

# Guidelines for inclusion of patient-reported outcomes in clinical trial protocols

SPIRIT-PRO Group

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# Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols

## The SPIRIT-PRO Extension

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**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).

**DESIGN, SETTING, AND PARTICIPANTS** The SPIRIT-PRO Extension was developed following the Enhancing Quality and Transparency of Health Research (EQUATOR) Network's methodological framework for guideline development. This included (1) a systematic review of existing PRO-specific protocol guidance to generate a list of potential PRO-specific protocol items (published in 2014); (2) refinements to the list and removal of duplicate items by the International Society for Quality of Life Research (ISOQOL) Protocol Checklist Taskforce; (3) an international stakeholder survey of clinical trial research personnel, PRO methodologists, health economists, psychometricians, patient advocates, funders, industry representatives, journal editors, policy makers, ethicists, and researchers responsible for evidence synthesis (distributed by 38 international partner organizations in October 2016); (4) an international Delphi exercise (n = 137 invited; October 2016 to February 2017); and (5) consensus meeting (n = 30 invited; May 2017). Prior to voting, consensus meeting participants were informed of the results of the Delphi exercise and given data from structured reviews evaluating the PRO protocol content of 3 defined samples of trial protocols.

**RESULTS** The systematic review identified 162 PRO-specific protocol recommendations from 54 sources. The ISOQOL Taskforce (n = 21) reduced this to 56 items, which were considered by 138 international stakeholder survey participants and 99 Delphi panelists. The final wording of the SPIRIT-PRO Extension was agreed on at a consensus meeting (n = 29 participants) and reviewed by external group of experts during a consultation period. Eleven extensions and 5 elaborations to the SPIRIT 2013 checklist were recommended for inclusion in clinical trial protocols in which PROs are a primary or key secondary outcome. Extension items focused on PRO-specific issues relating to the trial rationale, objectives, eligibility criteria, concepts used to evaluate the intervention, time points for assessment, PRO instrument selection and measurement properties, data collection plan, translation to other languages, proxy completion, strategies to minimize missing data, and whether PRO data will be monitored during the study to inform clinical care.

**CONCLUSIONS AND RELEVANCE** The SPIRIT-PRO guidelines provide recommendations for items that should be addressed and included in clinical trial protocols in which PROs are a primary or key secondary outcome. Improved design of clinical trials including PROs could help ensure high-quality data that may inform patient-centered care.

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**C**linical trial protocols are essential documents that describe the study design and conduct. A protocol should provide sufficient detail to enable funders, reviewers, and ethics committees to appraise the scientific, methodological, and ethical rigor of the trial and for the research team to conduct a high-quality study.<sup>1,2</sup> Although trial protocols serve as the foundation for study planning, conduct, reporting, and appraisal, they vary greatly in content and quality.<sup>1,2</sup> To address this issue, the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement was published in 2013.<sup>1,2</sup> SPIRIT provides an evidence-based list of items recommended for inclusion in trial protocols. It does not, however, provide specific guidance on protocol content relating to patient-reported outcomes (PROs), such as health-related quality of life or patient-reported symptoms.

The importance of PROs has been recognized by major international health policy and regulatory authorities and patients.<sup>3-5</sup> Patient-reported outcome results of trials, if captured in a scientifically rigorous way, may inform clinical decision making,<sup>6</sup> pharmaceutical labeling claims,<sup>4,5</sup> and product reimbursement and influence health care policy.<sup>6</sup> Despite this, the quality of PRO content in many protocols is often suboptimal, regardless of the degree of adherence to SPIRIT.<sup>7-9</sup> Because PROs are intrinsically subjective and require completion by patients within a specific time frame, they present a range of scientific and logistical challenges for researchers.<sup>10-12</sup> Comprehensive planning and instruction in the protocol can mitigate many PRO-specific issues through trial conduct and subsequent analysis and reporting. Protocol developers, particularly those not familiar with PRO methodology, may benefit from explanation of PRO-specific aspects to facilitate improvements in content.

