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

Authorship:

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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, sixteen PRO specific items are recommended for inclusion in clinical trial protocols.

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

Revision: 18 December 2017

Word Count: 3941

ABSTRACT (338/350 words)

Importance

Patient-reported outcome (PRO) data from clinical trials can provide valuable evidence to inform shared-decision making, labelling 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 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: (i) a systematic review of existing PRO-specific protocol guidance to generate a list of candidate PRO-specific protocol items (published 2014); (ii) refinements to the list and removal of duplicate items by the International Society for Quality of Life Research (ISOQOL) PROtocol Checklist Taskforce; (iii) 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, October 2016); (iv) an international Delphi exercise (n=137 invited; October 2016 to February 2017)and 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 three 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 stakeholders and 99 Delphi panelists. The final wording of the SPIRIT-PRO Extension was agreed at a consensus meeting (n=29 participants) and reviewed by external stakeholders during a consultation period. Eleven extensions and five elaborations to the SPIRIT 2013 checklist are recommended for inclusion in clinical trial protocols where 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, timepoints for assessment, PRO instrument selection and measurement properties, data collection plan, translation to other languages, proxy completion, strategies to minimise missing data and whether PRO data will be monitored during the study to inform clinical care.

Conclusions and relevance

These 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.

INTRODUCTION

Clinical 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 trial's scientific, methodological and ethical rigor and for the research team to deliver a high quality study.[1,2] Although they serve as the foundation for study planning, conduct, reporting, and appraisal, trial protocols vary greatly in content and quality.[1,2] To address this issue, the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) Statement was published in 2013.[1,2] 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 (HRQOL) or patient-reported symptoms.

The importance of PROs has been recognized by major international health policy and regulatory authorities and patients.[3-5] PRO trial results, if captured in a scientifically rigorous way, may inform clinical decision-making[6], pharmaceutical labelling claims[4-5], product reimbursement and influence healthcare policy.[6] Despite this, the quality of PRO content in many protocols is often suboptimal, regardless of the degree of adherence to SPIRIT.[7-9] 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 and data collection staff.[10-12] 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).[13] This article 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).[14] This included: a systematic review of existing PRO-specific protocol guidance[15]; an international stakeholder survey; Delphi exercise and consensus meeting; followed by consultation on the final SPIRIT-PRO Extension.[14] The systematic review comprised a search of MEDLINE, EMBASE, CINHAL 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 members of the UK Clinical Research Collaboration registered clinical trials units, international experts and through citation and reference searches of included articles. Papers were deemed eligible if they contained guidance and/or a checklist on PRO related trial protocol content.[15]

eFigure 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 towards the final set of items included in SPIRIT PRO. eTable 1 in Supplement 1 outlines the participant characteristics. Patient partners contributed to the co-design of the research, grant application, have provided input throughout the study and are coauthors.

Ethical Review of Study

Ethical approval was provided by The University of Birmingham Ethical Review Board (Reference: ERN_16-0819). Participant information was provided to potential participants 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[15]. The International Society for Quality of Life Research (ISOQOL) PROtocol Checklist Taskforce comprising international experts in PROs research and clinical trials

(eTable 1 and Acknowledgments, Supplement 1) reduced this list to 56 candidate items by removing or merging duplicate items, meaning 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: 'not important' (1-3), 'important but not critical' (4-6) and 'critical' (7-9). Respondents provided separate ratings according to whether a PRO was included as a primary versus secondary outcome in a trial.

International stakeholder survey

In 2016, 38 international partner organizations (detailed in Supplement 1) invited their members with relevant expertise to complete an online survey. From these organizations, a total 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, key experts (n=114) from the ISOQOL PROtocol Checklist Taskforce, international partner organizations and other experts known or recommended to the SPIRIT-PRO Executive 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. Delphi panelists (n=99) 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.[16]

Consensus meeting

Using the Stakeholder and Delphi survey results, the SPIRIT-PRO Operations Team (MC, DK, RMB, AS, MK) 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), which incorporated information drawn from the Delphi survey and three separate

reviews of PRO protocol content (n= 207 protocols): protocols from the UK National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme[7]; cancer trial protocols from the NIHR[8] and international ovarian cancer protocols[9]. Twenty-nine participants purposively sampled from the Delphi panel attended the two-day consensus meeting hosted by the University of Birmingham, England, in May 2017 (eTable 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 where PROs are a primary or key secondary outcome (as defined in Glossary). Delegates anonymously voted using Turning point© (v5.1, 2012)/Responseware© software to either: include the candidate item as recommended; exclude the item; or initiate further discussion. Key research evidence (Round 2 Delphi survey results and systematic review data) presented to meeting participants is provided 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 (SAP).

