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SPIRIT-PRO Extension explanation and elaboration: guidelines for inclusion of patient-reported outcomes in protocols of clinical trials

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Research Methods & Reporting

SPIRIT-PRO Extension explanation and elaboration: guidelines for inclusion of patient-reported outcomes in protocols of clinical trials

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Abstract

Patient reported outcomes (PROs) are used in clinical trials to provide valuable evidence on the impact of disease and treatment on patients' symptoms, function and quality of life. High-quality PRO data from trials can inform shared decision-making, regulatory and economic analyses, and health policy. Recent evidence suggests the PRO content of past trial protocols was often incomplete or unclear, leading to research waste. To address this issue, international, consensus-based, PRO-specific guidelines were developed: the SPIRIT-PRO Extension. The SPIRIT-PRO Extension is a sixteen-item checklist which aims to improve the content and quality of aspects of clinical trial protocols relating to PRO data collection to minimise research waste, and ultimately better inform patient-centred care.

This SPIRIT-PRO Explanation and Elaboration (E&E) paper provides information to promote understanding and facilitate uptake of the recommended checklist items, including a comprehensive protocol template. For each SPIRIT-PRO item, we provide a detailed description, one or more examples from existing trial protocols and supporting empirical evidence of the item's importance. We recommend this paper and protocol template be used alongside the SPIRIT 2013 and SPIRIT-PRO Extension paper to optimise the transparent development and review of trial protocols with PROs.

Article Summary

Strengths and limitations of this study

- The SPIRIT-PRO Extension aims to improve the completeness and transparency of trial protocols where patient-reported outcomes (PROs) are a primary or key secondary outcomes and was developed following EQUATOR Network Guidance.
- This Explanation and Elaboration paper provides information to promote understanding and facilitate uptake of the recommended PRO protocol SPIRIT-PRO checklist items for clinical trials.
- A comprehensive protocol template and selected examples from existing trial protocols are provided to facilitate implementation.
- The protocol template and explanation and elaboration paper were developed with multi-stakeholder international input including: trialists, PRO methodologists, psychometricians, patient partners, industry representatives, journal editors, regulators and ethicists.
- Although the guidance is limited in focus to clinical trials, many of the SPIRIT-PRO items may also provide useful prompts about PRO content for cohort studies and other non-randomised designs.

Background

Clinical trial protocols are essential documents intended to include the study rationale, intervention, trial design methods, study processes, outcomes, sample size, data collection procedures, proposed analyses and ethical considerations. Provision of sufficient detail is necessary to enable the research team to conduct a high-quality, reproducible study. It also facilitates external appraisal of the scientific, methodological, and ethical rigor of the trial by relevant stakeholders.^{1 2} Although trial protocols serve as the foundation for study planning, conduct, reporting, and appraisal, they vary greatly in content and quality.^{1 2} Appraisals of the patient reported outcome (PRO) content of over 350 past trial protocols revealed that many protocols lack specific information needed for high-quality PRO data collection and evidence generation (Supplement 1).³⁻⁵ As a result, research personnel and potential research participants may not appreciate the purpose of PRO data collection,⁶ and the need for standardised PRO assessment methods. This may result in high levels of missing data and poor-quality or non-reporting of PRO trial results, which may hinder the potential for PRO evidence to be used in regulatory decision-making, health policy and clinical care.⁶⁻⁸ For example, a recent review of cancer portfolio trials illustrates this point; recommended PRO protocol content was frequently not addressed and PRO data from 61 trials, including 49 568 participants, was unpublished.⁹ Another trial also cited poor PRO completion rates as the reason for not publishing PRO data – and the corresponding trial protocol included only sparse guidance related to the PRO study.⁷

In 2013, core protocol guidelines applicable to all types of trials was published based on expert consensus and research evidence, in the form of the SPIRIT 2013 Statement (Standard Protocol Items: Recommendations for Interventional Trials). Its corresponding SPIRIT 2013 Explanation and Elaboration (E&E) paper provides important information to promote full understanding of, and assist protocol writers to implement, the 33 checklist recommendations.^{1 2} However, SPIRIT 2013 does not provide specific recommendations about PRO endpoints. PROs can provide valuable information on the risks, benefits and tolerability of an intervention. PRO data are intrinsically subjective, requiring completion by patient-participants within a specific time frame and, as a result, present a range of scientific and logistical challenges for researchers which should be addressed in the trial protocol.^{6 10-12}

To address this issue, international stakeholders worked to develop the SPIRIT-PRO Extension, with the aim of improving PRO content of trial protocols and supporting documents, for use in conjunction with SPIRIT 2013 Guidelines and E&E papers.^{1 2} The SPIRIT-PRO Extension was published in 2018 and comprises 11 extensions (new, PRO-specific items) and 5 elaborations (an elaboration of an existing SPIRIT 2013 item as applied to clinical trials assessing PROs) recommended for inclusion in clinical trial protocols that have PROs as primary or key secondary outcomes (Table 1).¹⁰ The SPIRIT-PRO Extension paper reports the 16 items and describes the methods used to develop the checklist, but does not provide detailed implementation instructions or examples. This SPIRIT-PRO E&E paper aims to promote understanding of the guidelines, provide real examples of SPIRIT-PRO items being addressed from a range of different trials and facilitate uptake of the recommended checklist items. In addition, we describe the development of a new PRO protocol template for use in protocol development. Additional information and resources

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3 regarding the SPIRIT Initiative are available on the SPIRIT website (www.spirit-statement.org).
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7 **Table 1. SPIRIT 2013 and SPIRIT-PRO Extension checklist: Recommended**
8 **Items to Address in a Clinical Trial Protocol**
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SPIRIT Section	SPIRIT Item No.	SPIRIT Item Description	SPIRIT-PRO Item No.	SPIRIT-PRO Extension or Elaboration Item Description	Please specify which page(s) of the protocol this item is addressed on.
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	SPIRIT5a-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, end-point 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	SPIRIT6a-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	SPIRIT7-PRO Extension	State specific PRO objectives or hypotheses (including relevant PRO concepts/domains).	
Trial design	8	Description of trial design, including type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, noninferiority, exploratory)			
Methods: Participants, Interventions, and Outcomes					

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Study setting	9	Description of study settings (e.g., 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 (e.g., surgeons, psychotherapists)	SPIRIT10-PRO Extension	Specify any PRO-specific eligibility criteria (e.g. language/reading requirements or pre-randomisation 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.	
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 (e.g., 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 (e.g., 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 (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome; explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	SPIRIT12-PRO Extension	Specify the PRO concepts/domains used to evaluate the intervention (e.g., overall health-related quality of life, specific domain, specific symptom) and, for each one, the analysis metric (e.g., change from baseline, final value, time to event) and the principal time point or period of interest.	
Participant timeline	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 in Chan et al) ^{1 2}	SPIRIT13-PRO Extension	Include a schedule of PRO assessments, providing a rationale for the time points, and justifying if the initial assessment is not pre-randomisation. 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	SPIRIT14-PRO Elaboration	When a PRO is the primary end point, state the required sample size (and how it was	

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		determined, including clinical and statistical assumptions supporting any sample size calculations		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 enrolment to reach target sample size			
Methods: Assignment of Interventions (for Clinical Trials)					
Allocation					
Sequence generation	16a	Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., 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 (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned			

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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 (e.g., 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 (e.g., duplicate measurements, training of assessors) and description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known; reference to where data collection forms can be found, if not in the protocol	SPIRIT-18a (i)-PRO Extension	Justify the PRO instrument to be used and describe domains, number of items, recall period, and instrument scaling and scoring (e.g., range and direction of scores indicating a good or poor outcome). Evidence of PRO instrument measurement properties, interpretation guidelines, and patient acceptability and burden should be provided or cited if available, ideally in the population of interest. State whether the measure will be used in accordance with any	

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				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 (e.g., paper, telephone, electronic, other) and setting (e.g., clinic, home, other).	
			SPIRIT-18a (iii)-PRO Extension	Specify whether more than 1 language version will be used and state whether translated versions have been developed using currently recommended methods.	
			SPIRIT-18a (iv)-PRO Extension	When the trial context requires someone other than a trial participant to answer on his or her behalf (a proxy-reported outcome), state and justify the use of a proxy respondent. Provide or cite evidence of the validity of proxy assessment 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 (e.g., 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	SPIRIT20a-PRO Elaboration	State PRO analysis methods, including any plans for addressing multiplicity/type I (α) error.	
	20b	Methods for any additional analyses (e.g., subgroup and adjusted analyses)			
	20c	Definition of analysis population relating to protocol nonadherence (e.g., as randomized analysis) and any statistical methods to handle missing data (e.g., multiple imputation)	SPIRIT20c-PRO Elaboration	State how missing data will be described and outline the methods for handling missing items or entire assessments (e.g., approach to imputation and sensitivity analyses).	
Methods: Monitoring					
	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			

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		(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			
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	SPIRIT22-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)			
Ethics and Dissemination					
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board approval			
Protocol amendments	25	Plans for communicating important protocol modifications (e.g., changes to eligibility criteria,			

		outcomes, analyses) to relevant parties (e.g., 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 post-trial care	30	Provisions, if any, for ancillary and post-trial 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			
Appendixes					
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			

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3 The development of the SPIRIT-PRO Extension followed the Enhancing Quality and
4 Transparency of Health Research (EQUATOR) Network's methodological framework
5 for guideline development,¹³ and has been published elsewhere.¹⁰ Ethical approval
6 was provided by the University of Birmingham Ethical Review Board (ERN_16-
7 0819). Briefly, these methods included:

- 8 1) a systematic review of existing PRO-specific protocol guidelines to generate
9 the list of potential PRO-specific protocol items¹⁴;
- 10 2) refinements to the list and removal of duplicate items by the International
11 Society for Quality of Life Research (ISOQOL) Protocol Checklist Taskforce;
- 12 3) an international stakeholder survey of trial research personnel, PRO
13 methodologists, health economists, psychometricians, patient advocates,
14 funders, industry representatives, journal editors, policy makers, ethicists, and
15 researchers responsible for evidence synthesis (distributed by 38 international
16 partner organisations);
- 17 4) an international Delphi exercise;
- 18 5) a consensus meeting in May 2017 to finalise the guidelines and
19 implementation strategy.

20 International stakeholders provided feedback on the final wording of the SPIRIT-
21 PRO Extension during a final three-week consultation period. Following minor edits,
22 the guidelines were finalised and agreed by the SPIRIT-PRO Group.¹⁰

23 **Development of the PRO protocol template**

24 A PRO protocol template was developed to support implementation of the SPIRIT-
25 PRO guidance (ethical approval ERN_19-0939). The draft template was reviewed by
26 members of the project team and broader SPIRIT-PRO Group, including patient
27 partners. In addition, an international advisory group (IAG), comprising of global
28 PRO leads from major pharmaceutical companies, regulators and academics, was
29 convened to review and provide additional feedback on the template.

30 Teleconference meetings were held with members of the SPIRIT-PRO Group and
31 the IAG to discuss the feedback received. Based on the feedback the template was
32 revised and sent to all for final comments. After a final consultation period the PRO
33 protocol template was revised and finalised.

34 **Patient and Public Involvement**

35 Patient partners were involved in the design, conduct, reporting, and dissemination
36 plans of our research, including development of the SPIRIT-PRO Extension, the E&E
37 paper, protocol template, tools to support implementation by patient partners, and
38 are included as coauthors.

39 **Glossary**

40 **Concept:** "The specific measurement goal (i.e., the thing that is to be measured by a
41 PRO instrument). In clinical trials, a PRO instrument can be used to measure the
42 effect of a medical intervention on one or more concepts. PRO concepts represent
43 aspects of how patients function or feel related to a health condition or its
44 treatment."¹⁵

45 **Domain:** "A sub concept represented by a score of an instrument that measures a
46 larger concept comprised of multiple domains. For example, psychological function is
47 a larger concept with multiple domains (emotional and cognitive function) that are
48 measured by relevant items."¹⁵

1
2
3 **Endpoint***: the variable to be analysed. It is a precisely defined variable intended to
4 reflect an outcome of interest that is statistically analysed to address a particular
5 research question. A precise definition of an endpoint typically specifies the type of
6 assessments made, the timing of those assessments, the assessment tools used,
7 and possibly other details, as applicable, such as how multiple assessments within
8 an individual are to be combined¹⁶ (e.g. change from baseline at 6 weeks in mean
9 fatigue score).¹⁷

10
11 **Health-related quality of life**: “a multidimensional concept that usually includes self-
12 report of the way in which physical, emotional, social, or other domains of well-being
13 are affected by a disease or its treatment”.¹⁸

14 **Important or key secondary PROs/end points**: Some PRO measures (particularly
15 health-related quality-of-life measures) are multidimensional, producing several
16 domain-specific outcome scales; e.g., pain, fatigue, physical function, psychological
17 distress. For any particular trial, it is likely that a particular PRO or PRO domain(s)
18 will be more relevant than others, reflecting the expected effect(s) of the trial
19 intervention(s) in the target patient population. These relevant PRO(s) and/or
20 domain(s) may additionally constitute the important or key secondary PROs
21 (identified a priori and specified as such in the trial protocol and statistical analysis
22 plan) and will be the focus of hypothesis testing. In a regulatory environment, these
23 outcomes may support a labelling claim. Because these outcomes are linked with
24 hypotheses (CONSORT PRO Extension 2b),¹⁸ they may be subject to P-value
25 adjustment (or “ α spending”). Beyond efficacy/effectiveness, PROs may also be
26 used to capture and provide evidence of safety and tolerability (e.g. using the
27 Patient-Reported Outcomes version of the Common Terminology Criteria for
28 Adverse Events (PRO-CTCAETM)).¹⁹

29
30 **Instrument**: “A means to capture data (e.g., a questionnaire) plus all the information
31 and documentation that supports its use. Generally, that includes clearly defined
32 methods and instructions for administration or responding, a standard format for data
33 collection, and well-documented methods for scoring, analysis, and interpretation of
34 results in the target patient population.”¹⁵

35
36 **Intervention/treatment**: A process or action that is the focus of a clinical study.
37 Interventions include drugs, medical devices, procedures, vaccines, and other
38 products that are either investigational or already available. Interventions can also
39 include non-invasive approaches, such as education or modifying diet and
40 exercise.²⁰

41
42 **Item**: “an individual question, statement, or task (and its standardized response
43 options) that is evaluated by the patient to address a particular concept”.¹⁵

44
45 **Observer-reported outcome**: “a measurement based on a report of observable
46 signs, events or behaviours related to a patient’s health condition by someone other
47 than the patient or a health care professional”.²¹

48
49 **Outcome***: the variable to be measured. It is the measurable characteristic that is
50 influenced or affected by an individual’s baseline state or an intervention as in a
51 clinical trial or other exposure¹⁶ (e.g. a fatigue score).