The aim of this international project was to develop an evidence-based extension of the SPIRIT 2013 statement, identifying additional PRO items recommended for inclusion in clinical trial protocols (extensions), and to elaborate on the existing SPIRIT 2013 statement specifically as applied to PROs (elaborations).<sup>13</sup> This Special Communication describes the methods used to gain consensus on each additional SPIRIT-PRO extension/elaboration, provides a brief explanatory rationale, and includes PRO-specific items that may be included in supplemental trial documents.

## SPIRIT-PRO Development Methods

The SPIRIT-PRO Extension was developed according to the Enhancing Quality and Transparency of Health Research (EQUATOR) Network's methodological framework for guideline development (eFigure 1 in [Supplement 1](#)).<sup>14</sup> This included a systematic review of existing PRO-specific protocol guidance,<sup>15</sup> 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.<sup>14</sup> The systematic review comprised a search of the MEDLINE, EMBASE, CINAHL, and Cochrane Library databases (inception to February 2013) using the key words *patient-reported outcomes* or *health-related quality of life* in combination with *guidance*, *guidelines*, or *checklist*. Further guidance documents were identified via Google, Google Scholar, requests to

### Key Points

**Question** What information should be included in a clinical trial protocol when a patient-reported outcome (PRO) is a primary or key secondary outcome?

**Findings** Following an international consensus development process using the Enhancing Quality and Transparency of Health Research (EQUATOR) methodology, 16 PRO-specific items were recommended for inclusion in clinical trial protocols.

**Meaning** Inclusion of these items in clinical trial protocols may help improve the quality of PRO data.

members of the UK Clinical Research Collaboration registered clinical trials units, international experts, and citation and reference searches of included articles. Articles were deemed eligible if they contained guidance, a checklist, or both regarding PRO-related trial protocol content.<sup>15</sup>

eFigure 1 in [Supplement 1](#) summarizes the methods and participants involved in the development of SPIRIT-PRO, the numbers of candidate items considered at each step, and the flow toward the final set of items included in SPIRIT-PRO. The eTable in [Supplement 1](#) outlines the participant characteristics. Patient partners contributed to the co-design of the research and grant application and have provided input throughout the study.

### Ethical Review of Study

Ethical approval was provided by the University of Birmingham Ethical Review Board (ERN\_16-0819). Participant information was provided to potential participants electronically prior to survey completion and in advance of the consensus meeting. Survey participants provided electronic informed consent, and written consent was provided by the consensus meeting participants.

### Systematic Review of Existing PRO-Specific Protocol Guidance and Development of the Delphi and Stakeholder Survey

Our systematic review of existing PRO protocol guidance identified 162 PRO-specific protocol recommendations from 54 sources, such as the need to specify the timing of PRO assessment, the provision of PRO data collection and analyses plans, and specification/justification for the chosen PRO questionnaire.<sup>15</sup> The International Society for Quality of Life Research (ISOQOL) Protocol Checklist Taskforce comprising international experts in PROs research and clinical trials (eTable and eAppendix in [Supplement 1](#)) reduced this list to 56 candidate items by removing or merging duplicate items, meaning that 56 items were included in the subsequent identical stakeholder and Delphi surveys. Survey participants were asked to rate the importance of including each of the 56 candidate items in the final SPIRIT-PRO Extension using a 9-point scale ranging from not important (1-3) to important but not critical (4-6) and critical (7-9). Respondents provided separate ratings according to whether a PRO was included as a primary vs secondary outcome in a trial.

### International Stakeholder Survey

In 2016, an anonymized online international stakeholder survey was conducted targeting clinical trial research personnel, PRO

**Box. Glossary**

**SPIRIT:** Standard Protocol Items: Recommendations for Interventional Trials<sup>1,2</sup>

**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

**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

**Patient-reported outcome (PRO):** an outcome reported directly by patients themselves and not interpreted by an observer; PROs may include patient assessments of health status, quality of life, or symptoms<sup>17</sup>

**Proxy-reported outcome:** "a measurement based on a report by someone other than the patient reporting as if he or she is the patient"<sup>4</sup>

**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"<sup>17</sup>

**Primary outcome/end point:** the most important outcome in a trial, providing the most clinically relevant evidence directly related to the primary objective of the trial