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 our Delphi panel and international partners during a three week consultation period. Final edits in response to feedback were made by the Operations Team and agreed 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 should be routinely addressed in all clinical trial protocols where PROs are a primary or key secondary outcome (11 extensions; 5 elaborations). Further information regarding the SPIRIT 2013 items is detailed in references[1,2]. Table 1 lists the items of the SPIRIT 2013 checklist (left column) and

the SPIRIT-PRO extensions/elaborations (right-hand column). The 11 extensions and 5 elaborations incorporated 34 of the original 56 candidate items, as 27 items were merged by consensus. One new item was generated through discussion (SPIRIT-18a-PRO Extension (iii)). Definitions of key terms are contained in the Glossary (Box). Below we provide a brief explanation for each PRO extension/elaboration, including references to supporting empirical evidence where 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[15], and in line with the development of the original SPIRIT statement[1, 2] , was underpinned by a strong pragmatic rationale.

Administrative Information

Specify the individual(s) responsible for the PRO content of the trial protocol: SPIRIT-5a-PRO Elaboration. *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. Where patients have actively contributed to this process, this should be documented as per recent guidance for the reporting of patient and public involvement.[17]

Describe the PRO specific research question and rationale for PRO assessment, and summarize PRO findings in relevant studies: SPIRIT-6a-PRO Extension. *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.[7-9] Consequently, staff and patients may not understand why PROs are being assessed, and missing data may result.[7-12] When the PRO is a secondary outcome, a brief rationale may be adequate.

State specific PRO objectives or hypotheses (including relevant PRO concepts/domains): **SPIRIT-7-PRO Extension.** *Explanation:* PRO measures may be multidimensional (eg, HRQOL) or unidimensional (eg, specific symptoms such as pain) and assessments may be scheduled at several time points during a trial. 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 (see also PRO elaboration 20a below).[4]

Methods: Participants, interventions, and outcomes

Specify any PRO-specific eligibility criteria (eg, language/reading requirements or pre-randomization[18] 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: SPIRIT-10-PRO Extension.** *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; whilst in some trials it may not be possible to collect PROs in the entire population (eg, due to non-availability of validated questionnaires in all languages)[8]; in such instances the rationale for the sampling method should be described.

Specify the PRO concepts/domains used to evaluate the intervention (eg, overall HRQOL, 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: SPIRIT-12-PRO Extension. *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*.[4,19]

Include a schedule of PRO assessments, providing a rationale for the time points, and justifying if the initial assessment is not pre-randomization. Specify: time windows; whether PRO collection is prior to clinical assessments; and if using multiple questionnaires, whether order of administration will be standardized: SPIRIT-13-PRO Extension. *Explanation:* Provision of an easy to follow schedule will assist staff and may help reduce missing data.[18] 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 as baseline PRO data are often used as a covariate in analyses and is 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.[20] Allowable time windows for each scheduled PRO assessment should be specified to ensure that PRO data collection captures the impact of the clinical event(s) of interest.

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: SPIRIT-14-PRO Elaboration. *Explanation:* In studies in which PROs are the primary outcome/endpoint, the target sample size will generally be based on an *a priori* sample size calculation for that endpoint.[19] Ideally the criteria for clinical significance (eg, minimal important difference and/or responder definition) should be specified when known.[21,22] If PROs are the secondary endpoint, researchers should specify whether the sample size provides sufficient power to test the principal PRO hypotheses.[19]

Methods: Data collection, management, and analysis

Justify the PRO instrument to be used, and describe domains, number of 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 provided or cited if available, ideally in the population of interest. State whether the measure will be used in accordance with any user manual and specify and justify deviations if planned: SPIRIT-18a(i)-PRO Extension. *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.[23] 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 and cognitive and/or emotional burden). Justification for the measures selected will help trial personnel understand why specific measures are being used.[10] 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.