52
53 **Patient-reported outcome (PRO)**: A PRO is any report of the status of a patient’s
54 health condition that comes directly from the patient, without interpretation of the
55 patient’s response by a clinician or anyone else and may include patient
56 assessments of health status, quality of life, or symptoms.^{15 18} PROs are assessed
57 by self-reported questionnaires, referred to as PRO measures (PROMs) or
58 instruments.¹⁶

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3 **Primary outcome:** the most important outcome in a trial, pre-specified in the
4 protocol, providing the most clinically relevant evidence directly related to the primary
5 objective of the trial.

6 **Proxy-reported outcome:** “a measurement based on a report by someone other
7 than the patient reporting as if he or she is the patient”.¹⁵

8 **Secondary outcomes:** outcomes pre-specified in the protocol to assess additional
9 effects of the intervention; some PROs may be identified as important or key
10 secondary outcomes.

11 **SPIRIT:** Standard Protocol Items: Recommendations for Interventional Trials.^{1 2}

12 **SPIRIT Elaboration item:** an elaboration of an existing SPIRIT item as applied to a
13 specific context; in this instance, as applied to clinical trials assessing PROs.

14 **SPIRIT-PRO Extension item:** an additional checklist item describing PRO protocol
15 content to address an aspect of PRO assessment that is not adequately covered by
16 SPIRIT, as judged by available evidence and expert opinion.

17 **Time window:** a predefined time frame before and after the protocol-specified PRO
18 assessment time point whereby the result would still be deemed to be clinically
19 relevant.²²

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

31 32 33 **Purpose and Development of the Explanation and Elaboration paper and PRO 34 Protocol Template**

35
36 The SPIRIT-PRO Extension, this Explanation and Elaboration and the included PRO
37 protocol template are intended to guide the development of trial protocols for ethical
38 review where PROs are a primary or key secondary outcome, including single and
39 multi-arm trials. We recommend that authors also consider inclusion of checklist
40 items when PROs are exploratory in nature, as appropriate. Protocols may be
41 formatted in accordance with local requirements, however they need to address the
42 SPIRIT-PRO items completely and transparently. The examples provided in this E&E
43 document and protocol template are not intended to be prescriptive about how
44 information is included in protocols, nor how trials be conducted. Trialists may, for
45 example, wish to include a PRO specific, dedicated section in the protocol with
46 content informed by the SPIRIT-PRO checklist, whilst others may wish to add PRO
47 content to existing sections of the protocol.

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53 Modelled after other reporting guidelines,^{2 23 24} this E&E paper presents each
54 checklist item with at least one example from a trial protocol, followed by an
55 explanation of the rationale and main issues to address, to facilitate understanding
56 and usage. The guidelines are intended to be used in conjunction with the SPIRIT-
57 PRO Extension, SPIRIT 2013 Statement and E&E paper and other relevant
58 extensions.^{1 2 10 25} Empirical data and references to support each SPIRIT-PRO item
59 are provided. Real-world examples for each SPIRIT-PRO item, quoted verbatim, are
60

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3 presented to reflect how key elements could be appropriately described in a trial
4 protocol. These examples were obtained from E&E paper authors, public websites,
5 journals, trial investigators, and industry sponsors. Some examples illustrate a
6 specific component of a checklist item, while others encompass all key
7 recommendations for an item. Reference numbers cited in the original quoted text
8 are denoted by [Reference] to distinguish them from references cited in this E&E
9 paper. Health-related quality of life (HRQL) has been used consistently to replace
10 terms for quality of life in examples.
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For peer review only

Administrative Information

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

Example

Trial name: Multicenter Randomized Controlled Trial of Conventional Versus Laparoscopic Surgery for Colorectal Cancer Within an Enhanced Recovery Programme (EnROL)

PRO endpoints: 1°, 2°

“EnROL Trial Management Group

Chief Investigator/Clinical Coordinator

RK, [address, telephone]

Co-Investigator

DK, [address, telephone]

Deputy Clinical Coordinator

TR, [address, telephone]

Trial Management/QA

SP, [address, telephone]; *JB*, [address, telephone], *LD*, [address, telephone]; *AF*, [address, telephone]

Nurse Advisor

SB, [address, telephone]

Statistics

SD, [address, telephone]

Health Economics

PF, [address, telephone]

Quality of Life

JMB, [address, telephone]

Translational Science Advisor

PQ, [address, telephone]

Collaborating Surgeons

HW, [address, telephone]; *MG*, [address, telephone]²⁶

Explanation

For trials assessing PROs, input from a person with expertise in PRO methodology early in the development phase of the protocol will improve its completeness and quality.¹⁰ Providing names and contact details of those contributing to the PRO-specific aspects of the protocol provides recognition, accountability and transparency. It aids identification of competing interests and prevents ghost authorship. It also provides a named point of contact to resolve any PRO-specific queries from other research team members, protocol reviewers, and sites (during trial start-up and conduct). Acknowledgements of PRO protocol input from patient-partners as per guidelines for the reporting of patient and public involvement is also recommended.²⁷ Patient and public involvement in all aspects of trial design, including but not limited to: selection of outcomes and measures, timepoints, mode of assessment, and reporting, can help minimise burden and ensure that data collected is patient-centred and relevant to participants and to the future patients who will benefit from the research.

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2
3 Only 7 of 75 (9%) protocols that included PROs from the United Kingdom (UK)
4 National Institute for Health Research (NIHR) Health Technology Assessment
5 programme explicitly described who was responsible for the PRO component
6 (Supplement 1).³

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

10 11 12 13 **Example**

14
15 **Trial name: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the**
16 **Efficacy and Safety of Idelalisib (GS-1101) in Combination with Rituximab for Previously**
17 **Treated Chronic Lymphocytic Leukemia**

18
19 **PRO endpoints: 2°**

20 21 22 **“3.5. Endpoint Selection Rationale**

23 24 3.5.2.2. Health-Related Quality of Life (HRQL)

25 Direct patient reporting of outcomes using standardized methods has become an increasingly
26 important component of therapeutic assessment. Evaluation of patient-reported outcomes
27 (PROs) is particularly relevant in patients who cannot be cured of disease [Reference].

28 PRO questionnaires have been previously used in CLL [chronic lymphocytic leukaemia] to understand
29 how patients differ from the general population in terms of health concerns [References], to
30 understand differences in perceptions of well-being in younger vs older patients [References], to
31 determine how treatment affects HRQL [References], and to assess the pharmacoeconomic cost of
32 improvements in HRQL [Reference].

33 Patients with CLL have overtly impaired well-being relative to comparable controls
34 [References]. Fatigue is cited as a common complaint, being present in the substantial majority of
35 patients. Impairment of HRQL prior to any treatment is apparent in those with B symptoms or in
36 patients with anemia, supporting the concept of initiating treatment when patients experience
37 symptomatic disease. Factors associated with lower overall HRQL have included older age, greater
38 fatigue, severity of co-morbid health conditions, advanced stage, and ongoing treatment for CLL
39 [Reference]. Younger patients appear to have worse emotional and social well-being but older
40 patients experience worse physical HRQL [Reference]. In comparative evaluation of
41 chemotherapy-containing regimens, differences in HRQL between therapies (eg, fludarabine
42 vs fludarabine-cyclophosphamide vs chlorambucil) reflected differences in toxicity while
43 greater efficacy was associated with improved HRQL [References].

44 In this Phase 3 study of GS-1101 and rituximab, it is postulated that incremental
45 GS-1101-mediated tumor control will be correlated with greater positive changes in HRQL
46 and that assessments of the drug's safety profile will be supported by HRQL evaluations.”²⁸

47 48 49 **Explanation**

50
51 A summary of available PRO evidence and a clearly defined PRO question is
52 required in the background section of the protocol, or a dedicated PRO section if
53 appropriate. Researchers should demonstrate the need for the research and identify
54 the PRO specific research question to demonstrate the scientific approach and
55 integrity of the PRO study. This should include a review of existing PRO evidence
56 from relevant trials and observational studies (e.g. same/similar target population or
57 intervention). This will avoid duplication of research, establish the burden of disease
58 from the patient perspective, identify likely effects of treatment, and inform
59

objectives, hypotheses, selection of measures, endpoint definition and analyses (covered by subsequent SPIRIT-PRO items).

Many protocols include PROs without specifying the PRO-specific research question and without a rationale or any reference to PROs in related studies.^{3 4 9}

Provision of this information can inform and motivate research personnel to take note of PRO assessment methods and adhere to standardisation of PRO assessment (e.g. when, where, how and who of PRO assessment, as outlined in the protocol under subsequent SPIRIT-PRO items).^{6 11} Staff who understand the importance of PROs in a trial are able to share this understanding with participants. The combined effect of motivated and co-operative staff and participants may help reduce missing PRO data rates.²⁹ This information is also relevant to research ethics committees/IRBs and funders responsible for reviewing the scientific integrity and ethical aspects of the trial.

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

Examples

Trial group name: Trans Tasman Radiation Oncology Group (TROG)

Trial name: A randomised phase III trial of high dose palliative radiotherapy (HDPRT) versus concurrent chemotherapy + HDPRT (C-HDPRT) in patients with good performance status, locally advanced or metastatic NSCLC with symptoms predominantly due to intrathoracic disease who are not suitable for radical chemo-radiotherapy (TROG 11.03 P-LUNG GP)

PRO endpoints: 1°, 2°

“Objectives-

The Primary objective is to compare, in this group of patients, high dose palliative radiotherapy (HDPRT) versus concurrent chemotherapy and HDPRT (C-HDPRT), with respect to

- The relief of dyspnoea, cough, haemoptysis and chest pain as assessed by change in total symptom burden from baseline to six weeks after the completion of treatment.
- Response for each component symptom separately (dyspnoea, cough, haemoptysis, chest pain)

The secondary objectives are to compare the two regimens in terms of; Dysphagia during treatment, Thoracic symptom response rate, Duration of thoracic symptom response , HRQL, Toxicity, Progression-free survival and Overall survival.

The exploratory/tertiary objectives are;

- to determine how much improvement in HRQL and symptom palliation would be necessary to make the inconvenience due to the longer duration of radiotherapy of C-HDPRT worthwhile, relative to HDPRT. This objective will be addressed in the Patient Preferences Substudy.
- Analyse serum protein glycosylation changes and exosomes to identify potential biomarkers of disease response and progression. Prospectively collect and bank tumour tissue and blood samples from this cohort of patients for future evaluation of potential biological markers”³⁰

Trial name: Evaluating different rate control therapies in permanent atrial fibrillation: A prospective, randomised, open-label, blinded endpoint trial comparing digoxin and beta-blockers as initial rate control therapy (RATE-AF)

PRO endpoints: 1°, 2°, exploratory

“3.1 Hypothesis

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3 Null Hypothesis for primary outcome: No difference in patient-reported quality of life (measured using
4 the physical functioning domain of the SF36 questionnaire) when comparing a strategy of digoxin
5 versus beta-blocker therapy for initial rate control in patients with permanent AF.

6 Alternative Hypothesis :Use of digoxin or beta-blocker therapy as initial rate control in patients with
7 permanent AF is superior based on patient reported quality of life (measured using the physical
8 functioning domain of the SF36 questionnaire).

9 3.2 Primary objective

- 10 - Patient-reported quality of life (HRQL), with a predefined focus on physical well-being using
11 the SF-36 physical component summary at six months.

12 3.3 Secondary objectives

- 13 - Generic and AF-specific patient-reported HRQL using the SF-36 global and domain-specific
14 scores, the AFEQT overall score and the EQ-5D-5L summary index and visual analogue
15 scale at six and twelve months.
- 16 - Echocardiographic left-ventricular ejection fraction (LVEF) and diastolic function (E/e' and
17 composite of diastolic indices) at twelve months.
- 18 - Functional assessment, including 6-minute walking distance achieved, change in European
19 Heart Rhythm Association (EHRA) class and cognitive function at six and twelve months.
- 20 - Change in B-type natriuretic peptide (BNP) levels as a surrogate for total cardiac strain at six
21 months.
- 22 - Change in heart rate from baseline and group comparison using 24-hour ambulatory ECG."³¹

23 Explanation

24
25
26 The PRO objectives should reflect the research question to be addressed in the trial
27 (SPIRIT-6a-PRO Extension) and be described in the context of the population,
28 intervention, comparator, outcome and time-point (PICOT) and the estimand
29 framework.³² Study objectives may focus on measuring treatment benefit
30 (superiority), non-inferiority, equivalence. Alternatively, or in addition to one of these
31 objectives, the trial may focus on assessing the safety and tolerability from the
32 patient perspective, or may be more exploratory in nature, where results are
33 presented but no comparative conclusions can be drawn. The PRO-specific study
34 objectives need to clearly align with the proposed analyses methods (SPIRIT-20a-
35 PRO Elaboration). Critically, as described in work by the SISAQOL Consortium,³³
36 four key attributes need to be considered *a priori* for each PRO domain:
37
38
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- 40 1) Broad PRO research objective/research question;
- 41 2) Between-group PRO objective;
- 42 3) Within-treatment group PRO assumption for the treatment or control arm;
- 43 4) Within-patient/within-treatment PRO objective (please note this component of
44 the objective directly addresses the SPIRIT-12-PRO Extension).

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47 More detailed information on how these can be applied are described in the
48 SISAQOL consensus recommendations.³³ Although the SISAQOL recommendations
49 were published for oncology trials, the principles apply more broadly. Pre-
50 specification of objectives and hypotheses encourages identification of key PRO
51 domains and time-points. This is particularly important because PRO data are
52 multidimensional in two important ways. First, there is often more than one relevant
53 PRO in a trial, particularly when the high-level outcome of interest is health-related
54 quality of life (HRQL). Many HRQL questionnaires yield separate scores for distinct
55 dimensions, such as physical, emotional and social functioning, as well as key
56 symptoms such as fatigue and pain. Second, PRO assessments are typically
57 scheduled at several time points during a trial, such as baseline, end of treatment,
58 then a series of longer-term follow-ups. Pre-specification of objectives and
59
60

hypotheses – focussing on the most important PRO domains and time points – is a good way to reduce multiple statistical testing and avoid selective reporting of PROs based on statistically significant results. Exploratory, hypothesis generating, analyses can also be undertaken but should be specified as such in the final trial report.¹⁸ This links to the SPIRIT-20a-PRO Elaboration, which includes plans for addressing multiplicity/type 1 (α) error. The objectives are generally phrased using neutral wording (e.g. “to compare the effect of treatment A versus treatment B on fatigue”) rather than in terms of a particular direction of effect.^{2 34} In contrast, the PRO hypothesis states the predicted effect of the interventions on the trial outcomes (e.g. “patients allocated to treatment A will have less fatigue than those allocated to treatment B”).³⁵⁻³⁷

Despite the importance of clearly defined PRO objectives and hypotheses, a review of trial protocols determined that 23% failed to include PRO-specific objectives and 81% were missing a clear PRO hypothesis.³

Methods: Participants, Interventions, and Outcomes

SPIRIT-10-PRO Extension: Specify any PRO-specific eligibility criteria (e.g. language/reading requirements or pre-randomisation completion of PRO).²⁹ If PROs will not be collected from the entire study sample, provide a rationale and describe the method for obtaining the PRO subsample.