**Secondary outcomes/end point(s):** outcomes prespecified in the protocol to assess additional effects of the intervention; some PROs may be identified as important or key secondary outcomes

**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; eg, 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 labeling claim. Because these outcomes are linked with hypotheses (CONSORT PRO Extension 2b),<sup>17</sup> they may be subject to *P*-value adjustment (or "α spending"). Patient-reported outcomes not only may provide evidence of efficacy/effectiveness but also may be intended to capture and provide evidence of safety and tolerability (eg, PRO-CTCAE).<sup>18</sup>

**Concept:** "The specific measurement goal (ie, 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."<sup>4</sup>

**Domain:** "A subconcept represented by a score of an instrument that measures a larger concept comprised of multiple domains. For example, psychological function is the larger concept containing the domains subdivided into items describing emotional function and cognitive function."<sup>4</sup>

**Instrument:** "A means to capture data (eg, 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."<sup>4</sup>

**Item:** "an individual question, statement, or task (and its standardized response options) that is evaluated by the patient to address a particular concept"<sup>4</sup>

**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<sup>19</sup>

methodologists, health economists, psychometricians, patient advocates, funders, industry representatives, journal editors, policy makers, ethicists, and researchers responsible for evidence synthesis. Respondents were self-selected volunteers from a sample of eligible individuals recruited via 38 international partner organizations (listed in the eAppendix in [Supplement 1](#)). From these organizations, 138 participants provided anonymized survey results, which informed round 2 of the Delphi panel exercise.

### International Delphi Exercise

In parallel with the international stakeholder survey, 114 key experts from the ISOQOL Protocol Checklist Taskforce, international partner organizations, and other experts known or recommended to the SPIRIT-PRO Executive (eAppendix in [Supplement 1](#)) were invited to join an international, multidisciplinary expert Delphi panel. Delphi panelists were advised not to complete the stakeholder survey to avoid double counting of results. Ninety-nine Delphi panelists completed 2 rounds of online surveys, and results informed the subsequent international consensus meeting. Data collected from the stakeholder and round 1 Delphi surveys were anonymized, and the item-level results were provided to the

Delphi panel for consideration prior to voting in Delphi round 2. Further details and the results of the Delphi and stakeholder surveys are available on the study website.<sup>16</sup>

### Consensus Meeting

Using the results from the stakeholder survey and Delphi process, the SPIRIT-PRO Operations Team (M.C., D.K., R.M.B., A.S., and M.K.) mapped the 56 candidate SPIRIT-PRO items to corresponding SPIRIT-2013 items, revising wording as needed to address stakeholder/Delphi panelist comments. For each candidate SPIRIT-PRO item, the Operations Team presented the consensus meeting delegates with recommendations for SPIRIT elaborations and extensions (see **Box** for definitions) based on a decision tree (eFigure 2 in [Supplement 1](#)) that incorporated information drawn from the Delphi survey and 3 separate reviews of PRO protocol content (n = 207 protocols): protocols from the UK National Institute for Health Research (NIHR) Health Technology Assessment program<sup>7</sup>; cancer trial protocols from the NIHR<sup>8</sup>; and international ovarian cancer protocols.<sup>9</sup> Twenty-nine participants purposively sampled from the Delphi panel attended the 2-day consensus meeting hosted by the University of Birmingham in May 2017 (eTable in [Supplement 1](#)). The meeting was designed to

seek consensus on the content of the SPIRIT-PRO Extension. Meeting participants were invited to consider the focus of the guidance and agreed that it should apply to trials in which PROs are a primary or key secondary outcome (as defined in the glossary [Box]). Delegates anonymously voted using Turning Point)/Responseware software, version 5.1 (Turning Technologies LLC), to (1) include the candidate item as recommended; (2) exclude the item; (3) or initiate further discussion. Key research evidence (round 2 Delphi survey results and systematic review data) presented to meeting participants is available in [Supplement 2](#). Consensus meeting participants were also invited to review Delphi results for recommendation on where to include each of the candidate items in addition to or instead of the trial protocol (eg, guidance/training for trial staff, information/guidance for study participants, or the statistical analysis plan).

