Specifying PRO Methods Appropriately: The SPIRIT-PRO Extension Protocol Guidance

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PROTEUS
Patient-Reported Outcomes Tools: Engaging Users and Stakeholders

The PROTEUS Consortium

Patient-Reported Outcome Tools: Engaging Users & Stakeholders

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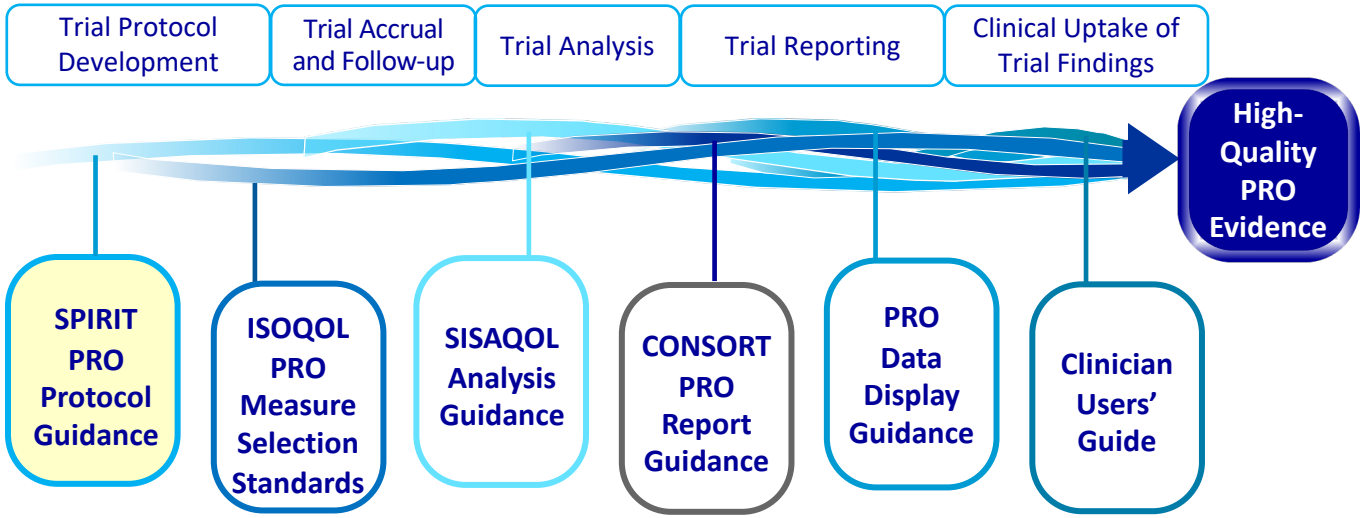
Overview of Presentations

