collection methods	SPIRIT-18a(i)-PRO Extension	Justify the PRO instrument to be used and describe domains, number of items, recall period, and 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(ii)-PRO Extension	Include a data collection plan outlining permitted mode(s) of administration (e.g., paper, telephone, electronic, other) and setting (e.g., clinic, home, other).	
	SPIRIT-18a(iii)-PRO Extension	Specify whether more than 1 language version will be used and state whether translated versions have been developed using currently recommended methods.	
	SPIRIT-18a(iv)-PRO Extension	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.	
	SPIRIT-18b(i)-PRO Extension	Specify PRO data collection and management strategies for minimizing avoidable missing data.	
	SPIRIT-18b(ii)-PRO Elaboration	Describe the process of PRO assessment for participants who discontinue or deviate from the assigned intervention protocol.	
Statistical methods	SPIRIT-20a-PRO Elaboration	State PRO analysis methods, including any plans for addressing multiplicity/ type I (α) error.	
	SPIRIT-20c-PRO Elaboration	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).	
Methods: Monitoring			
Harms	SPIRIT-22-PRO Extension	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.	

References

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.

Calvert M, et al. SPIRIT-PRO Extension explanation and elaboration: guidance for inclusion of patient-reported outcomes in protocols of clinical trials. *BMJ Open* 2021;0:e045105. doi:10.1136/bmjopen-2020-045105.

Chan A-W, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med*. 2013;158(3):200-207.

Chan A-W, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586.

Mercieca-Bebber R, et al. Design, implementation and reporting strategies to reduce the instance and impact of missing patient-reported outcome data: a systematic review. *BMJ Open* 2016;6(6):e010938.

Further Reading

Cruz Rivera S, et al. “Give Us The Tools!” - Development of knowledge transfer tools to support the involvement of patient partners in the development of clinical trial protocols with patient-reported outcomes (PROs), in accordance with SPIRIT-PRO Extension. *BMJ Open* 2021; doi: 10.1136/bmjopen-2020-046450.

FDA Guidance on PROs: https://www.fda.gov/media/77832/download

Kyte D, Draper H, Calvert M. Patient-reported outcome alerts: ethical and logistical considerations in clinical trials. *JAMA*. 2013;310(12):1229-1230.

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Please Note: When referencing information included in this Chapter, we recommend citing the primary sources rather than this Handbook.