### Final Consultation

Following the consensus meeting, attendees commented on wording and agreed on the penultimate SPIRIT-PRO Extension content. Broader feedback on the final guidance was sought from the Delphi panel and international partners during a 3-week consultation period. Final edits in response to feedback were made by the Operations Team and agreed on by the SPIRIT-PRO Group.

## Results

### SPIRIT-PRO Checklist Items and Explanation

The final SPIRIT-PRO Extension recommends that, in conjunction with existing SPIRIT 2013 items, 16 items (11 extensions and 5 elaborations) should be routinely addressed in all clinical trial protocols in which PROs are a primary or key secondary outcome. Further information regarding the SPIRIT 2013 items has been published by Chan et al.<sup>1,2</sup> The [Table](#) lists the items of the SPIRIT 2013 checklist and the SPIRIT-PRO extensions and elaborations. In total, the 11 extensions and 5 elaborations incorporated content from 34 of the original 56 candidate items, comprising 27 items that were merged during the consensus meeting and a further 7 items that remained unchanged. One new item, SPIRIT-18a(iii)-PRO Extension, was generated through discussion. Definitions of key terms are contained in the glossary (Box). A brief explanation for each PRO extension or elaboration is included herein, with references to supporting empirical evidence when available (items 6a through 22). Item 5a was not supported by empirical evidence but was supported by expert opinion drawn from our systematic review of PRO protocol guidance<sup>15</sup> and, in line with the development of the original SPIRIT statement,<sup>1,2</sup> was underpinned by a strong pragmatic rationale.

### Administrative Information

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

*Explanation:* Providing information (eg, 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.<sup>21</sup>

**SPIRIT-6a-PRO Extension:** Describe the PRO-specific research question and rationale for PRO assessment and summarize PRO findings in relevant studies.

*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. Evidence suggests that many trials include PROs without specifying the PRO-specific research question and without a rationale or any reference to PROs in related studies.<sup>7-9</sup> Consequently, staff and patients may not understand why PROs are being assessed, and missing data may result.<sup>7,12</sup> When the PRO is a secondary outcome, a brief rationale may be adequate.

**SPIRIT-7-PRO Extension:** State specific PRO objectives or hypotheses (including relevant PRO concepts/domains).

*Explanation:* PRO measures may be multidimensional (eg, health-related quality of life) or unidimensional (eg, specific symptoms such as pain), and assessments may be scheduled at several time points during a trial. Prespecification 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 (see also PRO elaboration 20a below).<sup>4</sup>

### Methods: Participants, Interventions, and Outcomes

**SPIRIT-10-PRO Extension:** Specify any PRO-specific eligibility criteria (eg, language/reading requirements or prerandomization<sup>22</sup> 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.

*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 (eg, because of nonavailability of validated questionnaires in all languages)<sup>8</sup>; in such instances, the rationale for the sampling method should be described.

**SPIRIT-12-PRO Extension:** Specify the PRO concepts/domains used to evaluate the intervention (eg, overall health-related quality of life, specific domain, specific symptom) and, for each one, the analysis metric (eg, 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.<sup>4,23</sup>

**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.

*Explanation:* Provision of an easy-to-follow schedule will assist staff and may help reduce missing data.<sup>22</sup> Collecting PRO data prior

**Table. SPIRIT 2013 and SPIRIT-PRO Extension Checklist: Recommended Items to Address in a Clinical Trial Protocol<sup>a</sup>**