Introduction to PROs and PROTEUS

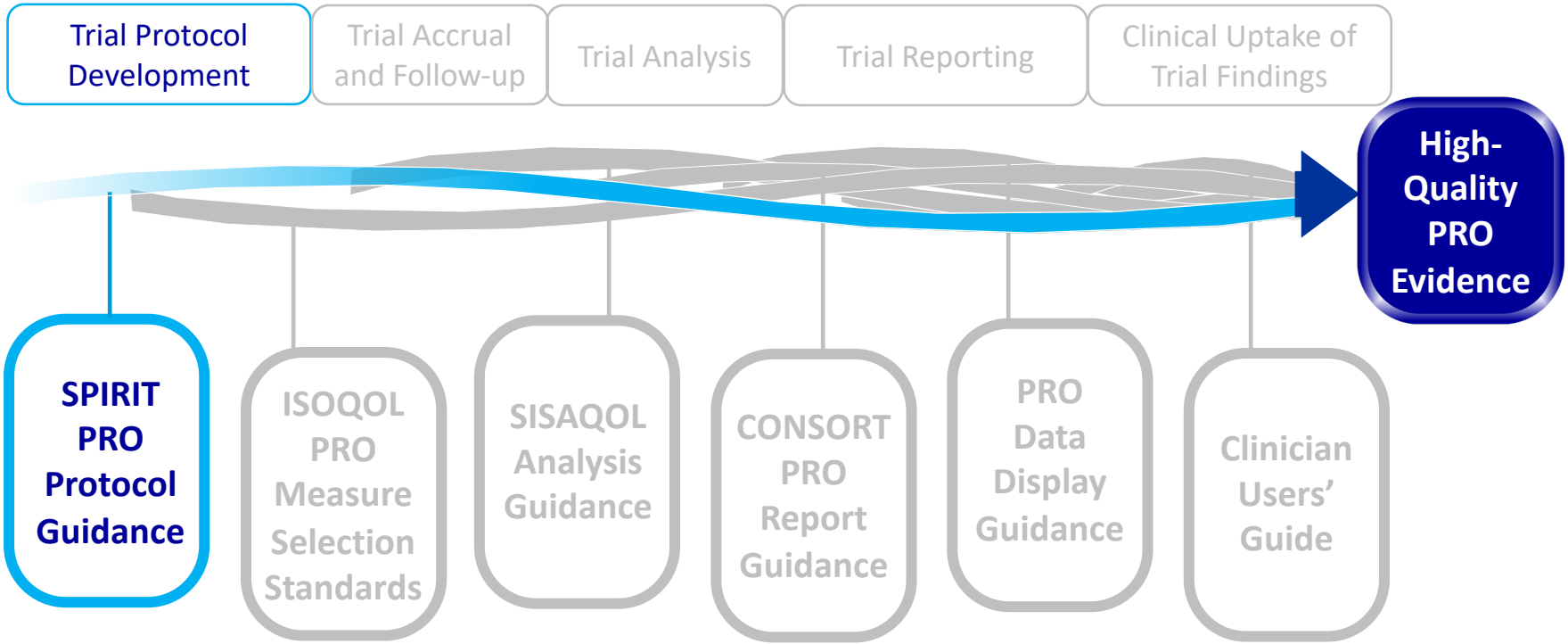
Introduction to the PROTEUS Tools



Overview of Tool Recommendations

How to Apply the Tools

Specifying PRO Methods Appropriately



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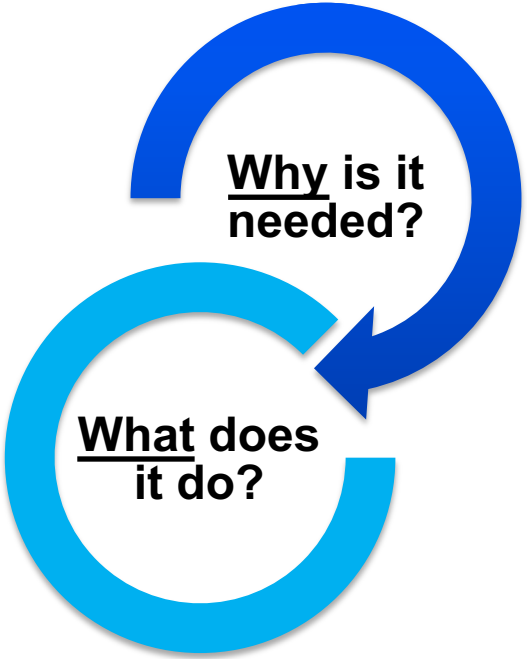
Specifying PRO Methods Appropriately