Example

Trial group name: South West Oncology Group (SWOG)

Trial name: Health Status and Quality of Life in Patients With Early Stage Hodgkin's Disease: A Companion Study to SWOG-9133 (SWOG S9208)

PRO endpoints: 1°, 2°

“Eligibility Criteria

Ages Eligible for Study:	18 Years and older (Adult, Older Adult)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	No
Sampling Method:	Non-Probability Sample

Study Population: Community Sample

Criteria: DISEASE CHARACTERISTICS: Patients must be eligible for and registered to SWOG-9133

PATIENT CHARACTERISTICS: Patients must be able to complete the questionnaires in English. If they are not able to complete questionnaires in English, patients may be registered to SWOG-9133 without participating in SWOG-9208.”

The Symptom and Personal Information Questionnaire #1, the Cancer Rehabilitation Evaluation System Short Form (CARES-SF) and Cover Sheet must be completed prior to registration and randomization on SWOG-9133.³⁸

Explanation

Any eligibility criteria relevant to PRO assessment should be considered during the trial design and clearly specified in the protocol for consistent use by research

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3 personnel. In some trials, the baseline PRO assessment is required before
4 randomisation as an eligibility criterion.²⁹ This helps to ensure there will be a valid
5 baseline questionnaire from all patients, which is essential for calculation of change
6 scores, or inclusion as a covariate in modelling longitudinal PRO data. For unblinded
7 trials, this also ensures PRO data are collected before participants are aware of the
8 randomisation which may affect some aspects of the participant's response, e.g.
9 anxiety/emotional well-being.³⁹ In the absence of such an eligibility criterion, there is
10 a risk that the baseline assessment may be conducted after randomisation but
11 before the intervention is administered, resulting in detection bias. The maximum
12 time between this assessment and randomization should be defined and should not
13 be too long.
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15

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17 It may not always be possible to collect PROs from all study participants, e.g. due to
18 non-availability of questionnaires in appropriate languages (see SPIRIT-18a(iii)-PRO
19 Extension),⁹ literacy requirements or due to cognitive function (see SPIRIT-18a(iv)-
20 PRO Extension). These PRO-relevant exclusions typically should not preclude the
21 affected participants from enrolling in the trial, unless the PRO is the primary
22 outcome. Evidence suggests eligibility criteria as stated in trial protocols often differ
23 from what is finally reported in the trial publication,⁴⁰ and data on use of other
24 language or culturally appropriate PRO instruments is often missing from the
25 protocol.^{13 41}
26
27

28
29 Where the needs of specific groups have been identified (e.g. not fluent in English)
30 but not accommodated in the study protocol (e.g. non-English language versions not
31 available, assistance with reading and writing English version not permitted), this
32 should be stated, and the rationale for the sampling method described and justified.
33 Trialists should aim to be as inclusive as possible. Given the significance of PROs,
34 the research community has a moral obligation to, where possible, to address gaps
35 in availability of culturally validated PRO instruments. In the meantime, the
36 implications for generalisability of findings should be discussed in subsequent
37 publications.¹⁸
38
39

40 **SPIRIT-12-PRO Extension: Specify the PRO concepts/domains used to**
41 **evaluate the intervention (e.g., overall health-related quality of life, specific**
42 **domain, specific symptom) and, for each one, the analysis metric (e.g., change**
43 **from baseline, final value, time to event) and the principal time point or period**
44 **of interest.**
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46

47 **Examples**

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49 **Trial name: Evaluating different rate control therapies in permanent atrial fibrillation: A**
50 **prospective, randomised, open-label, blinded endpoint trial comparing digoxin and beta-**
51 **blockers as initial rate control therapy (RATE-AF)**
52

53 **PRO endpoints: 1°, 2°, exploratory**

54 **“12.1.1 Primary Outcome**

55 Patient-reported quality of life (HRQL) - SF-36 physical component summary score at six months

56 **12.1.2 Secondary Outcomes**

57 **Patient-reported HRQL:**
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- SF-36 global and domain-specific scores at 6 and 12 months
- EQ-5D-5L summary index and visual analogue scale at six and twelve months
- AFEQT overall score at six and twelve months³¹

Trial name: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Rituximab for Previously Treated Chronic Lymphocytic Leukemia

PRO endpoints: 2°

“Change in HRQL domain and symptom scores based on the Functional Assessment of Cancer Therapy: Leukemia (FACT-Leu)... defined as the change from baseline and the time to definitive increments or decrements of 10%, 20%, and 40% from baseline; time to definitive increment (better than baseline by the specified amount) is the interval from randomization to the first timepoint when the HRQL measure is consistently better than at baseline (including that timepoint as well as all the subsequent timepoints) in a subject whose last HRQL score is better than at baseline; and time to definitive HRQL decrement (worse than baseline by the specified amount) is the interval from randomization to the earliest of death or the first timepoint when the HRQL measure is consistently worse than at baseline (including that timepoint as well as all the subsequent timepoints) in a subject whose last performance status score is worse than at baseline.”²⁸

Explanation

For each outcome, including PROs, the trial protocol should define four components: the specific measurement variable, which corresponds to the data collected directly from trial participants (e.g., Beck Depression Inventory score, all cause mortality); the participant-level analysis metric, which corresponds to the format of the outcome data that will be used from each trial participant for analysis (e.g., change from baseline, final value, time to event); the method of aggregation, which refers to the summary measure format for each study group (e.g., mean, proportion with score > 2); and the specific measurement time point of interest for analysis.¹ Many PRO questionnaires are multidimensional, assessing multiple facets of the impact of a disease and its treatment and usually include multiple assessments over the course of the trial. The multidimensional nature of PROs is most apparent in HRQL questionnaires, which often include various aspects of functioning and symptoms, which are often scored as distinct ‘domains’. These domains may not be affected equally by the trial interventions. The SPIRIT-7-PRO Extension encourages protocol writers to identify the domains that are most likely to be affected in the trial objectives and hypotheses, drawing on previous evidence (SPIRIT-6a-PRO Extension). The SPIRIT-12-PRO Extension item reinforces the statement of these key domains, and also the most important time-points (i.e. where greatest impact of interventions are expected), and develops that concept further by encouraging protocol contributors to think about how these PRO domains and time-points will be analysed, i.e. the analysis metric.³³ To ensure transparency and credibility of the analysis, it is recommended that there is pre-specification of the PRO concepts/domains, analysis metric(s) and time-point(s) of interest, whether the PRO is a primary, secondary or exploratory outcome. These should closely align with the study hypotheses/objectives and the nature and trajectory of the disease or condition under investigation.^{33 42} The selected key domains, time-points, and analysis metric

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3 should be used to specify the PRO endpoints, integrated in the full endpoint model of
4 the trial.
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7 A clearly defined endpoint model, organizing all trial outcomes (PRO and non-PRO),
8 typically in primary, secondary and exploratory endpoints, allows rigorous control of
9 the evidence demonstration, especially the control of the statistical testing. Each
10 PRO endpoint in the model should explicitly specify a single domain and a single
11 time horizon. The endpoint model enables procedures for Type I error control (risk of
12 false positive finding) (see SPIRIT-20a-PRO Elaboration). Broadly, the concepts and
13 domains (sub concepts) measured by a PRO may be 'proximal' in nature, i.e. direct
14 impact of the disease and treatment (e.g. symptoms such as pain, fatigue, nausea,
15 rash and anxiety) or more distal, "knock-on" effects, (e.g. functional status and global
16 quality of life), as illustrated for ovarian cancer in (Figure 1, inspired by the Wilson
17 and Cleary model⁴³). Of note, the Food and Drug Administration (FDA) are
18 increasingly focused on the individual measurement of well-defined concepts that
19 impact on HRQL but are more proximal to a therapy's effect on the patient and the
20 patient's disease: symptomatic adverse events, physical function, and, where
21 appropriate, a measure of the key symptoms of the disease.⁴⁴

22
23 Common analysis metrics may include magnitude of event at time t , proportion of
24 responders at time t , overall PRO score over time or response patterns/profiles.
25 These should be pre-specified alongside the levels of statistical and clinical
26 significance for the study and any responder definition in use.¹⁵ Time-points for
27 analysis should be chosen to best address the research question, whilst taking into
28 account aspects such as the natural history of the disease/condition and its
29 treatment, the PRO measurement properties and recall period, and participant
30 completion burden.^{15 45}
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34 The example, Idelalisib and Rituximab Improve Progression-Free Survival Over
35 Rituximab Alone in Unfit Patients with Relapsed Chronic Lymphocytic Leukemia: A
36 Phase 3 Study, illustrates a 'time to event' PRO endpoint or analysis metric, where
37 the event is definitive improvement or definitive deterioration in a PRO. This
38 approach allows repeated PRO measurements to be converted to a single measure:
39 time to definitive increment or decrement. This requires quite complex and specific
40 criteria for degree and duration of change. Also, this particular example does not
41 specify any key domains of the FACT-Leu, but rather applies this analysis metric to
42 all HRQL domain and symptom scores. In contrast, the RATE-AF example identifies
43 a single score (the SF-36 physical component score), and a specific time-point (6
44 months) as the primary outcome, with other SF-36 domains, questionnaires and
45 time-points specified as secondary outcomes.
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53 **Figure 1 Proximal and distal effects of therapy on patient symptoms and**
54 **quality of life** adapted from Wilson and Cleary, 1995.⁴³
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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-randomisation. Specify time windows, whether PRO collection is prior to clinical assessments, and, if using multiple questionnaires, whether order of administration will be standardised.

Examples

Trial group: TROG

Trial name: A randomised phase III trial of high dose palliative radiotherapy (HDPRT) versus concurrent chemotherapy + HDPRT (C-HDPRT) in patients with good performance status, locally advanced or metastatic NSCLC with symptoms predominantly due to intrathoracic disease who are not suitable for radical chemo-radiotherapy (TROG 11.03 P-LUNG GP).³⁰

PRO endpoints: 1°, 2°

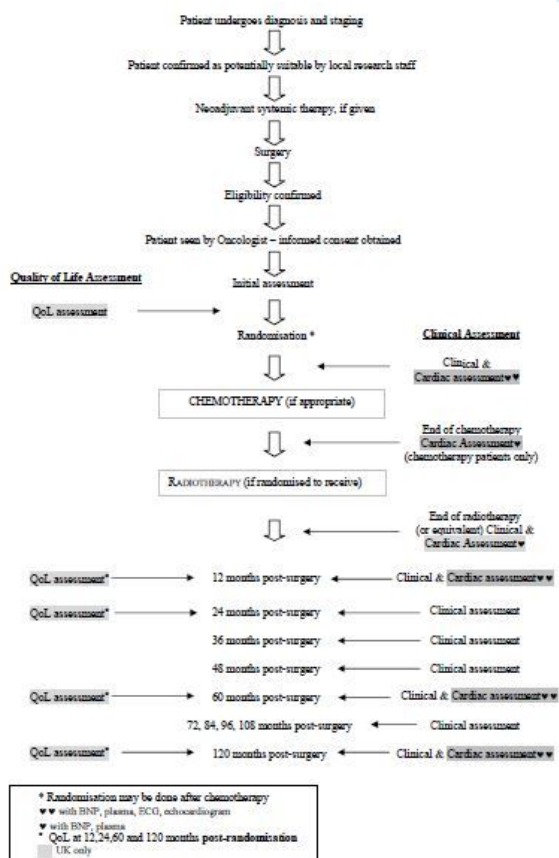
Assessment Time Point	Beginning of Acceptable time limit	End of Acceptable time limit
1. Pre-Registration	Date of signing consent	Date patient made aware of treatment arm to which they have been assigned
2. Pre-Treatment	Date patient made aware of treatment arm to which they have been assigned	Date of first radiation dose
3. During Treatment	Day of treatment	Before next treatment (eg If patient given QOL form on Monday then QOL should be completed before treatment on Tuesday)
4. End of Treatment	Date of last treatment	Five days after last treatment
5. Two weeks after end of treatment	1 week after end of treatment	3 weeks after end of treatment
6. Six weeks after end of treatment	Five weeks after end of treatment	Eight weeks after end of treatment
7. Three months after end of treatment	Nine weeks after end of treatment	Eighteen weeks after end of treatment
8. Six months after end of treatment	Five months after end of treatment	Nine months after end of treatment

Trial group: UK Medical Research Council Scottish Cancer Trials Breast Group in association with: Breast International Group
Trial name: MRC phase III randomised trial to assess the role of adjuvant chest wall irradiation in 'intermediate risk' operable breast cancer following mastectomy (MRC SUPREMO TRIAL (BIG 2-04))

PRO endpoints: 2°

Visits(a)	Patients Involved	Screening	Post (+/-) chemo pre (+/-) RT	Post (+/-) RT	1 yr	2 yr	3 yr	4 yr	5 yr	6 yr	7 yr	8 yr	9 yr	10 yr	Recurrence ^b
					4	5	6	7	8	9	10	11	12	13	
Investigations		Baseline 1	2	3											
Informed consent	All	X													
Medical history & examination (b)	All	X		X	X	X	X	X	X	X	X	X	X	X	X
Staging tests	All	X													
Contralateral mammography	All	X			A mammogram of the opposite breast, if appropriate, is recommended at least in alternate years for 10 years from the date of mastectomy										
Blood sampling	If consented to TRANS-SUPREMO	X													X
Tumour paraffin block from primary tumour ^c	All	X													
Tumour paraffin block at recurrence if available ^c	All														X
Acute/Late morbidity ^d	All			X	X	X	X	X	X	X	X	X	X	X	X
Cardiac symptoms and examination	If consented to cardiac sub study	X	X ^e	X	X				X					X	X
Blood sampling for BNP	If consented to cardiac sub study	X	X ^e	X	X				X					X	X
Electrocardiogram	If consented to cardiac sub study	X			X ^f				X ^f					X	X ^g
Echocardiogram	If consented to cardiac sub study	X			X ^f				X ^f					X	X ^g
QoL and EQSD economic assessment	If consented to QoL sub study	X			X	X			X					X	X ^g

(d) Baseline (pre randomisation) quality of life assessment will be conducted in the clinic. All subsequent quality of life assessment questionnaires will be mailed to the patient.⁴⁶



Explanation

A clear and concise schedule of PRO assessments can: assist trial staff to be organised and prepared for participant visits, inform study participants about the methods and expectations of trial participation, and facilitate review of participant burden by research ethics committees/IRBs.²⁹ The scheduled PRO assessments should provide the data required to address the study's PRO objectives. When selecting appropriate time-points for assessment, it is important to consider the natural history of disease/progression, the hypothesised impact of therapy over time and practical considerations such as alignment of assessments with clinic visits and recall period of PRO measures. PRO assessments should be described in the protocol text and in the schedule of assessment table along with the other clinical data collection activities, for ease of reference. This is recommended whether the PRO is completed by the participant during study visits or outside of the study visits (e.g. at home).