SPIRIT Section	SPIRIT Item No.	SPIRIT Item Description	SPIRIT-PRO Item No.	SPIRIT-PRO Extension or Elaboration Item Description	Addressed on Page No. <sup>b</sup>
<b>Administrative Information</b>					
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym			
Trial registration	2a	Trial identifier and registry name (if not yet registered, name of intended registry)			
	2b	All items from the World Health Organization Trial Registration Data Set			
Protocol version	3	Date and version identifier			
Funding	4	Sources and types of financial, material, and other support			
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	SPIRIT-5a-PRO Elaboration	Specify the individual(s) responsible for the PRO content of the trial protocol.	
	5b	Name and contact information for the trial sponsor			
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities			
	5d	Composition, roles, and responsibilities of the coordinating center, steering committee, end-point adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see item 21a for data monitoring committee)			
<b>Introduction</b>					
Background and rationale	6a	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	SPIRIT-6a-PRO Extension	Describe the PRO-specific research question and rationale for PRO assessment and summarize PRO findings in relevant studies.	
	6b	Explanation for choice of comparators			
Objectives	7	Specific objectives or hypotheses	SPIRIT-7-PRO Extension	State specific PRO objectives or hypotheses (including relevant PRO concepts/domains).	
Trial design	8	Description of trial design, including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)			
<b>Methods: Participants, Interventions, and Outcomes</b>					
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected; reference to where list of study sites can be obtained			
Eligibility criteria	10	Inclusion and exclusion criteria for participants; if applicable, eligibility criteria for study centers and individuals who will perform the interventions (eg, surgeons, psychotherapists)	SPIRIT-10-PRO Extension	Specify any PRO-specific eligibility criteria (eg, 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.	

(continued)

**Table. SPIRIT 2013 and SPIRIT-PRO Extension Checklist: Recommended Items to Address in a Clinical Trial Protocol<sup>2</sup> (continued)**

SPIRIT Section	SPIRIT Item No.	SPIRIT Item Description	SPIRIT-PRO Item No.	SPIRIT-PRO Extension or Elaboration Item Description	Addressed on Page No. <sup>b</sup>
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered			
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)			
	11c	Strategies to improve adherence to intervention protocols and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)			
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial			
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), 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	SPIRIT-12-PRO Extension	Specify the PRO concepts/domains used to evaluate the intervention (eg, overall health-related quality of life, specific domain, specific symptom) and, for each one, the analysis metric (eg, change from baseline, final value, time to event) and the principal time point or period of interest.	
Participant timeline	13	Time schedule of enrollment, interventions (including any run-ins and washouts), assessments, and visits for participants; a schematic diagram is highly recommended (see figure in Chan et al <sup>1,2</sup> )	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	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	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.	
Recruitment	15	Strategies for achieving adequate participant enrollment to reach target sample size			
<b>Methods: Assignment of Interventions (for Clinical Trials)</b>					
<b>Allocation</b>					
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions.			
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned			
Implementation	16c	Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions			
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts) and how			
	17b	If blinded, circumstances under which unblinding is permissible and procedure for revealing a participant's allocated intervention during the trial			

(continued)

Table. SPIRIT 2013 and SPIRIT-PRO Extension Checklist: Recommended Items to Address in a Clinical Trial Protocol<sup>a</sup> (continued)

SPIRIT Section	SPIRIT Item No.	SPIRIT Item Description	SPIRIT-PRO Item No.	SPIRIT-PRO Extension or Elaboration Item Description	Addressed on Page No. <sup>b</sup>
<b>Methods: Data Collection, Management, and Analysis</b>					
Data collection methods	18a	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 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	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 (eg, 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 the permitted mode(s) of administration (eg, paper, telephone, electronic, other) and setting (eg, 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 if available.	
	18b	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	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.	
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values); reference to where details of data management procedures can be found, if not in the protocol			
Statistical methods	20a	Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	SPIRIT-20a-PRO Elaboration	State PRO analysis methods, including any plans for addressing multiplicity/type I (α) error.	
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)			
	20c	Definition of analysis population relating to protocol nonadherence (eg, as randomized analysis) and any statistical methods to handle missing data (eg, multiple imputation)	SPIRIT-20c-PRO Elaboration	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).	
<b>Methods: Monitoring</b>					
	21a	Composition of data monitoring committee; summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol (alternatively, an explanation of why a data monitoring committee is not needed)			
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial			

(continued)

**Table. SPIRIT 2013 and SPIRIT-PRO Extension Checklist: Recommended Items to Address in a Clinical Trial Protocol<sup>a</sup> (continued)**