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

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

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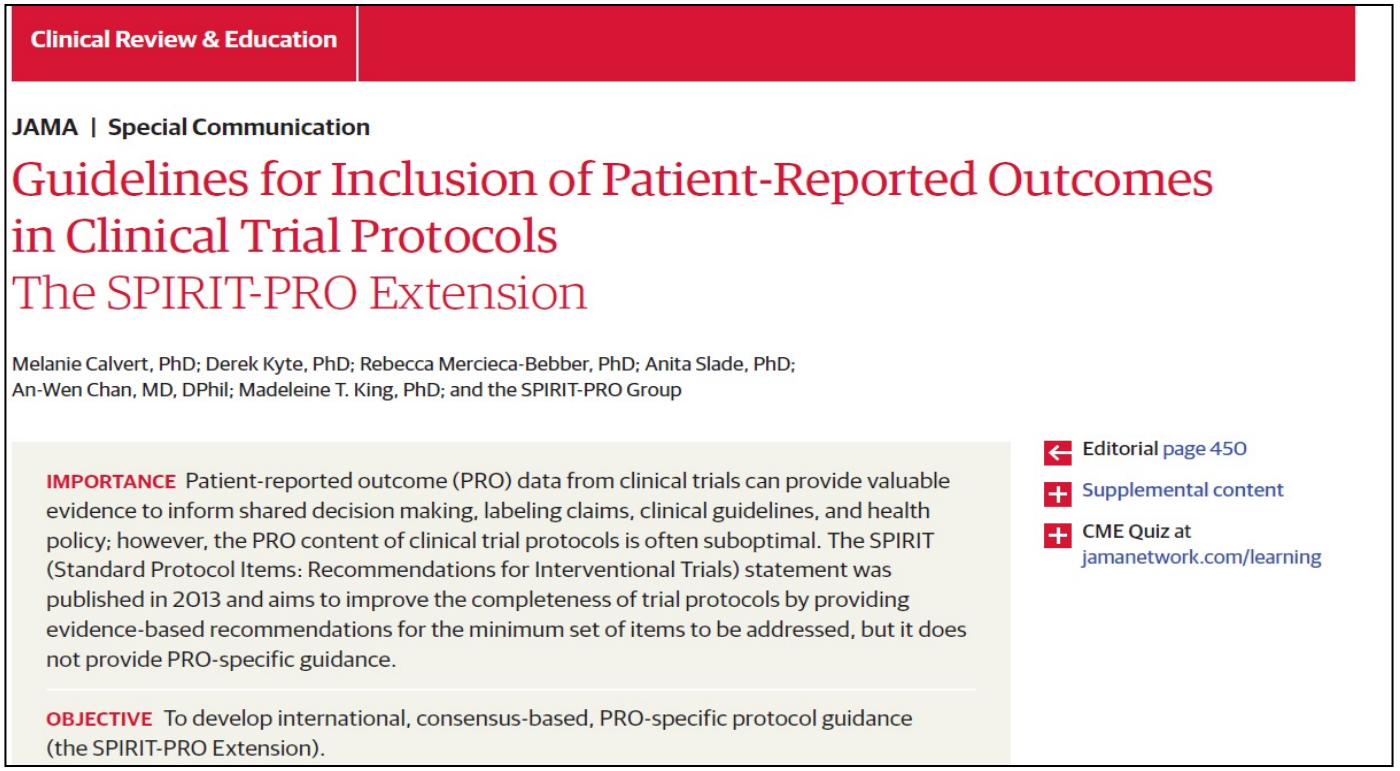
Specifying PRO Methods Appropriately



Clinical Review & Education

JAMA | Special Communication

Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols
The SPIRIT-PRO Extension

Melanie Calvert, PhD; Derek Kyte, PhD; Rebecca Mercieca-Bebber, PhD; Anita Slade, PhD; An-Wen Chan, MD, DPhil; Madeleine T. King, PhD; and the SPIRIT-PRO Group

IMPORTANCE 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. The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement was published in 2013 and aims to improve the completeness of trial protocols by providing evidence-based recommendations for the minimum set of items to be addressed, but it does not provide PRO-specific guidance.

OBJECTIVE To develop international, consensus-based, PRO-specific protocol guidance (the SPIRIT-PRO Extension).

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Supplemental content

CME Quiz at jamanetwork.com/learning

Calvert et al, JAMA 2018, 319(5), 483-494

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Disclaimer: Please note that views of authors, Delphi and stakeholder participants are individual views and may not represent the views of the broader stakeholder group or host institution.