The timing of the baseline PRO assessment relative to other study-related events is important and therefore should be specified in the schedule of assessments. Collecting PRO data prior to randomisation helps ensure an unbiased baseline assessment, and if specified as an eligibility criterion, can promote data completeness (SPIRIT-10-PRO Extension). Baseline PRO data are often used as a covariate in analyses and are essential to calculating change from baseline, however, collecting data from enrolled patients prior to randomisation can be logistically challenging. One approach is to have participants complete the baseline PRO assessment immediately after providing consent, while the site staff obtain the randomisation assignment from the study system. However, there may be scenarios in which pre-randomisation PRO assessment is unnecessary or not possible, for example, emergency surgery trials.

Stating the time-windows for each PRO assessment clearly in the protocol text and schedule of assessments table or footnote will help staff adhere to them. Examples of time-windows for PRO assessment are similar to time-windows for other types of assessments, such as a study visit that may occur on Day 10-14 post-baseline, or on Day 30 +/- 3 days post-surgery. Time-windows for each scheduled PRO assessment require an unambiguous reference point, to ensure that PRO data collection captures clinically relevant time points of interest. In deciding the size of the time-window for a PRO assessment, consider the trade-off between a smaller, more precise, time-window and a larger more feasible window. One approach is to specify a time-window that is a little larger than the ideal and not allow exceptions; this approach is more consistent than setting a smaller time-window and allowing exceptions. Often PRO assessments that occur during active treatment, e.g. chemotherapy, have a smaller time-window to capture acute toxicity that arise and resolve relatively quickly, while those occurring many months or years after treatment completion can have a larger window if the participant's outcomes are expected to stabilise over time.

When the PRO assessment occurs during a research or clinic visit, it is recommended that PRO assessment is standardised to be completed prior to clinical consultation, assessments or procedures. For example, if a PRO instrument assesses participants' experiences of pain in the past 7 days, and the study visit

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3 includes a bone marrow biopsy, the schedule of assessments should indicate that
4 the PRO assessment be completed prior to the biopsy. This will prevent the pain
5 assessment from capturing pain associated with the biopsy, reduce risk of missing
6 data as participants may not feel well enough to complete PROs following their
7 procedure, and offer a “routine” for study staff responsible for data collection.
8 When more than one PRO questionnaire is scheduled, it is recommended that the
9 order of questionnaires is standardised, with those higher in the endpoint hierarchy
10 being collected first.
11
12

13 These two forms of standardisation of PRO administration are examples of the more
14 general principle in research methodology that standardisation of methods reduces
15 unwanted sources of variation, whether random (i.e. no net effect on estimates of
16 interest, such as the impact of interventions on PROs) or systematic (i.e. causing
17 bias).
18
19

20 **SPIRIT-14-PRO Elaboration: When a PRO is the primary end point, state the**
21 **required sample size (and how it was determined) and recruitment target**
22 **(accounting for expected loss to follow-up). If sample size is not established**
23 **based on the PRO end point, then discuss the power of the principal PRO**
24 **analyses.**
25
26

27 Examples

28 **Trial name: The chronic autoimmune thyroiditis quality of life selenium trial (CATALYST)**

29 **PRO endpoints: 1°**

30 “The primary outcome is thyroid-related quality of life during 12 months’ intervention, as measured by
31 a composite score from the ThyPRO questionnaire. Sample size estimation is based on this outcome.
32 The trial should be sufficiently powered to identify a difference between the intervention and the
33 control group of four points on the 0 to 100 ThyPRO composite scale, corresponding to a small to
34 moderate effect. In previously obtained data, the standard deviation of ThyPRO-scores (sigma level)
35 was 20 points. With a correlation between observations on the same participant of 0.50, and a power
36 of 80% and a type I error probability (two-sided α level) of 0.05, a sample size of 236 experimental
37 participants and 236 control participants is required. The sample size estimate is based on a design
38 with five repeated measurements having a compound symmetry covariance structure.”⁴⁷
39
40
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43 **Trial name: Cosmesis and body image after single-port laparoscopic or conventional**
44 **laparoscopic cholecystectomy: a multicenter double blinded randomised controlled trial**
45 **(SPOCC-trial)**
46

47 **PRO endpoints: 1°, 2°**

48 “The primary endpoint of the study concerns patient’s satisfaction with cosmesis and body image 12
49 weeks after surgery. This endpoint is assessed using a validated cosmesis and body image score
50 (CBIS) that was previously used in surgery for Crohn’s disease and in donor nephrectomy. This score
51 is calculated on an 8-item multiple choice type questionnaire . . . ranging between 8 and 48 points...
52 A clinically relevant improvement of the cosmesis and body image score (CBIS) is defined as an
53 improvement of 20% of the cosmesis score (8 points). Given the reported standard deviation of the
54 CBIS between 4-6 and using (alpha = 0.05 and beta = 0.90), two groups of 49 patients are needed.
55 This is based on a two-sided significance level (alpha) of 0.05 and a power of 0.90. Estimating a 10%
56 dropout rate, which is common in randomized controlled trials, 55 patients will be randomized per
57 arm.”⁴⁸
58
59

60 **Trial group: TROG**

Trial name: A randomised phase III study of radiation doses and fractionation schedules for ductal carcinoma in situ (DCIS) of the breast (BIG 3-07/TROG 07.01)

PRO endpoints: 2°

The sample size for this trial, based on the primary endpoint (time to local recurrence of invasive or intraductal breast cancer in the ipsilateral breast), was 1600 patients. The sample size for the PRO substudy was determined a priori, and was less than that required for the primary endpoint, as explained in the protocol excerpt below. Therefore, patients recruited after the PRO-specific target sample size was achieved did not complete PRO questionnaires, saving trial resources in data collection and management.

“Sample size determination: For the quality of life study aiming to detect a difference between the tumour bed boost and no boost groups of 0.2 standard deviations of a continuous scale such as fatigue or physical symptoms, with 80% power at a two-sided alpha level of 5%, the required sample size is 790 patients. To allow for attrition at a rate of 5% per year, 1020 patients are required to participate in the quality of life study.”⁴⁹

Explanation

As with any primary endpoint, including those that focus on PRO, the criteria and methods for estimating the necessary sample size should be specified, with adjustments for expected discontinuation from the clinical study.⁴⁵ Ideally, the criteria for clinical significance (e.g. minimal important difference, clinically meaningful within-patient change threshold, responder definition) should be specified when known.^{50 51} It is important to note that the FDA is more interested in what constitutes a meaningful within-patient change in score from the patient perspective.¹⁵

In cases where the PRO is specified as a key secondary endpoint, the statistical power based on the estimated sample size for the primary endpoint, should be determined. If overpowered, specifying a smaller PRO-specific sample size will save trial resources, as illustrated in the BIG 3-07/TROG 07.01 example. When sufficient power may be achieved by collecting PROs from a representative subset of participants, the sampling strategy should be clearly described.

Only 50.7% of NIHR Health Technology Assessment clinical trial protocols address sample size and statistical power for PRO specified as secondary endpoints.³ If the clinical trial is international in scope, the sampling across countries may be influenced by availability of language translations.⁵² In addition, the variability of measurement between countries may inflate type 2 error (reduces power).

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 (e.g., range and direction of scores indicating a good or poor outcome). Evidence of PRO instrument measurement properties, interpretation guidelines, and patient acceptability and burden should be provided or cited if available, ideally in the population of interest. State whether the measure will be used in accordance with any user manual and specify and justify deviations if planned.

Examples

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2
3 **Trial name: Impact of a multimodal support intervention after a "mild" stroke (YOU CALL- WE**
4 **CALL)**

5
6 **PRO endpoints: 1°, 2°**

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8 "A number of quality of life tools were reviewed (e.g. SF-36, Stroke Impact Scale, Quality of Life
9 Index) and the tool chosen was a compromise between psychometric properties and adequacy of
10 content for mild stroke. The 32 item questionnaire Quality of Life Index (QLI) [Reference] which was
11 developed from Ferran's conceptual model of quality of life and which has been used with a stroke
12 clientele [Reference] was chosen as the primary outcome. Each item of the QLI as relating to four life
13 domains (health and functioning, socio-economic, psychological/spiritual and family), is evaluated in
14 terms of satisfaction and importance on a six-point scale. Scores for each domain and a global score
15 are expressed from 0-to-30, with a higher score indicating a better quality of life. These four life
16 domains relate well with the main issues covered through the WE CALL intervention. It has shown to
17 have adequate psychometric properties (concurrent validity, test-retest reliability and high internal
18 consistency: $\alpha = 0.90$) [Reference] and thus should be responsive to therapy-induced change
19 [References]. A one point difference was observed in the first six months post-stroke descriptive
20 follow-up ($n = 63$) for an effect size of 0.33 [References]. A two-point difference is considered a
21 clinically meaningful change leading to a moderate effect size of 0.66."⁵³

22
23 **Trial name: A randomised phase II/III multi-centre clinical trial of definitive chemoradiation,**
24 **with or without cetuximab, in carcinoma of the oesophagus (SCOPE 1: Study of**
25 **Chemoradiotherapy in Oesophageal Cancer Plus or Minus Erbitux)**

26
27 **PRO endpoints: 2°**

28
29 **"HRQL instruments**

30 Generic domains of HRQL will be assessed with the EORTC core Quality of Life Questionnaire, the
31 EORTC QLQ-C30 [Reference]. This instrument has been well validated in many international clinical
32 trials in oncology including oesophageal adenocarcinoma and squamous cell cancer. Disease specific
33 and CRT associated symptoms and side effects will be assessed with the oesophageal cancer
34 specific module, the EORTC QLQ-OES18 [Reference]. This has been validated and tested in patients
35 receiving definitive CRT. The module includes scales assessing dysphagia, eating restrictions, reflux,
36 dry mouth and problems with saliva and deglutition. The Dermatology Life Quality Index (DLQI) will
37 also be administered [Reference]. This is a well validated, easy to use index which assesses the
38 impact of dermatological conditions on patients' HRQL [Reference]. It has been included to accurately
39 assess the impact of the acneiform eruption commonly seen with cetuximab.⁵⁴

40
41 **Explanation**

42 The justification for the selection of PRO instrument(s) is required in the trial
43 protocol. This will help trial personnel and participants understand why specific
44 measures are being used and how they directly address the trial objectives and
45 stakeholder needs.¹¹ For example, regulatory agencies often focus on physical
46 symptoms and functioning to inform licensing and labelling claims, whereas patients
47 and health-policy makers may be more interested in broader aspects of HRQL, such
48 as engaging in social activities and emotional wellbeing.^{55 56} For regulatory trials, it is
49 prudent to seek regulatory advice at an early stage of trial development regarding
50 the acceptability of the instrument and the approach to PRO assessment.
51 Stakeholder-relevant PROs can be identified through patient involvement, qualitative
52 research, or core outcome sets,^{56 57} which alongside clinical outcomes, often include
53 outcomes such as symptom burden, functioning, and disease control, which can be
54 measured using PRO instruments.
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58 Appropriately developed and evaluated PRO instruments can provide more sensitive
59 and specific measurements of the effects of medical intervention, thereby increasing
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2
3 the efficiency of clinical trials that attempt to measure the meaningful treatment
4 benefits of those therapies.⁵⁸⁻⁶⁰ Irrespective of whether the trial is conducted for
5 regulatory purposes, FDA guidance and ISOQOL guidance provide a useful
6 conceptual framework to assist in the selection of measures.^{15 61} Identifying and
7 selecting valid, reliable tools that are acceptable to patients from the target
8 population may prove challenging. The Consensus Based Standards for the
9 Selection of Health Measurement Instruments (COSMIN) initiative and the
10 Evaluating the Measurement of Patient Reported Outcomes programme provide
11 useful guidance to support the review of measurement properties.^{56 62 63}
12 Ideally, the PRO instrument(s) will have been validated in the target population and
13 this evidence cited. This will help reviewers understand if claims being supported by
14 the PRO instrument can be substantiated by the evidence for using that instrument
15 in that, or a related, population. Further details on the domains, number of items,
16 recall period, instrument scaling and scoring (e.g. range and direction of scores
17 indicating a good or poor outcome) should be provided. This will assist trial
18 personnel in the collection and analysis of the PRO data. Questionnaires should be
19 used in accordance with user manuals to promote good data quality and ensure
20 standardized scoring. Deviations from user manuals or different ways of capturing
21 PRO data may invalidate the measure; therefore any deviations should be declared
22 and transparently reported.¹⁸

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27 If in the trial there are plans to use a questionnaire which has not been validated in
28 the trial's target population, or if a new instrument is being developed alongside the
29 trial, it is important to explain this in the protocol. Including an outline of any plans for
30 the evaluation of its measurement properties using the trial data, if this will be
31 undertaken, and if not why. This should be in accordance with established current
32 guidelines for PRO validation.⁶⁴

33
34
35 Although all the reviewed NIHR Health Technology Assessment clinical trial
36 protocols identified the PRO instrument to be used in the trial, few justified their use
37 in relation to the study hypotheses, PRO instrument measurement properties, or
38 expected participant burden (41.3%, 37.3% and 14.7% respectively).³
39 Patient partners involved in the design of the study can assist with the selection of
40 PRO instruments and provide feedback on the likely acceptability of the questions,
41 and participant burden (e.g., time taken for completion, cognitive burden, emotional
42 burden, repetition across questionnaires).⁶⁵ The number of PRO
43 instruments/questions to be assessed in a trial requires careful justification.
44 Minimising participant burden has been identified as a strategy to reduce risk of
45 missing PRO data, improve recruitment and retention.²⁹

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49 **SPRIT-18a(ii)-PRO Extension: Include a data collection plan outlining the**
50 **permitted mode(s) of administration (e.g., paper, telephone, electronic, other)**
51 **and setting (e.g., clinic, home, other).**

52 53 54 **Examples**

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57 **Trial name: Early surgery versus optimal current step-up practice for chronic pancreatitis: a**
58 **multi-centre randomised control trial (ESCAPE)**

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60 **PRO endpoints: 1°, 2°**

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“The Izbicki pain score will be assessed every two weeks during a follow-up period of 18 months. For this end, the Izbicki pain score will be assessed via a web questionnaire. Patients who do not have an email will be given a folder with Izbicki pain score forms and return envelopes. Patients will be contacted by telephone every two weeks and reminded to fill in the questionnaire and send it to the trial coordinators. The Izbicki pain score is a one page questionnaire, easily completed in less than 3 minutes. The folder with the Izbicki score forms will be re-filled at every outpatient clinic visit (scheduled every 6 months).”⁶⁶

Trial name: a randomised multi-stage phase II/III study of Sunitinib comparing temporary cessation with allowing continuation, at the time of maximal radiological response, in the first-line treatment of locally advanced/metastatic Renal Cancer (STAR)

PRO endpoints: 1°, 2°

Quality of life questionnaires during the first 6 months will be administered in clinic in order to support participant use before postal questionnaires are instituted after 6 months for the EQ-5DTM/EQ-VASTM (FACT-G and FSKI will continued to be collected at clinic visits). Clinic staff should remind participants of the importance of the quality of life assessments at each clinic visit.