SPIRIT Section	SPIRIT Item No.	SPIRIT Item Description	SPIRIT-PRO Item No.	SPIRIT-PRO Extension or Elaboration Item Description	Addressed on Page No. <sup>b</sup>
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	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; eg, in the participant information sheet and consent form.	
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and sponsor(s)			
<b>Ethics and Dissemination</b>					
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board approval			
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, research ethics committees/institutional review boards, trial participants, trial registries, journals, regulators)			
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized surrogates and how (see item 32)			
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable			
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained to protect confidentiality before, during, and after the trial			
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site			
Access to data	29	Statement of who will have access to the final trial data set and disclosure of contractual agreements that limit such access for investigators			
Ancillary and posttrial care	30	Provisions, if any, for ancillary and posttrial care and for compensation to those who are harmed by trial participation			
Dissemination policy	31a	Plans for investigators and sponsor(s) to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data-sharing arrangements), including any publication restrictions			
	31b	Authorship eligibility guidelines and any intended use of professional writers			
	31c	Plans, if any, for granting public access to the full protocol, participant-level data set, and statistical code			
<b>Appendixes</b>					
Informed consent materials	32	Model consent form and other related documentation given to participants and authorized surrogates			
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable			

Abbreviations: SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; PRO, patient-reported outcome.

<sup>a</sup> It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.<sup>1,2,20</sup> Amendments to the protocol should be tracked and dated.

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<sup>b</sup> Indicates page numbers to be completed by authors during protocol development.

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.<sup>24</sup> 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-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.

*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.<sup>23</sup> Ideally, the criteria for clinical significance (eg, minimal important difference, responder definition) should be specified when known.<sup>25,26</sup> If PROs are a secondary end point, researchers should specify whether the sample size provides sufficient power to test the principal PRO hypotheses.<sup>23</sup>

#### Methods: Data Collection, Management, and Analysis

**SPIRIT-18a(i)-PRO Extension:** Justify the PRO instrument to be used and describe domains, number of items, recall period, instrument scaling and scoring (eg, 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.

*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.<sup>27</sup> Consideration should be given to the number of questionnaires to be used, acceptability of the questions, and the likely patient burden (eg, time taken for completion, cognitive burden, emotional burden). Justification for the measures selected will help trial personnel understand why specific measures are being used.<sup>10</sup> 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-18a(ii)-PRO Extension:** Include a data collection plan outlining the permitted mode(s) of administration (eg, paper, telephone, electronic, other) and setting (eg, 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. Increasingly, electronic PRO assessment is undertaken in trials, so evidence of equivalence between different modes of administration should be considered.<sup>28</sup> 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.<sup>28,29</sup> The setting for PRO data collection should be described and standardized across trial intervention groups and sites.

**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.

*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.<sup>11,30</sup> 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-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 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.<sup>17</sup> 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."<sup>5</sup> The US Food and Drug Administration also discourages the use of proxy-reported outcomes to inform labeling claims, recommending observer reports instead.<sup>4</sup>

**SPIRIT-18b(i)-PRO Extension:** Specify PRO data collection and management strategies for minimizing avoidable missing data.

*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.<sup>31</sup> It is important to note that not all missing PRO data are avoidable: patients 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. A recent systematic review provides a range of design, implementation, and reporting strategies to help minimize and address missing PRO data.<sup>22</sup> 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.<sup>22</sup>

**SPIRIT-18b(ii)-PRO Elaboration:** Describe the process of PRO assessment for participants who discontinue or deviate from the 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,<sup>32</sup> ensures that staff collect all required PRO data in a standardized and timely way, and may assist ethical appraisal of the study.

**SPIRIT-20a-PRO Elaboration: State PRO analysis methods, including any plans for addressing multiplicity/type I ( $\alpha$ ) error.**

*Explanation:* Many questionnaires, such as health-related quality-of-life measures, are multidimensional and therefore may yield several summary scores (eg, 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).<sup>23</sup> 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, whereby multiple end points are tested in a defined sequence that contains the overall type I error to the desired level, or conventional nonhierarchical methods (eg, Bonferroni correction), should be specified a priori.<sup>4</sup> The protocol should either fully address these issues or provide a summary with reference to where full details can be found (eg, in the statistical analysis plan).