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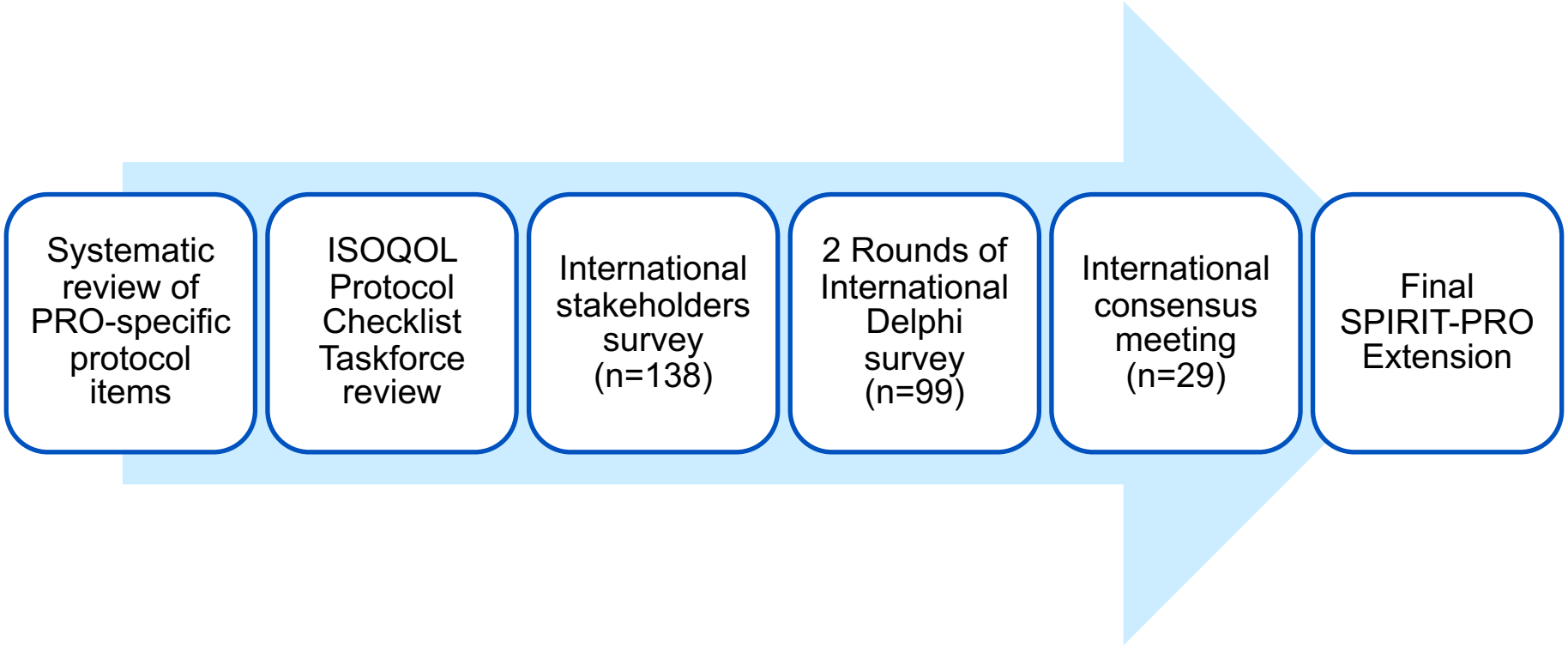
Why Do We Need a SPIRIT-PRO Extension?

- Protocol quality can be poor
- Data quality is variable
- Reporting is suboptimal
- Preventing/hindering uptake in practice
- SPIRIT 2013 (Standard Protocol Items: Recommendations for Interventional Trials) 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



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Overview of SPIRIT-PRO Protocol Guidance

- To be used in conjunction with the SPIRIT 2013 Statement and related extensions
- 5 elaborations on existing SPIRIT 2013 checklist items as applied to PROs in RCT protocols
- 11 extensions – additional PRO-specific items recommended for RCT protocols where PROs are a primary or important secondary outcome

SPIRIT
Standard Protocol Items: Recommendations for Interventional Trials

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SPIRIT Protocol Section

Administrative Information & Introduction

SPIRIT Item 5a - Roles & Responsibilities

SPIRIT 2013:

Names, affiliations, and roles of protocol contributors.

PRO Elaboration 2018:

Specify the individual(s) responsible for the PRO content of the trial protocol.

Explanation:

Promotes transparency and accountability.

Identifies appropriate point of contact for resolution of any PRO-specific queries.

When patients have actively contributed, document this.

SPIRIT Item 6a - Background & Rationale

SPIRIT 2013:

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.

PRO Extension 2018:

Describe the PRO specific research question and rationale for PRO assessment, and summarize PRO findings in relevant studies.

Explanation:

Helps select measures, specify hypotheses and analyses.

Helps staff and patients understand why PROs are being assessed, which may reduce missing data.

When PRO is secondary outcome, a brief rationale may be adequate.

SPIRIT Item 7 - Objectives

SPIRIT 2013:

Specific objectives or hypotheses.

PRO Extension 2018:

State specific PRO objectives or hypotheses (including relevant PRO concepts/domains).

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.

SPIRIT Protocol Section

Methods: Participants, Interventions, and Outcomes

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SPIRIT Item 10 - Eligibility Criteria

SPIRIT 2013:

Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centers and individuals who will perform the interventions (eg, surgeons, psychotherapists).

PRO Extension 2018:

Specify any PRO-specific eligibility criteria (eg, 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:

In some trials it may not be possible to collect PROs in the entire population (eg, validated questionnaires not available in all languages).

In large trials, sufficient power may be achieved by collecting PROs from a representative subset of participants.

SPIRIT Item 12 - Outcomes

SPIRIT 2013:

Primary, secondary, and other outcomes, including the specific measurement variable, analysis metric, method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended.

PRO Extension 2018:

Specify the PRO concepts/ domains used to evaluate the intervention (eg, overall HRQOL, specific domain, specific symptom).