Due to the importance of HRQL data in this trial, measures will be taken to ensure maximum compliance of questionnaire completion. For the two-weekly questionnaires which participants complete at home from the 24-week time-point, where the participant consents to this, reminders for completion are sent by email or text message to the participant by the research team at CTRU: this is an optional part of the STAR Informed Consent Form. Where a HRQL questionnaire would be completed at a hospital clinic visit, but the local research team forget to give this to the participant, of the participant no longer attends clinic visits at hospital during their follow-up period, a questionnaire for the local research team will send this out by post to the participant’s home after checking the participant’s status and establishing it is appropriate to do so.^{67 68}

Explanation

Standardisation of all aspects of PRO administration is vital to PRO data quality. It is therefore critical that research personnel and trial participants understand how, when, and where PRO data will be collected in the study.¹⁰ The study protocol should specify the permitted mode(s), method(s) and setting(s) of PRO data collection, including the permitted “back-up” options and pre-planned reminders. For example, when PRO assessment is conducted in clinic via a tablet computer, paper forms could be permitted (and available) as a back-up option for instances when the tablet is not available or functioning properly. Offering alternative modes of completion may help improve response rates.²⁹ Of note, the FDA has previously recommended that there is a back-up plan for electronic PRO data collection (e.g., web-, phone-, or paper-based) implemented in case of malfunctions with electronic devices.⁶⁹

Electronic PRO assessment is increasingly available in trials, but traditional paper-based methods may still be useful or required in some situations. It is therefore important to know whether there are systematic differences induced by mode of administration. A recent meta-analysis that included 31 studies that randomised participants to different data collection modes found no evidence of bias associated with paper versus electronic administration.⁷⁰ These results support the use of multiple modes of administration within a research study, which may be a useful strategy for reducing missing PRO data. If evidence of equivalence between different modes of administration is available for the specific PRO questionnaires in a trial, it should be considered in determining the PRO administration plan. If electronic

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3 administration has not been attempted before for the trial PRO questionnaires, and
4 only minor modifications to layout/presentation are needed with respect to the paper-
5 based versions, it is advisable to pilot-test usability and conduct cognitive debriefing
6 to assess equivalence.^{70 71} The International Society for Pharmacoeconomics and
7 Outcomes Research (ISPOR) provide useful guidance on key considerations for
8 PRO data collection including multiple modes.^{71 72}
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10
11 The setting for PRO data collection, for example in clinic or at home (or clinic at
12 baseline, with follow up at home), should be described and standardized across trial
13 intervention groups and sites. Differential use of settings and modes of
14 administration by treatment arm should be avoided as these may lead to different
15 response rates and potentially biased results.¹¹
16

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18 The protocol should also specify the types of assistance trial staff can provide
19 patients for completing the PRO assessment. Respondents should be encouraged to
20 self-complete as far as possible. Some respondents may require some assistance,
21 however, the greater the degree of assistance, the greater the potential to influence
22 a respondent's responses. Assistance should therefore be limited, provided only by a
23 trained member of the research team, or a trained third party, the permissible types
24 of assistance should be clearly specified in the protocol and reviewed in staff
25 training. Allowable assistance might include instructions on how patients can input
26 their answer on the tablet, clarifying the response options, reading questions to the
27 participant, or recording the participants' answer on the form/tablet. This level of
28 assistance facilitates self-administration of the PRO instrument. Completion of a
29 PRO instrument with an interpreter, caregiver or family member should be avoided
30 as these individuals have not been trained, and may influence the individual's
31 responses, either directly by expressing opinions that influence the participant to
32 alter their answers, or indirectly, for example if the respondent seeks to avoid
33 embarrassment or to provide a more acceptable answer (social desirability bias).
34
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38 Further, use of a human language interpreter should be avoided. When planning a
39 study, common languages spoken by patients attending the recruiting centres should
40 be considered so that validated language translations of chosen PRO instruments
41 can be obtained (see SPIRIT-18a(iii)-PRO Extension).
42

43
44 Interviewer administration of PRO instruments should be avoided, but where
45 necessary, should be clearly justified in the protocol. Interviewers should read
46 questions verbatim, ideally using a PRO instrument that has been validated in that
47 mode. Similarly, proxy or observer completion requires a proxy-validated/observer-
48 reported version of the PRO instrument (see SPIRIT-18a(iv)-PRO Extension).
49

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51 **SPIRIT-18a(iii)-PRO Extension: Specify whether more than one language**
52 **version will be used and state whether translated versions have been**
53 **developed using currently recommended methods.**
54

55 Example

56
57 Trial name: A Phase 3, Randomized, Open Label Trial of Lenalidomide/dexamethasone With or
58 Without Elotuzumab in Relapsed or Refractory Multiple Myeloma (ELOQUENT – 2)

59
60 PRO endpoints: 2°, exploratory

“5.8 Outcomes Research Assessments

5.8.1 HRQL Assessments

To assess the impact of treatment, subject’s quality of life will be measured using 3 validated HRQL instruments: the European Organization for Research and Treatment of Cancer Quality of life Questionnaire- Core (EORTC QLQ-C30), the myeloma-specific module (QLQ-MY20) and the Brief Pain Inventory- Short Form (BPI-SF)...

Non-English speaking subjects will complete the questionnaire using validated language transitions developed and recommended for each instrument... The BPI-SF has demonstrated both reliability and validity across cultures and languages, and has been used to study the effectiveness of pain treatment.[Reference] A score of 6 on a scale of 0 to 10 on any single item is generally considered to be clinically significant.[Reference] Pre-testing was carried out in the UK, Norway, Sweden, Denmark, and Germany. Field testing of the module has been conducted in a range of Phase 3 trials.[Reference] The module has been validated in a large number of languages (see www.eortc.be/home/qol).⁷³

Explanation

Trials involving participants with different language requirements require measures that have been translated and culturally adapted using appropriate methodology.^{10 12 74 75} Providing culture- and language- appropriate PRO instruments for use in the trial can lead to a reduction in missing data, ability to recruit people from ethnic minority groups, lower attrition rates and improved generalizability of trial results.⁷⁶ If the countries/languages are not known at the time of protocol writing then more general protocol content may be appropriate:

“multiple language validated versions are available [provide references where these can be found] and the correct language for this patient should be used”.

At present the extent to which this is happening is not clear. A review of protocols and/or subsequent publications from cancer clinical trials with a PRO endpoint, registered on the National Institute for Health Research portfolio examined reporting of ethnically diverse recruitment and the use of culturally and linguistically validated PRO instruments. The review found a lack of transparency around the use of culturally and linguistically appropriate PRO instruments. Of the 88 studies reviewed only 14(17%) reported any type of data on ethnic diversity. Although eight studies were multicentre, multi-national cancer clinical trials, none identified if translated versions of PRO instruments were being used.⁷⁷

There are clear guidelines for translating PRO instruments,^{74 78} and plans to use translated versions, should be specified in the protocol, citing references when available.¹⁰ Specification of use of translated versions in the protocol will help reporting in accordance with CONSORT-PRO.^{18 74 75} It must not be assumed that linguistic translation equates to cross cultural adaptation (preparing the instrument for use in another setting). A number of studies^{79 80} have recommended that cross cultural equivalence is also an important consideration.^{74 75 81}

Using different language versions of PRO instruments to collect data in a trial ideally requires evidence to support the psychometric equivalence of data being reported, especially if data are going to be pooled for clinical trial evaluation.^{52 82 83} Where such evidence is unavailable, pre-specification in the statistical analysis plan (SAP) of exploratory analyses to assess whether there are differences between PROs by

language group may be appropriate. The language in which each patient complete the questionnaire should be recorded in the database to inform such analyses.⁵²

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.

Examples

Trial name: Cognitive Rehabilitation in Pediatric Acquired Brain Injury - a Randomized Controlled Trial (CORE-pABI)

PRO endpoints: 1°, 2°

“[Paediatric Acquired Brain Injury] constitutes a major disruption to child development and may affect cognitive, behavioural, emotional, social as well as academic function.

The primary outcome measure is the BRIEF, parent report.[*Reference*] BRIEF is an 86-item standardised questionnaire that captures parents perceptions of a child’s EF in his or her everyday environment. Each item’s frequency of occurrence is rated on a 3-point Likert scale from 1(never) to 3 (often). It has demonstrated good reliability, with high test-retest reliability (rs=0.88 for teachers, .82 for parents), internal consistency (Cronbach’s α s=0.80– 0.98), and moderate correlations have been detected between teacher and parent ratings (rs=0.32–0.34). The questionnaire has been applied to several clinical groups in Norway.”⁸⁴

Trial name: Evaluating the effectiveness and cost effectiveness of Dementia Care Mapping (DCM) to enable person-centred care for people with dementia and their carers: a cluster randomised controlled trial in care homes (DCM EPIC study 1.0)

PRO endpoints: 2°

“Relative/friend criteria

To be eligible to provide proxy data about a resident, relatives/friends must: Have visited the resident on a regular basis over the past month (i.e. at least once per week) Be willing to provide data at a time convenient to them Have sufficient proficiency in English to contribute to the data collection required for the research”⁸⁵

Explanation

In some contexts, such as trials involving young children or cognitively impaired participants or participants who are unable to reliably self-report for other reasons, it may be necessary for a proxy - someone other than a trial participant, to report the participant’s outcomes on their behalf as though they are the patient.^{10 86}

Proxy reports should be used only when necessary. 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.”^{15 42} The US FDA also discourages the use of proxy-reported outcomes to inform labelling claims, recommending observer reports for observable phenomenon only (e.g. vomiting, but not nausea) instead.

In contexts such as cancer, dementia or palliative care it is reasonable to anticipate the need for proxy response, throughout all or some of the trial. Previous studies have shown varying levels of agreement between participant and proxy ratings,

dependant on the variable being measured, the quality, duration, and stability of the relationship between proxy and participant.^{87 88}

A trial protocol should indicate clearly who is eligible to provide the proxy report, with explicit administration guidelines for completion of proxy measures including how the report is to be captured, whether that same individual must be the “consistent rater” across all time-points of assessment (this is preferable, for consistency), or whether varying proxy reports will be permissible. This information should also be provided for observer-reported outcomes.

Just as the measurement properties of the PRO instrument should be specified, so should the properties of measures to be used by proxy reporters.

Given known issues with patient and proxy reporter discordance,⁸⁸⁻⁹¹ while patient-participants are still able to self-complete, collecting both participant and proxy-reported data enables quantification of the size and direction of any bias, that may later be adjusted for, if needed. Further data may be gathered about the proxy (e.g. age, relationship to the patient, gender, proxy literacy, relationship and exposure to the patient,⁹²) as these variables may guide interpretation of results and any subgroup/sensitivity analyses. Whether proxy-reported data will be analysed separately or pooled with participant-reported data should also be detailed. Any such plans should be specified in the protocol and SAP. This information should also be provided for observer-reported outcomes.

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

Examples

Trial group: National Cancer Institute, Naples

Trial name: Phase III randomized multicentre trial of Carboplatin + Liposomal Doxorubicin vs Carboplatin + Paclitaxel in patients with ovarian cancer (MITO-2 (Multicentre Italian Trials in Ovarian Cancer-2))

PRO endpoints: 2°

“Operating procedure

- It is fundamental that the Researchers take great care when collecting the questionnaires, in order to allow good compliance by the patients participating in the protocol.
- The quality of life form must be filled in by the patient herself.
- The quality of life form must be filled in before the clinical examination, and thus before the discussion with the examining doctor which may provide favourable or unfavourable information about the disease's status.
- When supplying the form to the patient, it is important to explain how to fill it in without going into details about the contents of the questions.
- After the form has been returned, check that the patient has answered all the questions and ask her to reply to any questions she has skipped.
- The quality of life questionnaires must be filled in using a black or blue pen.”⁹³

Trial group: National Cancer Institute of Canada Clinical Trials Group (NCIC CTG)

Trial name: A double blind randomization to Letrozole or placebo for women previously diagnosed with primary breast cancer completing five years of adjuvant aromatase inhibitor

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2
3 **either as initial therapy or after Tamoxifen (including those in the MA.17 Study) (NCIC CTG:**
4 **MA.17R)**

5
6 **PRO endpoints: 2°**

7
8 **“4.9 Quality of Life**

9 Mandatory for NCIC CTG centres and optional for centers within other cooperative groups:
10 Patient is able (i.e. sufficiently fluent) and willing to complete the two quality of life questionnaires in
11 either English or French. The baseline assessment must have been completed prior to randomization.
12 Inability (illiteracy in English or French, loss of sight, or other equivalent reason) to complete
13 questionnaires will not make the patient ineligible for the study. However ability but unwillingness to
14 complete the questionnaires will make the patient ineligible.”⁹⁴

15 16 17 **Explanation**

18
19 Missing PRO data are a particular problem because data cannot be obtained
20 retrospectively or from medical records. Missing PRO data may arise from different
21 sources⁹⁵ and, broadly speaking, missing data can be attributed to causes that are
22 unavoidable or avoidable. Unavoidable reasons may include if a participant has died
23 or become too unwell to self-complete PRO instruments. Avoidable reasons may
24 include some type of human error that could have been prevented. Examples of
25 avoidable missing data include: staff failing to hand out a scheduled questionnaire; a
26 participant not realising the questionnaire is double-sided so missing half of the
27 questions; an electronic PRO device not being charged; the internet or server being
28 down; or when the PRO assessment is overly burdensome on the patient (e.g. due
29 to the burden of multiple questionnaires at one time or repetitive scales) so the
30 patient decides not to complete it.