**SPIRIT-20c-PRO Elaboration: 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:* 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 (ie, 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.<sup>32</sup> Inappropriate method selection may lead to potentially biased and misleading results.<sup>22,32</sup> The protocol should acknowledge and summarize these issues, with full details provided in the statistical analysis plan.

### **Methods: Monitoring**

**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; eg, 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.<sup>10,11,33</sup> To protect the interests of trial participants and minimize potential bias, it is important to specify plans for monitoring.<sup>34</sup> 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.

### **Supplementary Trial Documents**

**Supplement 3** outlines additional items recommended for inclusion in other trial documentation, such as the statistical analysis plan, participant information sheet, and training and guidance documents for staff.

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## **Discussion**

The SPIRIT-PRO Extension provides international consensus-based guidance on PRO-specific information that should be included in clinical trial protocols. It comprises 16 items: 5 elaborations to existing SPIRIT 2013 items in the context of PROs and 11 new extensions for use alongside the existing SPIRIT 2013 guidance.<sup>1,2</sup> It is important to note that these are minimum requirements and that there may be value in including additional items in the protocols, in supplementary information, or in both, as outlined in **Supplement 3**. Although this guidance has been developed for trials for which PROs are a primary or key secondary outcome, research groups that create protocols are encouraged to consider use of this guidance in all trials or clinical research studies in which PROs are collected, including if PROs are exploratory end points. The guidance does not aim to be prescriptive regarding how information should be included, as this may vary depending on the research setting and local requirements. Further details of empirical evidence underpinning the SPIRIT-PRO items and examples for implementation will be provided in a future publication on the PROlearn<sup>35</sup> and SPIRIT Initiative<sup>20</sup> websites and will be facilitated through further development of the SPIRIT 2013 implementation tool SEPTRE<sup>20</sup> (SPIRIT Electronic Protocol Tool and Resource) and through dissemination via international partners (eAppendix in **Supplement 1**). Inclusion of PRO-specific protocol content will facilitate appraisal of the PRO elements by funders, reviewers, research ethics committees, and patient partners. The SPIRIT-PRO Extension is intended to encourage and facilitate careful planning of PRO components of trials and thereby improve PRO trial design. Consequently, this is expected to help staff and patients understand the rationale for PRO assessment, improve PRO data completeness and quality, facilitate high-quality analysis and reporting, and ultimately improve the quality of the global PRO evidence base.

To maximize the benefit of PRO data in policy and in practice, it is recommended that careful consideration be given to the selection of outcomes and measures,<sup>36,37</sup> analysis of PRO data,<sup>4,5,38</sup> and transparent reporting in accordance with CONSORT-PRO.<sup>17</sup> Patient and public involvement in all of these aspects can help ensure that PRO selection and application is transparent, relevant, and acceptable.<sup>39,40</sup> Consistent with this philosophy, patient partners have been involved in all aspects of the development of the SPIRIT-PRO Extension.<sup>39,40</sup> Ultimately, high-quality PRO trial results will help ensure that patients' voices are central to informing shared decision making, labeling claims, clinical guidelines, and health policy, making patient-centered care a reality.

This study has several limitations. First, as the international stakeholder survey included an anonymized nonprobability sample, we were unable to determine either the level or characteristics of nonresponders, meaning that the results of the survey could be affected by nonresponse bias. Second, respondents to the stakeholder survey were self-selecting and Delphi and

consensus meeting participants were purposively sampled based on their roles and expertise relating to PROs. Participants are therefore more likely to have more knowledge relating to PROs than broader research personnel. Third, the systematic review underpinning the process was conducted in 2013; however, throughout the guideline development process, the expert Delphi and consensus meeting participants are encouraged to highlight any additional relevant publications.

## Conclusions

The SPIRIT-PRO guidelines provide recommendations for items that should be addressed and included in clinical trial protocols in which PROs are a primary or key secondary outcome. Improved design of clinical trials including PROs could help ensure high-quality data that may inform patient-centered care.

### ARTICLE INFORMATION

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