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(ii)-PRO Extension. *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.[24] 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.[24,25] The setting for PRO data collection should be described and standardized across trial arms and sites.

Specify whether more than one language version will be used, and state whether translated versions have been developed using currently recommended methods: SPIRIT-18a(iii)-PRO Extension. *Explanation:* Multinational trials, or national trials involving participants with different languages, will require measures that have been translated, and culturally adapted where needed, using appropriate methodology.[11,26] This may influence the selection of measure to be used, since inclusivity of participants can help ensure the generalizability of trial results. Plans to use translated versions should be specified in the protocol, citing references where available.

Where 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: SPIRIT-18a(iv)-PRO Extension. *Explanation:* In some contexts, eg, trials involving young children, or cognitively impaired participants, it may be necessary for someone other than the trial participant to respond on their behalf. Clear justification and specification of proxy reporting in the protocol will allow external reviewers to assess potential bias and will facilitate trial reporting in accordance with CONSORT-PRO.[27] 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. Note that the European Medicines Agency (EMA) state 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'.[5] The US Food and Drug

Administration (FDA) also discourages the use of proxy reported outcomes to inform labelling claims, recommending observer reports instead.[4]

Specify PRO data collection and management strategies for minimising avoidable missing data: SPIRIT-18b(i)-PRO Extension. *Explanation:* Missing data is a particular problem for PROs since it is often those participants with the poorest outcomes in a trial that fail to complete planned PRO assessments and data cannot be obtained retrospectively beyond the timeframe of interest or from medical records. This is a potentially significant source of bias, and may reduce trial power.[28] It is important to note that not all missing PRO data is 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.[18] Examples of protocol content include: ensuring PRO endpoints 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.[18]

Describe the process of PRO assessment for participants who discontinue or deviate from their assigned intervention protocol: SPIRIT-18b(ii)-PRO Elaboration. *Explanation:* A clear plan for collection of PROs for trial participants who withdraw early from a study or who discontinue the intervention will help minimise bias,[29] ensure staff collect all required PRO data in a standardized and timely way, and may assist ethical appraisal of the study.

State PRO analysis methods including any plans for addressing multiplicity/type 1 (α) error: SPIRIT-20a-PRO Elaboration. *Explanation:* Many questionnaires, such as HRQOL measures, are multidimensional and therefore may yield several summary scores (eg, multiple domains and an overall score). Further, PROs are usually assessed at multiple time points. Statistical analysis of all domains and timepoints implies multiple hypothesis testing, which inflates the probability of false

positives (type 1 error, or 'alpha').[19] This can be contained by pre-specifying the key PRO domain(s) or overall score of interest, and the principal time point(s). Any plans to address multiplicity, such as step-wise or sequential analyses, whereby multiple endpoints are tested in a defined sequence that contains the overall type 1 error to the desired level, or conventional non-hierarchical methods (eg, Bonferroni correction), should be specified *a priori.*[4] 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 (SAP)).

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): SPIRIT-20c-PRO Elaboration. *Explanation:* There are two levels of missing PRO data: 1) patient completion of some, but not all items within an instrument; 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. Inappropriate method selection may lead to potentially biased and misleading results.[18,29] Common methods include complete case analysis, imputation (various approaches), a range of maximum likelihood modelling approaches, and sensitivity analysis.[29] The protocol should acknowledge these issues, and address them in summary, with full detail provided in the SAP.

Methods: Monitoring

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: SPIRIT-22-PRO Extension. *Explanation:* Evidence suggests the monitoring and management of 'PRO-alerts' (psychological distress or physical symptoms evident from PRO responses that may require an immediate response) varies across and within trials.[10,11,30] In order to protect the interests of trial participants and minimize potential bias, it is important to specify plans for monitoring.[31] If monitoring is not planned (for example in a low risk study where

alerts are not anticipated) then this should also be briefly stated in the protocol, the participant information sheet and 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 SAP, participant information sheet or in training/guidance documents for staff.