31
32 Although “unavoidable” types of missing data are more challenging for interpretation
33 because the missing data may be related to the measured outcome and it is
34 impossible to accurately calculate the extent of any associated bias,^{96 97} avoidable
35 types of missing data are also problematic.²⁹ Avoidable missing PRO data
36 compromise the interpretability, accuracy and value of PRO findings because study
37 power is reduced, which increases the risk of type 2 errors,⁹⁶ and because any
38 assumptions made during the analysis about missing PRO values are not
39 verifiable.⁹⁸

40
41 There are a range of design, implementation, and reporting strategies to help
42 minimise and address missing PRO data,²⁹ most of which can be addressed in the
43 trial protocol. Specific recommendations related to data collection and management
44 include: refraining from administering an excessive number of questionnaires to
45 participants (researchers should refrain from collecting more data than they really
46 need), using standardised and documented PRO administration procedures,
47 engaging and educating participants in the trial by providing updates or incentives,
48 maintaining participant records, employing active quality assurance measures (such
49 as real-time compliance/completion monitoring, sending reminders for upcoming or
50 missed assessments, checking completed questionnaires for missing items while the
51 participant is still present at clinic), appointing a dedicated staff member responsible
52 for PRO assessment at each centre, training staff about the importance of PROs as
53 well as procedures for assessment, offering an alternative mode of administration if
54 the participant is not able to complete the questionnaire via the primary mode (e.g.

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2
3 completing the questionnaire over the phone if the hardcopy cannot be completed at
4 the clinic within the acceptable time window) and recording reasons for missed
5 assessments using standardised forms.²⁹ From a regulatory perspective, the FDA
6 encourages maintaining consistency in assessment methods, however, this should
7 be balanced with reduction of missing data. If different modes are used, they should
8 be justified and presented in the study documentation.⁹⁹ If different modes are used
9 “FDA will review the comparability of data obtained when using multiple data
10 collection methods or administration modes within a single clinical trial to determine
11 whether the treatment effect varies by method or mode”.⁶⁹ Additional strategies are
12 described in the full review.²⁹
13
14

15
16 The MITO-2 and MA.17R examples above illustrate some of these strategies.
17 MA.17R comes from the Canadian Cancer Trials Group (CCTG), a multi-centre
18 cooperative oncology group that conducts clinical trials in cancer therapy, supportive
19 care and prevention. The CCTG requires completion of the PRO questionnaire(s) as
20 a pre-randomisation eligibility requirement (as per SPIRIT-10-PRO Extension). This
21 flags the importance of PRO data to investigators and clinical research associates,
22 indicating PROs are as important as other inclusion clinical criteria. It also helps to
23 maximize compliance.
24

25
26 Our prior work suggests that few trials actively specify such procedures in their
27 protocols; 46.7% HTA protocols³ and 38.5% of international ovarian cancer trials⁴
28 included strategies to minimise avoidable missing data.
29

30
31 **SPIRIT-18b(ii)-PRO Elaboration: Describe the process of PRO assessment for**
32 **participants who discontinue or deviate from the assigned intervention**
33 **protocol.**
34

35 36 **Examples**

37
38 **Trial name: A multi-centre, open-label, randomised, two-arm Phase III trial on the effect on**
39 **progression free survival of bevacizumab plus chemotherapy versus chemotherapy alone in**
40 **patients with platinum-resistant, epithelial ovarian, fallopian tube or primary peritoneal cancer**
41 **(AURELIA)**
42

43 **PRO endpoints: 2°**
44

45 **AURELIA** was a multi-centre, open-label, randomised, two-arm Phase III trial of bevacizumab plus
46 chemotherapy versus chemotherapy alone in patients with platinum-resistant, epithelial ovarian,
47 fallopian tube or primary peritoneal cancer [Reference]. The primary endpoint was progression-free
48 survival (PFS); quality of life was a secondary endpoint. The protocol stated that:
49

50 “Upon clear evidence of disease progression (PD) or toxicity, study therapy should be discontinued
51 permanently.”
52

53
54 The protocol also specified post-progression treatment options: women who had been on the
55 chemotherapy alone arm would have the option of bevacizumab alone or standard of care, while
56 those who had been on the chemotherapy plus bevacizumab arm would receive standard of care
57 treatment. The protocol stated that:
58
59
60

1
2
3 “In case the patient decides to prematurely discontinue study treatment (“refuses treatment”), she
4 should be asked if she can still be contacted for further information.” and that “After PD, patients will
5 be followed for survival only.”
6

7 However, it lacked an explicit statement about PRO assessment post-progression, which may explain
8 some inconsistency among sites, with some sites collecting PRO data post-progression, and other
9 not.
10

11 As stated in the AURELIA PRO paper (*ref, p1310*), “Only questionnaires completed until PD were
12 included in the main analyses. Questionnaires completed after PD were excluded based on the
13 medical assumption that these patients were unlikely to be benefiting from their study treatment, may
14 have been receiving another treatment, and were therefore not relevant to the intended comparison of
15 chemotherapy alone versus bevacizumab plus chemotherapy. However, post hoc sensitivity analyses
16 were performed to determine the impact of questionnaires completed after PD.” The latter analyses
17 were consistent with the main analyses, but could perhaps have been avoided, and patients saved
18 unnecessary HRQL assessment burden, if the protocol has contained a clear statement that HRQL
19 assessments should cease at disease progression.¹⁰⁰
20
21
22

23 **Trial group: Australasian Leukaemia & Lymphoma Group (ALLG); Trial name: BLAM- A phase**
24 **IIb study of Blinatumomab + Cytarabine (AraC) and Methotrexate in adult B-precursor Acute**
25 **Lymphoblastic Leukaemia (ALLG ALL8)**
26

27 **PRO endpoints: 2°**
28

29 ALLG ALL8 is a BLAM-A phase IIb study of Blinatumomab + Cytarabine (AraC) and Methotrexate in
30 adult B-precursor Acute Lymphoblastic Leukaemia (B-ALL). It is a single-arm study which aims to
31 demonstrate preliminary evidence of the benefit of frontline Blinatumomab in combination with
32 Cytarabine and Methotrexate in adult B-ALL, and to demonstrate the ability of this combination to
33 attain deep (MRDnegative) remissions and hence to reduce the need for allogeneic stem cell
34 transplantation. The ALLG ALL8 protocol specifies that the decision for allogeneic stem cell
35 transplantation is left up to the investigator, and that patients who proceed to allogeneic stem cell
36 transplant discontinue the assigned intervention protocol. Being recommended for allogeneic stem
37 cell transplant is therefore a withdrawal criteria. However, patients do not have to withdraw – it is
38 optional, the patient’s choice. The trial team is in fact interested in the experience of patients who
39 proceed to allogeneic stem cell transplant. So the protocol states:
40

41 “Subjects who proceed to allogeneic stem cell transplant who have not withdrawn consent to the
42 study should have FACT-Leu (HRQL questionnaire) assessments performed 6-monthly.”
43

44 This provides the trial team with the opportunity to document the experience of patients who proceed
45 to allogeneic stem cell transplant in terms of the range of common symptoms and aspects of well-
46 being assessed by FACT-Leu.¹⁰¹
47

48 **Explanation**

49 A clear plan for collection of PROs for trial participants who withdraw early from a
50 study or who discontinue the intervention helps minimize bias,¹⁰² ensures that staff
51 collect all required PRO data in a standardized and timely way, and may assist
52 ethical appraisal of the study.^{10 102}
53
54

55 Often, participants can provide valuable PRO data even after stopping the assigned
56 intervention protocol, whether due to personal choice and/or clinical
57 recommendation, as illustrated in the one-arm phase II trial ALLG ALL8 trial.
58 However, this does not hold in all contexts (as illustrated in the AURELIA trial), a
59
60

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3 randomised phase III trial, in which participants whose cancer had progressed on
4 their assigned treatments, were then often switched to alternative treatment.
5

6
7 Providing a clear description of the process of PRO assessment for participants who
8 discontinue or deviate from the assigned intervention protocol and how the data will
9 be used, enables all staff to follow a standardised procedure to collect the required
10 PRO data in timely way, and to avoid collecting data that will not contribute to
11 analysis.
12

13 Correspondingly, the SAP should be clear on how such data will be handled. In the
14 case where post-discontinuation/deviation PRO data are useful, the SAP should
15 state the study objective that these data will address and how they will be analysed.
16 Participants should also be aware of this process, so a simple and clear description
17 of whether or not they will be asked to continue to complete PRO questionnaires
18 after stopping or changing the treatment they were initially allocated to should be
19 included in the participant information sheet (PIS).
20
21

22 **SPIRIT-20a-PRO Elaboration: State PRO analysis methods, including any plans** 23 **for addressing multiplicity/type I (α) error.** 24

25 **Example** 26

27
28 **Trial name: A phase 3, randomized double-blind, placebo-controlled study of the efficacy and**
29 **safety of 2 doses of Tofacitinib (Cp-690,550) in subjects with active psoriatic arthritis and an**
30 **inadequate response to at least one TNF inhibitor (OPAL BEYOND)**
31

32 **PRO endpoints: 1°, 2°, exploratory**
33

34 “9.2.1. Analysis of Primary Endpoint 35

36
37 There are two primary endpoints in A3921125 and two doses of tofacitinib each of which will be
38 compared to placebo for each endpoint. In order to control for Type I error a step-wise testing
39 procedure will be used. This implies that a given endpoint for a given dose can only achieve
40 significance if the prior endpoint is significant. The order of the fixed sequence for testing against
41 placebo is as follows: tofacitinib 10mg ACR20 response rate at 3 months, tofacitinib 5mg ACR20
42 response rate at 3 months, tofacitinib 10mg HAQ-DI at 3 months, tofacitinib 5mg HAQ-DI at 3 months.
43 This gate-keeping or step-down approach strongly protects the Type I error rate at the 0.05 (2-sided)
44 level...
45

46 9.2.1.1. ACR20 Response 47

48 For all comparative analyses, the normal approximation for the difference in binomial proportions will
49 be used to test the superiority of each dose of tofacitinib to placebo and to generate confidence
50 intervals for the differences. The primary analysis will be ACR20 response rate at Month 3. The
51 ACR20 response rate will also be analysed at other time points as a secondary analysis.
52 Missing values due to a subject dropping from the study for any reason (e.g., lack of efficacy or
53 adverse event) will be handled by setting the ACR20 value to nonresponsive.
54

55 9.2.1.2. HAQ-DI 56

57 The HAQ-DI score will be expressed as a change from baseline. The primary timepoint will be at
58 Month 3. The analysis will be done using a repeated measure model that includes fixed effects of
59 treatment, visit (Week 2, Months 1, 2 and 3), treatment by visit interaction, geographic location and
60 baseline value. The model will use and fit an unstructured variance-covariance matrix. Full details will
be listed in the analysis plan.

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3
4 Additional analyses of the HAQ-DI will include a responder analysis at Month 3 where subjects with a
5 change of 0.3 will be considered responders and subjects who dropped from the study will be
6 considered nonresponsive. Another responder analysis will be conducted using a change of 0.35 at
7 the cutpoint for response [Reference]. The normal approximation for the difference in binomial
8 proportions will be used for these responder analyses.
9

10 9.2.2. Analysis of Secondary and other Endpoints

11
12 Key secondary efficacy variables are as follows: PASI75, enthesitis score, dactylitis severity score,
13 physical function domain of SF-36, and FACIT-F at Month 3. In order to strongly protect the study-
14 wise Type I error rate with respect to these key secondary endpoints and the primary endpoints, these
15 endpoints will be tested only if all endpoints/doses for the primary endpoints are statistically
16 significant. The order of testing is as listed above; for each endpoint, tofacitinib 10mg will be tested vs
17 placebo first, followed by tofacitinib 5mg. Testing stops at the first instance in which statistical
18 significance is not achieved...
19

20 Methods for analysing all other endpoints will be enumerated in the statistical analysis plan. Briefly,
21 binary variables (e.g., remission rates) will follow the analyses described above for binary variables
22 (e.g., ACR20) and continuous endpoints will follow the same type of analyses described above for
23 continuous endpoints (e.g., HAQ-DI). Descriptive statistics may also be calculated and displayed."¹⁰³
24

25 **Explanation**

26
27 Statistical analysis of multiple domains^{10 104} and time-points implies multiple
28 hypothesis testing, which inflates the probability of false-positive results (type I
29 error).⁴⁵ This can be contained by pre-specifying the key PRO domain(s) or overall
30 score of interest and the principal time-point(s) which cross-reference to SPIRIT-7-
31 PRO Extension and SPIRIT-12-PRO Extension.
32

33
34 Any plans to address multiplicity, such as stepwise or sequential analyses, whereby
35 multiple end points are tested in a defined sequence that contains the overall type I
36 error to the desired level, or conventional non-hierarchical methods (e.g. Bonferroni
37 correction), should be specified a priori.¹⁵ There are many strategies and/or choices
38 of methods that may be appropriate.¹⁰⁵ Family-wise type I error should be
39 considered for all of the applicable endpoints of the trials together and not for the
40 PRO endpoints separately. Some clinical trials include PROs as exploratory
41 endpoints and no adjustment is made for multiplicity in subscale scores administered
42 at multiple study visits. These analyses may only provide limited information on the
43 tolerability of the intervention.
44

45
46 Protocols should make some reference to key considerations for the analysis of the
47 trial PROs (including any plans for addressing multiple testing), but the detail is often
48 more appropriately included in the SAP, usually developed after the protocol. If no
49 adjustments for type I error are to be made, then this should be clearly stated.
50 However, clinical trial protocols in which PROs are secondary outcomes rarely
51 include any information about PRO statistical analyses, beyond any that are pre-
52 specified as primary or key secondary endpoints or when the sponsor is interested in
53 achieving a product label claim. Our review of trial protocols found that fewer than
54 2% provided information on the statistical analysis plans to address multiplicity for
55 the PRO endpoints.³
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SPIRIT-20c-PRO Elaboration: State how missing data will be described and outline the methods for handling missing items or entire assessments (e.g., approach to imputation and sensitivity analyses).

Example

Trial group: European Organisation for Research and Treatment of Cancer-Gynaecological Cancer Group, and Gynecologic Cancer Intergroup (EORTC-GCG and GCIG)

Trial name: A randomised, multicentre, phase III study of Erlotinib versus observation in patients with no evidence of disease progression after first line, platinum-based chemotherapy for high-risk ovarian epithelial, primary peritoneal, or fallopian tube cancer (EORTC 55041)

PRO endpoints: 2°

“10.3.2 Compliance

Missing data may hamper assessment of HRQL in clinical trials. This may occur because centers do not collect the questionnaires at the appropriate time (unit non-response), and also because patients may not reply to questions within the questionnaires (item non-response). The latter problem occurs less than 2% on average and should not be a problem. The former problem will be minimized by ensuring that participating centers are properly informed and motivated towards HRQL assessment. During the study, compliance with completing HRQL questionnaires will be investigated at each time point. The compliance of the HRQL assessments will also be reviewed twice a year and will be a part of the descriptive report by the Data Center for the Group's plenary sessions and, if possible, be presented by the EORTC Quality of Life Group's appointed liaison person.

The compliance rate between the two arms will be compared at each time point using a chi-square test. In order to adjust for the multiplicity of the tests, a Bonferroni adjustment will be made by which each test will be performed at the 0.01 significance level. Should follow-up compliance levels drop below 60% at subsequent bi-annual compliance reviews, then the Protocol Writing Committee would review this to either improve compliance or consider terminating the HRQL assessment in the trial...