For each of these, specify the analysis metric (eg, change from baseline, final value, time to event) and the principal time point or period of interest.

Explanation:

These should closely align with the trial objectives and hypotheses.

Reduces risk of multiple statistical testing.

SPIRIT Item 13 - Participant Timeline

SPIRIT 2013:

Time schedule of enrollment, interventions (including any run-ins and washouts), assessments, and visits for participants.

A schematic diagram is highly recommended.

PRO Extension 2018:

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 question-naires, whether order of administration standardized.

Explanation:

Will assist staff and may help reduce missing data.

Pre-randomization helps ensure unbiased baseline assessment; if eligibility criterion, ensures data completeness.

Time windows ensure that PROs captures the effect of the clinical event(s) of interest.

SPIRIT Item 14 - Sample Size

SPIRIT 2013:

Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations.

PRO Elaboration 2018:

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:

If PROs are primary: ideally, specify criteria for clinical significance (eg, minimal important difference) if known.

If PROs are secondary, specify whether the sample size provides sufficient power to test the principal PRO hypotheses.

SPIRIT Protocol Section

Methods: Data Collection, Management, and Analysis

SPIRIT Item 18a
Data Collection Methods

SPIRIT 2013:

Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, 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.

Four PRO Extensions 2018

SPIRIT Item 18a - Data Collection Methods

PRO Extension (i) 2018:

Justify the PRO instrument, describe domains, no. items, recall period, instrument scaling/scoring (eg, 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.

Consider 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 Item 18a - Data Collection Methods

PRO Extension (ii) 2018:

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

Explanation:

Research personnel and trial participants need to know how, when, and where PRO data will be collected.

The setting for PRO data collection should be described and standardized across trial intervention groups and sites.

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.

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SPIRIT Item 18a - 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:

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.

SPIRIT Item 18a - 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, eg, 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.

SPIRIT Item 18b - Data Collection Methods

SPIRIT 2013:

Plans for assessment and collection of outcome, baseline, and other trial data, including:

- any related processes to promote data quality (eg, duplicate measurements, training of assessors);

- a description of study instruments (eg, 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.

One PRO Extension & One PRO Elaboration 2018

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SPIRIT Item 18b - 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:

- participants with the poorest outcomes are often those who do not complete planned PRO assessments;

- PRO data cannot be obtained retrospectively.

Potentially source of bias, may reduce trial power.

Not all missing PRO data are avoidable: patients have the right to decide not to complete questionnaires.

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SPIRIT Item 18b - 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:

Ensures that staff collect all required PRO data in a standardized and timely way.

Helps minimize bias.

May assist ethical appraisal of the study.

SPIRIT 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:

Several domains and time points implies multiple hypothesis testing, inflates the probability of false-positive results (type I error).

Pre-specifying key PRO domain(s) and time point(s) helps (Item 12).

Protocol should either fully address or summarize and refer to where details can be found, eg, SAP.

SPIRIT Item 20c - Statistical Methods

SPIRIT 2013:

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

PRO Elaboration 2018:

State how missing data will be described and outline the methods for handling missing items or entire assessments (eg, approach to imputation and sensitivity analyses).

Explanation:

2 levels of missing PRO data:

1) Some items in a questionnaire are missed - whether/how these are imputed is specified in the instrument's scoring algorithm.

2) Entire PRO assessment missed - analysis requires assumptions about why those data were missing (ie, the missing data mechanism).

SPIRIT Protocol Section

Methods: Monitoring

SPIRIT 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, eg, in the participant information sheet and consent form.

Explanation:

To protect participant safety, PRO data may be monitored during a study for signs of psychological distress or physical symptoms that may require an immediate response: so-called ‘PRO Alerts’.

Monitoring and management must be standardized to minimize potential bias.

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

Recap

- Why is the SPIRIT-PRO Checklist needed?
  - PRO content of protocols is often incomplete and inconsistent
- What does the SPIRIT-PRO Checklist do?
  - Supplements the standard SPIRIT guidelines for writing RCT protocols
  - Recommends 16 items to be included in all RCT protocols in which PROs are a primary or important secondary outcome
  - If used, will ensure critical aspects of the PRO study are included in the protocol → high quality PRO data and evidence
- Implementation is the key! By following the SPIRIT-PRO recommendations, we can improve the quality and completeness of PRO content in protocols

Further Reading

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.

Calvert M, 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.*

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

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.

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