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.[1,2] It is important to note that these are minimum requirements, and that there may be value in including additional items in the protocol and/or in supplementary trial documents, as outlined in Supplement 3. While this guidance has been developed for trials where PROs are a primary or key secondary outcome we encourage protocol writers to consider use of this guidance in all trials or clinical research studies where PROs are collected, including if PROs are exploratory endpoints. 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 explanatory publication on the PROlearn[32] and SPIRIT Initiative[33] websites and will be facilitated through further development of the SPIRIT 2013 implementation tool SEPTRE[33] (SPIRIT Electronic Protocol Tool and Resource) and through dissemination via our international partners (see 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 practice, it is recommended that careful consideration be given to the selection of outcomes and measures[34,35], analysis of PRO data,[4,5,36] and transparent reporting in accordance with CONSORT-PRO.[27] Patient and public involvement in all of these aspects can help to ensure that PRO selection and application is transparent, relevant and acceptable.[37-38] Consistent with this philosophy, patient partners have been involved in all aspects of the development of the SPIRIT-PRO extension.[37-38] Ultimately, high quality PRO trial results will help ensure that the patient's voice is central to informing shared-decision making, labelling claims, clinical guidelines, and health policy, making patient-centered care a reality.

Limitations

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.

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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Author Contributions: Profs Calvert and King had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Prof Calvert and King co-chair the SPIRIT-PRO Group.

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Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Calvert, Kyte, King, Altman, Blazeby, Brown, Brundage, Coast, Draper, von Hildebrand, Mercieca-Bebber, Price, Roberts, Slade report a grant from Macmillan cancer support during the conduct of the study. Calvert and King co-chair the ISOQOL best practice for PROs in Trials PROtocol Taskforce and Calvert also reports personal fees from Astellas and grants from the National Institute for Health Research outside the submitted work. Velikova reports that she was past president of ISOQOL, past chair of EORTC Quality of Life Group and has received consultancy fees from Roche, Eisai and Novartis related to her clinical work in breast cancer, and grants from National Institute Health Research England, Yorkshire Cancer Research, Breast Cancer Now, EORTC Quality of Life Group, outside the submitted work. Scott participated in the SPIRIT-PRO Delphi panel and consensus meeting as part of her employment with Janssen-Cilag UK. She also holds Johnson & Johnson stock outside the submitted work. Golub reports stipends for teaching from Northwestern University Feinberg School of Medicine outside the submitted work. Kyte reports grants from the NIHR outside the submitted work. Travel and accommodation costs for consensus meeting participants were met by the University of Birmingham funded by the Macmillan Cancer Support Grant. No other disclosures were reported.

Funding/Support: This work was funded by Macmillan Cancer Support (grant number 5592105) and the University of Birmingham and was sponsored by the University of Birmingham. Professor King is supported by the Australian Government through Cancer Australia. JMB is partially supported by the MRC ConDuCT-II Hub for Trials Methodology Research. Professor Calvert, Dr Kyte and Dr Slade are funded by the NIHR Birmingham Biomedical Research Centre and the NIHR Surgical Reconstruction and Microbiology Research Centre. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

Role of the Funder/Sponsor: The funder/sponsor did not have any involvement in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication

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. This work reflects the views of the author and should not be construed to represent the views or policies of the U.S. Food and Drug Administration.

Additional Contributions: The SPIRIT-PRO Group gratefully acknowledge the additional contributions made by the SPIRIT-PRO Executive, the ISOQOL Best Practices for PROs in Randomized Clinical Trials PROtocol Checklist Taskforce, the international stakeholders responsible for stakeholder survey distribution and stakeholders who completed the stakeholder survey, Delphi Panellists, the SPIRIT-PRO International Consensus Meeting Participants and Anita Walker, University of Birmingham, UK for administrative support as detailed in Supplement 1.