10.4.3 Missing data

When performing HRQL analyses complications may arise due to large quantities of missing data. This issue has a bearing on whether a valid comparison of the treatment arms is being made. In HRQL research there are two main types of missing data: (1) item non-response, (2) unit nonresponse (the whole questionnaire is missing for a patient). As item non-response occurs less than 2% on average in the QLQ-C30 it is not such a major problem and thus the methods described in the EORTC QLQ-C30 scoring manual for handling item non-response will be used. For missing questionnaires, it is necessary to identify both the extent of missing questionnaires and the main process of missing data. Three different types of missing data processes may exist: missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR, informative dropout mechanism). These have distinct consequences for data analysis [Reference]. If the missing data process is considered to be non-ignorable (MNAR) then quality of life will be compared between groups using longitudinal data modeling techniques (i.e. Proc mixed in SAS with either selection models or pattern-mixture models) in combination with a logistic regression for the dropout process. If the missing data mechanism can be considered ignorable (MAR), then standard longitudinal data analysis will be used (proc mixed in SAS). If the data are MCAR then complete case analysis can be used without biasing the results.”¹⁰⁶

Explanation

Most clinical trials with PROs will have some missing PRO data,⁹⁸ yet a review of protocols found that less than half outlined statistical methods to deal with missing PRO data.³

There are two types of missing PRO data: 1) missing items, when the participant completes some but not all of the questions within a PRO instrument, and 2) missing

1
2
3 assessments, when the participant does not complete a scheduled assessment at all
4 (i.e. there are no PRO data available for analysis from the participant at that
5 assessment time point). The latter type is more serious, as it potentially affects the
6 choice of analysis method and the interpretation and generalisability of the results.
7 The trial protocol should explain how both types of missing data will be handled in
8 the analysis.
9

10
11 1) Handling missing items: many PRO scoring manuals provide guidance for
12 handling missing items. A common approach is to impute the mean score of the
13 completed items, if less than one-half of items comprising the scale are missing.¹⁰⁷
14 ¹⁰⁸ This approach is possible for multi-item scales but it is not possible to impute
15 scores for single item scales. Always consult the scoring manual to determine how to
16 handle missing items, and cite the manual in the protocol. Missing items of PRO
17 instruments that are underpinned by modern psychometrics techniques (Item
18 Response Theory or Rasch Measurement Theory) are naturally handled without
19 requiring imputation.^{33 109}
20
21

22
23 2) Handling missed assessments: missing assessments present a major problem for
24 PRO analyses; lead to a loss of power and wider confidence intervals from a lack of
25 precision,^{110 111} and potentially to biased results. The risk of bias depends on the
26 underlying cause of why data are missing (called the “missing data mechanism”),
27 and this in turn should influence the choice of statistical analysis methods.
28 In order to gain insights into the mechanism of missing PRO data, it is helpful to
29 ascertain and record reasons for missed PRO assessments during trial conduct. The
30 protocol needs to describe how these reasons will be collected in a standardised
31 manner. Typically a standard form is used (which can be included in the Appendix
32 along with the PRO questionnaires). Also, the form can be used to collect additional
33 data (referred to as “auxiliary data”) related to “missingness” or the PRO,²⁹ which
34 should be specified in the protocol.
35
36

37
38 The trial protocol should also provide a summary of how missing data will be
39 described and handled in the analysis,¹⁰ and state that comprehensive details about
40 the planned analysis will be provided in a subsequent SAP.¹¹² The SISAQOL
41 consortium have developed a taxonomy of research objectives that can be matched
42 with appropriate statistical methods for PRO analysis, standardised statistical
43 terminology relating to missing data, and are determining appropriate ways to
44 manage missing data, currently focused in an oncology setting. A simulation study
45 was done to assess whether it was possible to have a threshold to define substantial
46 missing data.¹¹³ Although no agreement was reached for a threshold, the simulation
47 study showed that the effect of missing data rates on PRO findings depends on the
48 type of missing data (i.e., informative or non-informative missing data). It was
49 recommended that collecting reasons for missing data is key in assessing the effect
50 of missing data for PRO findings.³³ Additionally, SISAQOL is developing a set of
51 macros to describe patterns of missing data, and to evaluate imputation methods for
52 use in sensitivity analysis.^{33 35 37}
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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 standardised way. Describe how this process will be explained to participants; e.g., in the participant information sheet and consent form.

Example

Trial name: The use of an electronic Patient-Reported Outcome Measure in the Management of Patients with Advanced Chronic Kidney Disease (RePROM)

PRO endpoints: 2°

Protocol:

"If, when reviewing the completed EQ-5D-5L questionnaire, the research nurse becomes concerned for the wellbeing of the participant, they should discuss their concerns with the participant directly, working in partnership to determine the best course of action. With the participant's permission, the research nurse may need to consult with the PI and/or treating clinician to address these concerns. In exceptional circumstances, the research nurse may consult with the PI and/or treating clinician without the permission of the participant if they are concerned for the participant's safety."

Patient information sheet:

"If the study research nurse becomes concerned for your wellbeing during a study review, they will discuss their concerns with you, to determine the best course of action. With your permission, the research nurse may need to consult with a senior member of the study and/or your treating clinician to address these concerns. In exceptional circumstances, the research nurse may need to do this without your prior permission if they are concerned for your safety."

Consent form:

"I understand that if the study research nurse becomes concerned for my wellbeing during a study review, they will discuss their concerns with me to determine the best course of action. With my permission, the research nurse may need to consult with a senior member of the study and/or my treating clinician to address these concerns. In exceptional circumstances, the research nurse may need to do this without my prior permission if they are concerned for my safety."¹¹⁴

Explanation

To protect participant safety, PRO data may be monitored during a study for signs of psychological distress or physical symptoms that may require an immediate response: so-called 'PRO Alerts'.¹¹⁵ Examples of PRO data that may raise concern include signs of psychological distress, poor physical well-being, or high symptom burden presenting as extreme scores on questionnaires. Concerns can also arise when additional information is provided by the participant (for example, through free text report), or in discussions between the participant and research staff.¹¹⁵ The nature of some studies may mean that participants are more at risk than in others. In studies where prior risk assessment deems the probability of PRO alerts being generated by participants to be minimal, PRO data may not be reviewed until the end of the trial for pragmatic reasons, however, concerning PRO data, may still arise during the course of the study.^{11 116} If monitoring is not planned this should be stated. If monitoring is planned, steps for how PRO alerts will be dealt with should be included in the trial protocol, to provide immediate reassurance to concerned trial staff about how to proceed and promote appropriate clinical management and transparency considering professional obligations to patient care. Any arising

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3 interventions should be recorded. Evidence suggests the absence of such
4 information leads to inconsistent handling of concerning data including administration
5 of non-prespecified interventions to aid the trial participant which risks co-
6 intervention bias i.e., bias caused by “any intervention other than the experimental
7 maneuver that alters the frequency of a trial’s outcome of interest”.^{12 116 117} Identifying
8 participants at risk and in need of urgent attention through PRO monitoring is an
9 ethical issue as is acknowledging that information identified in the completion of a
10 PRO too may be shared with the clinical team when the need arises. Information
11 about how the trial staff will respond to concerns, or alternative support mechanisms
12 where monitoring is not taking place, should be provided to participants (in
13 participant information and consent documentation). This information provided in the
14 patient information sheet (PIS) will manage participant expectations and ensure
15 transparent and explicit communication about the intended use of PRO study data in
16 fulfilment of contemporary data protection laws, for example, the European Union
17 General Data Protection Regulation.¹¹⁸

21
22 There is no regulatory requirement from the US FDA that PRO data measuring
23 symptomatic side effects be monitored and alerts for these items created. However,
24 it is good practice to remind participants at each PRO assessment whether their data
25 is or is not being monitored in real time. In the case PRO data are not being
26 monitored, participants should be reminded to speak to clinical staff if they are
27 experiencing a specific problem, symptom or side effect.

30 **Box Regulatory/HTA perspective**

32 Regulatory agencies, such as the MHRA, EMA and FDA are placing more focus on
33 capturing the patient experience when developing drugs.^{15 42 55 119} However poorly
34 defined PRO objectives have hindered the utility of PROs in regulatory decisions.
35 Accurate and well-defined PRO methods can provide the patients’ perspective on
36 the impact of a treatment on disease-related symptoms and symptomatic adverse
37 events. Efforts to improve PRO clinical trial standards are welcomed and the SPIRIT-
38 PRO extension provides an additional resource for drug developers to consider in
39 their development programmes. Alongside these guidelines and other regulatory
40 guidance documents, the importance of seeking early scientific advice directly from
41 the regulatory authorities and health technology assessment bodies such as NICE
42 cannot be understated, where advice can be given on the acceptability of a particular
43 approach. Therefore, raising PRO standards is key to the successful integration of
44 PROs in drug development programmes, ensuring that the impact of medicines on a
45 disease can be captured from the patient’s perspectives.

51 **Box Patient perspective**

52
53 What is the question that doctors and nurses ask their patients more than any other?
54 “How are you feeling?” That is why we need PROs in clinical research. They allow
55 patients to answer that question in a systematic and measurable way, which will
56 benefit others and from which we may well benefit ourselves at some point.
57 For patients, including PROs in health and social care research studies is vital in
58 assessing whether or not our health and/or wellbeing are improving. Well-designed
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3 PRO instruments will help assess our general health and emotional mood, our ability
4 to complete our daily tasks, and our self-measured levels of pain and/or fatigue.
5 PROs are very different from the clinical measures used to assess the effectiveness
6 of new drugs or other treatments, yet for us, it is the PROs that measure “tolerability”
7 and thus the real-life “effectiveness” of the drug or intervention as a medicine or
8 treatment.
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11 The ultimate measure of the performance of any health service must be in whether
12 or not it helps people recover from an acute illness, live well with a chronic condition,
13 and face the end of life with dignity—and people's own reports on their own condition
14 are the only valid way to gauge success. So if a drug or treatment is to be trialled for
15 use in health-care delivery, it is essential that PROs are included in the success
16 criteria.
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19 It is equally essential therefore that participants on the study understand the
20 importance of completing PRO assessments and to understand how and why the
21 data is collected. This should not be too onerous for researchers to explain to
22 patients. Patients who choose to participate in clinical trials do so because they wish
23 to benefit others and if possible, to benefit themselves. PROs are a means of doing
24 both – provided that the reporting and recording are not too much of a burden. ‘We
25 must do all that we can to make patient-reported outcome assessment feasible and
26 credible. If we fail in our task we will have left out the heart of all health-care
27 research: the patient.’¹²⁰
28
29

30
31 And when we do complete our PROs on your research study, please let us know
32 what happens to the study, what you know now that you didn't know before, and how
33 that will be used to help people. Because that's why we participate in research; it's to
34 help people like us.
35

36 **Protocol template**

37
38 The PRO protocol template [\[journal to link to template\]](#) aims to support protocol
39 writing for pharmaceutical companies, funders, clinicians and international trials
40 groups by providing PRO content that can be incorporated directly into the relevant
41 sections of existing clinical trial protocols or retained as a dedicated PRO section
42 within the protocol.
43
44

45 **Supplementary Trial Documents**

46
47 Supplement 2 outlines additional items recommended for inclusion in other trial
48 documentation, such as the SAP, participant information sheet, and training and
49 guidance documents for staff.^{10 121} This is not an exhaustive list and further PRO
50 content may be warranted in training materials and patient facing documents
51 dependant on the trial. We recommend input from PRO experts working in
52 conjunction with the clinical team, trials unit, or Contract Research Organisation
53 (CRO) and patient partners involved in the co-design of research with regulatory
54 input as required to optimise the protocol and supplementary resources.
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57 **Discussion**

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3 This paper provides a detailed rationale, implementation instructions and real-world
4 examples to assist investigators to develop the PRO-specific components of clinical
5 trial protocols, in accordance with the 16 items of the SPIRIT-PRO Extension. This
6 SPIRIT-PRO Extension E&E paper is recommended for use alongside the original
7 SPIRIT 2013 and SPIRIT-PRO guidelines.^{1 2 10} The mission of the SPIRIT-PRO
8 Group is to improve the design and standardisation of PRO components of clinical
9 trials and thereby ensure high-quality PRO data to inform patient-centered care. To
10 further facilitate uptake of the SPIRIT-PRO items, we have provided a PRO-specific
11 protocol template covering all the SPIRIT-PRO items. This can be used in two ways:
12 either incorporated item-by-item into relevant sections of existing clinical trial
13 protocols or retained whole as a dedicated PRO section within a trial protocol. The
14 use of a template should support investigators to address all required SPIRIT-PRO
15 checklist items comprehensively and meaningfully, in conjunction with the real-world
16 examples provided for each SPIRIT-PRO item in this manuscript.
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21 The overall aim of the SPIRIT-PRO Extension and E&E is to improve the
22 completeness, quality and transparency of PRO sections of clinical trial protocols,
23 where PROs are a primary or key secondary outcome. We also recommend use of
24 the guidelines to support development of protocols where PROs data are exploratory
25 in nature, including single-arm trials with PRO endpoints. Many of the SPIRIT-PRO
26 items may also provide useful prompts about PRO content for cohort studies and
27 other non-randomised designs. The SPIRIT-PRO guidelines,¹⁰ and E&E paper aim
28 to facilitate development of high quality PRO protocol content, which will ultimately
29 also facilitate the review of protocols by research ethics committees/IRBs, scientific
30 review groups, and funders. Improved PRO protocol content has been associated
31 with more complete reporting which will help facilitate the critical appraisal of final
32 trial reports and results³ and use of PRO data to inform patient-centered care.
33 Several SPIRIT-PRO items correspond to items on the CONSORT (Consolidated
34 Standards of Reporting Trials) -PRO checklist.^{10 18} This is particularly important since
35 reviews of PRO reporting indicate that, where published PRO trial data were
36 available, there was often considerable delay between publication of primary
37 outcomes and the PRO results and standards of reporting were poor.^{4 5 7 9 122-125}
38 Worryingly, a recent review of cancer trials suggested that 49,568 participants were
39 involved in studies that failed to publish their PRO data and that poor reporting was
40 associated with suboptimal PRO protocol content.⁹ This finding is consistent with
41 findings from Schandelmaier et al. which demonstrated that 52% of cancer trials
42 specified HRQL outcomes in their protocols, however, only 20% reported any HRQL
43 data in associated publications.¹²² Non-reporting of PRO findings is widespread,^{7 9}
44 ¹²²⁻¹³⁰ meaning patient-centred information may not be available to benefit patients,
45 clinicians, and regulators. Non-reporting of these important patient data is unethical
46 and is a waste of limited health-care research resources.¹³¹⁻¹³³ In the EU Clinical
47 Trials Regulation (536/2014) there will be a requirement for results of all primary
48 endpoint and patient relevant secondary endpoints to be reported within 12 months
49 of the end of the study.¹³⁴ The provision of a protocol template alongside example
50 excerpts from trial protocols will help facilitate protocol developers understand how to
51 write high quality PRO protocol content and support more complete reporting of
52 results.
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58 In a companion paper,¹³⁵ we also present tools for patient advocates involved in the
59 co-design of trial protocols or the review of protocols through roles on ethics
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3 committees or funding committees with PRO endpoints to further optimise study
4 design and facilitate patient involvement. It is essential that patients' experiences,
5 perspectives, needs, and priorities are captured and meaningfully incorporated. The
6 SPIRIT-PRO Group and regulatory agencies strongly support the early and
7 continued involvement of patients and members of the public in trial design and
8 conduct.^{119 136}
9