Glossary Box

SPIRIT
Standard Protocol Items: Recommendations for Interventional Trials[1,2]

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.[27]

Proxy-Reported Outcome
'A measurement based on a report by someone other than the patient reporting as if he or she is the patient.'[4]

Health-Related Quality of Life (HRQOL)
'HRQOL is a multidimensional concept that usually includes self-report of the way in which physical, emotional, social, or other domains of well-being are affected by a disease or its treatment.'[27]

Primary Outcome/ Endpoint
The most important outcome in a trial, providing the most clinically relevant evidence directly related to the primary objective of the trial.

Secondary Outcomes / Endpoint(s)
These are outcomes pre-specified 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 Patient-Reported Outcomes / Endpoints
Some PRO measures (particularly HRQOL measures) are multidimensional, producing several domain-specific outcome scales, e.g. pain, fatigue, physical function, psychological distress. For any particular trial, it is likely that a particular PRO or PRO domain(s) will be more relevant than others, reflecting the expected effect(s) of the trial intervention(s) in the target patient population. These relevant PRO(s) and/or domain(s) may additionally constitute the important or key secondary PROs (identified *a priori* and specified as such in the trial protocol and statistical analysis plan) and will be the focus of hypothesis testing. In a regulatory environment, these outcomes may support a labelling claim. Because these outcomes are linked with hypotheses (see CONSORT PRO Extension 2b)[27], they may be subject to P value adjustment (or 'alpha-spending'). Note: PROs may not only provide evidence of efficacy/effectiveness but may also be intended to capture and provide evidence of safety and tolerability (e.g. PRO-CTCAE).[39]

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.' [4]

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.'[4]

Instrument
'A means to capture data (ie, 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.'[4]

Item
'An individual question, statement, or task (and its standardized response options) that is evaluated by the patient to address a particular concept.'[4]

Time window
A pre-defined time frame before and after the protocol-specified PRO assessment time point whereby the result would still be deemed to be clinically relevant.[40]

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Table 1 SPIRIT 2013* and SPIRIT-PRO Extension checklist: recommended items to address in a clinical trial protocol *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license and is reproduced by JAMA with their permission. #Indicates page numbers to be completed by authors during protocol development.

SPIRIT Section	SPIRIT Item No	SPIRIT Item Description	Addressed on page number#	SPIRIT-PRO Item No	SPIRIT PRO Extension Item Description	Addressed on page number#
Administrative information						
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 centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)				
Introduction						

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)		
Methods: Participants, interventions, and outcomes				
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 centres 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 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.
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	**SPIRIT-12-PRO Extension**	Specify the PRO concepts/domains used to evaluate the intervention (eg, overall HRQOL, 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.

		for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended		
Participant timeline	**13**	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	**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 pre-randomization. Specify: time windows; whether PRO collection is prior to clinical assessments; and if using multiple questionnaires, whether order of administration will be standardized.
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**	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.
Recruitment	**15**	Strategies for achieving adequate participant enrolment to reach target sample size		
Methods: Assignment of interventions (for controlled trials)				
Allocation:				
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 enrol 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 enrol 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		
Methods: Data collection,				

management, and analysis				
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 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	**SPIRIT-18a(i)-PRO Extension**	Justify the PRO instrument to be used, and describe domains, number of 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 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 one language version will be used, and state whether translated versions have been developed using currently recommended methods.
			SPIRIT-18a(iv)-PRO Extension	Where 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.
	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 minimising avoidable missing data.
			SPIRIT-18b(ii)-PRO Elaboration	Describe the process of PRO assessment for participants who discontinue or deviate from their 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 analysing 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 1 (α) error.
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)		
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised 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).
Methods: Monitoring				
	21a	Composition of data monitoring committee (DMC); 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 DMC 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		
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 the sponsor		
Ethics and dissemination				
Research ethics approval	**24**	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval		
Protocol amendments	**25**	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)		

Consent or assent	**26a**	Who will obtain informed consent or assent from potential trial participants or authorised 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 in order 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 dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	**30**	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	**31a**	Plans for investigators and sponsor to communicate trial results to participants, healthcare 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 dataset, and statistical code
Appendices		
Informed consent materials	**32**	Model consent form and other related documentation given to participants and authorised 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

1, 2, 33