10
11 The next steps for the SPIRIT-PRO Initiative are to promote uptake and use of the
12 guidelines and implementation tools and development of ethical guidelines for
13 institutional review boards and ethics committees. The SPIRIT website (www.spirit-statement.org)
14 and PROlearn, a free resource on the optimal use of PROs in
15 research and routine practice (www.bham.ac.uk/prolearn) provides the latest
16 resources and information on the initiative, including a list of supporters. We invite
17 international stakeholders to assist in the evaluation of the SPIRIT Statement and
18 E&E paper by using the documents and providing feedback to inform future
19 revisions.
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22
23 SPIRIT-PRO forms part of a growing toolbox to promote the optimal use of PROs in
24 trials including guidance for the selection of measures,⁶¹ design (SPIRIT-PRO),¹⁰
25 analysis (SISAQOL),³³ reporting (CONSORT-PRO),¹³ and presentation of results
26 (Figure 2).¹³⁷⁻¹³⁹ These tools are currently being disseminated by the PROTEUS
27 Consortium (Patient-Reported Outcomes Tools: Engaging Users & Stakeholders)
28 who aim to partner with key patient, clinician, research, and regulatory groups
29 around the world to promote the uptake and use of these methodologic tools to
30 optimise the assessment and reporting of PROs in clinical trials
31 (<https://more.bham.ac.uk/proteus/>). Patient and public involvement in all of these
32 activities can help ensure that PRO selection, study implementation and application
33 is transparent, relevant, and acceptable. Consistent with this philosophy, patient
34 partners have been involved in all aspects of the development of the SPIRIT-PRO
35 Extension.^{10 140 141}
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39 **Figure 2 Resources to promote high quality PRO trial design, analysis and**
40 **dissemination. Adapted from**⁹
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45 Through widespread uptake and support, the potential to improve the completeness
46 and quality of trial protocols and the efficiency of their review can be fully realised.
47 Ultimately, high-quality PRO results can help ensure that important patient-centred
48 evidence on the efficacy, safety and tolerability of interventions is available to inform
49 shared decision making, labelling claims, clinical guidelines, and health policy.
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In memory of Doug Altman (1948-2018), statistician, pioneer, luminary. “To maximise the benefit to society, you need to not just do research, but do it well”.

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Concept and design: MJ Calvert, MT King.

Acquisition, analysis, or interpretation of data: MJ Calvert, MT King, R Mercieca-Bebber, OL Aiyegbusi, D Kyte, A Slade, A-W Chan, E Basch, JA Bell, AV Bennett, V Bhatnagar, J Blazeby, A Bottomley, J Brown, M Brundage, L Campbell, JC Cappelleri, H Draper, A Dueck, C Ells, L Frank, RM Golub, I Griebisch, K Haywood, BL King-Kallimanis, L Martin, S Mitchell, T Morel, L Nelson, JM Norquist, D O’Connor, MJ Palmer, D Patrick, G Price, A Regnault, A Retzer, D Revicki, J Scott, R Stephens, G Turner, A Valakas, G Velikova, M von Hildebrand, A Walker, L Wenzel.

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Data sharing

References to protocols available in the public domain are provided. Permissions to access unpublished protocols may be sought via request to Melanie Calvert: m.calvert@bham.ac.uk. Requests will be forwarded to the relevant research team for consideration.

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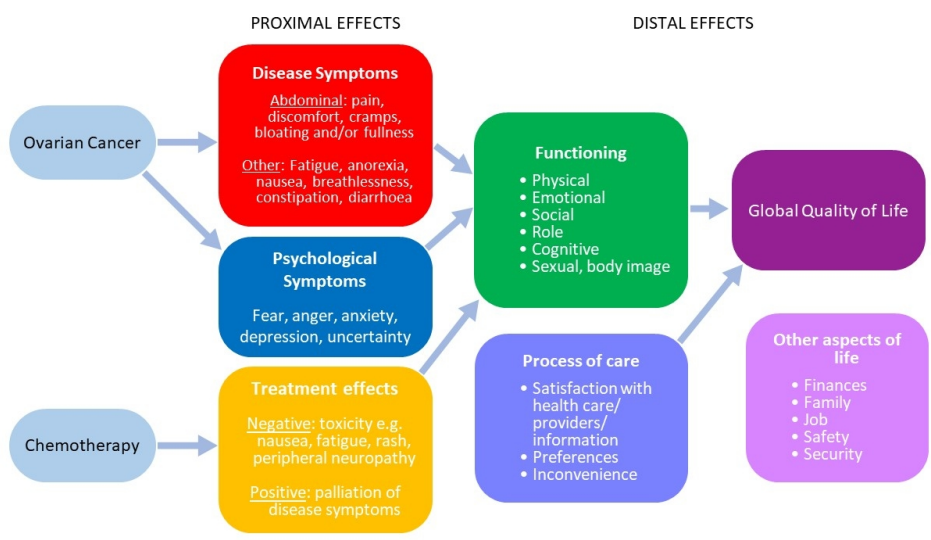
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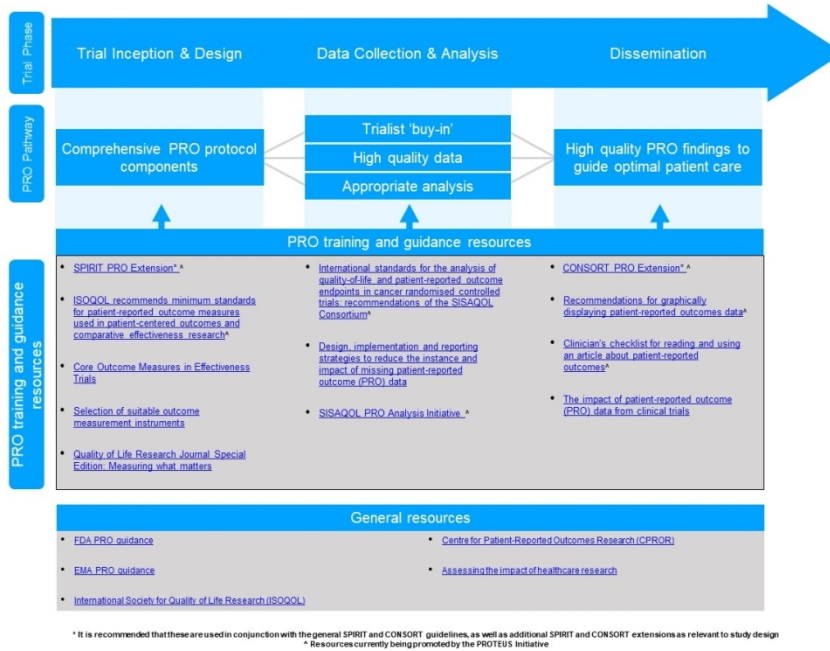
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REBUTTAL LETTER

Reviewer: 1

Recommendation:

Comments:

Calvert et al. report a document that supports the implementation of the SPIRIT-PRO recommendations. The authors provided examples from different trials for each of the checklist items, and a PRO protocol template. I find this document extremely useful as it gives tools for the design of clinical trials that include PROs as primary or secondary aims. Yet, given that the document is an extension of the SPIRIT-PRO, there is a significant amount of overlap with that document. Although the overlap is expected, it does reduce the originality of the publication.

Response: As with other E&E papers it is only natural that there will be overlap with the original publication. We need to ensure consistency with the original checklist. The JAMA paper describes the rationale and methods for the SPIRIT-PRO checklist, and includes the 16 final SPIRIT-PRO checklist items. This E&E aims to support the implementation of the guidance. As such, we have added examples (not included in the original manuscript) and further evidence to support each of the items co-authored by leading international experts including: regulators, PRO methodologists, trialists, patient partners. In addition, the manuscript includes a brand new protocol template to support implementation.

Furthermore, the document is focused on the implementation of specific guidance around the conduct of clinical trials and may not be of interest to the majority of the readership of the BMJ.

Response: A recent review of the Australian New Zealand Clinical Trials Registry suggested that 455 clinical trials include a PRO endpoint as the primary or secondary outcome, and similarly 26,337 trials registered on ClinicalTrials.gov between 2007-2013 included a PRO endpoint. Both reviews found that the use of PRO endpoints is increasing over time. Therefore we believe this manuscript would be of relevance to a large proportion of BMJO readers. Although the main focus of our manuscript is on clinical trials, we note that the methods proposed should be considered for broader PRO research. The guidance applies to all clinical disciplines and as such we believe this will be of major interest to BMJ Open readers.

The following are suggestions to improve the manuscript

There are several limitations about the SPIRIT-PRO extension manuscript, including the date of the last search for the systematic review.

Response: The systematic review was undertaken as part of the original development of the SPIRIT-PRO guidance (published in 2018), to identify items to inform the Delphi and consensus exercise, and finalise the content of SPIRIT-PRO guidelines. As such, it does not make sense to update the review. The SPIRIT-PRO Extension is the latest international consensus based guideline, and is endorsed by the EQUATOR network. We only mention the systematic search by way of background and to highlight the rigorous methodology use to develop the SPIRIT-PRO guidelines. The current manuscript does not address the development of SPIRIT-PRO, but rather provides support for its implementation.

It may be important to mention these limitations in this manuscript as well.

Response: As reasoned above we do not believe this is a limitation.

The methods used to develop this manuscript are short and do not give a clear overview of how the examples were found, chosen, and how those decisions were made.

Response: Thank you we have restructured the methods section. Protocol selection is described as follows (page 20):

Protocol excerpts for each checklist item were obtained from public websites, journals, trial investigators, and industry sponsors. In addition, protocols which adhered well to SPIRIT-PRO guidance were identified through a review of trial protocols (ref EPIC) and via international trials groups known to the coauthors. For those protocols unavailable in the public domain permission was sought to publish.

Real-world examples, quoted verbatim, were selected to reflect how key elements could be appropriately described in a trial protocol. Some examples illustrate a specific component of a checklist item, while others encompass all key recommendations for an item. Empirical data and references to support each SPIRIT-PRO item are provided. Reference numbers cited in the original quoted text are denoted by [Reference] to distinguish them from references cited in this E&E paper.

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4 Consider expanding in the introduction section the need for this manuscript. Why is SPIRIT-PRO not
5 enough? Perhaps some examples of where SPIRIT-PRO has been used and been unclear may help clarify
6 some of the subjectivity of the SPIRIT-PRO extension recommendations.

7 Response: The introduction already includes justification for the E&E paper. We have noted that the protocol
8 template is a new addition (page 5). The original SPIRIT-PRO manuscript describes the background,
9 rationale and methodology for developing the SPIRIT-POR guidance, as well as the final 16 items. This E&E
10 manuscript addresses how those items may be implemented in clinical trial protocols, and provides
11 supportive resources to assist researchers and investigators to do this in a rigorous, complete and high-
12 quality manner.

13 This E&E paper aims to promote understanding of the guidelines, provide examples from a range of different
14 trials and facilitate uptake of the recommended checklist items. In addition, we describe the development of
15 a new PRO protocol template for use in protocol development.

16 We have also added additional evidence and supporting reference (page 5)-

17 A recent review of cancer portfolio trials illustrates this point; PRO protocol content was frequently
18 inadequate and PRO data from trials including 49 568 participants remaining unpublished.

19 A key aspect of the use of PRO is participant burden. The authors mentioned this potential burden and the
20 importance of addressing it at the protocol stage. Yet, there is also the need to assess PRO related burden
21 during the trial conduct. Could the authors recommend ways to achieve this?

22 Response: Thank you for noting this point. We believe that patient and public involvement is key here and
23 we have included further text written by our patient partners on page 22. Qualitative work alongside the
24 trial could help assess participant burden but is beyond the scope of the SPIRIT-PRO protocol guidance.

25 Patient and public involvement in all aspects of trial design, including but not limited to: selection of
26 outcomes and measures, timepoints, mode of assessment, and reporting, can help minimise burden and
27 ensure that data collected is patient-centred and relevant to participants and to the future patients who will
28 benefit from the research.

30 Additional Questions:

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32 when they are sent to the authors. If the manuscript is accepted, your review, name and institution will be
33 published alongside the article.

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37 reviewer comments. If the article is selected for publication in another BMJ journal, depending on the
38 editorial policy of the journal your review may also be published. You will be contacted for your permission
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48 publication of this review

49 Please enter your name: Juan P. Brito

50
51 Job Title: Associate Professor of Medicine

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53 Institution: Mayo clinic

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55 Reimbursement for attending a symposium?: No

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3 A fee for speaking?: No

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5 A fee for organising education?: No

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14 in any way gain or lose financially from the publication of this paper?: No

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8 **SPIRIT-PRO**
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11 **PROtocol Template**
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For peer review only

About this PROtocol Template

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

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

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

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

Journal to add E&E paper reference please

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

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

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

Protocol writers can confirm that they have successfully adhered to the SPIRIT-PRO guideline using the checklist available here:

<https://jamanetwork.com/journals/jama/article-abstract/2671472>

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3 Protocol writers are encouraged to read and consider other relevant resources which
4 are beyond the scope of the SPIRIT-PRO Extension as detailed below:
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6 7 **References and useful resources:**

8 9 **Evidence-based recommendations for the minimum content of a clinical trial protocol**

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20 Enhancing the Quality and Transparency Of health Research (EQUATOR) Network:
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23 24 **Estimands**

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26 FDA-ASCO Public Workshop: 2019 Clinical Outcome Assessments in Cancer Clinical Trials
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Kluetz PG, Chingos DT, Basch EM, Mitchell SA. Patient-Reported Outcomes in Cancer Clinical Trials: Measuring Symptomatic Adverse Events With the National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *Am Soc Clin Oncol Educ Book* 2016;35:67-73. doi: 10.14694/EDBK_159514.

Tolerability

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

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

Analysis

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

<https://event.eortc.org/sisaqol/>

Coens C, Pe M, Dueck AC, Sloan J, Basch E, Calvert M, Campbell A, Cleeland C, Cocks K, Collette L, Devlin N, Dorme L, Flechtner HH, Gotay C, Griebisch I, Groenvold M, King M, Kluetz PG, Koller M, Malone DC, Martinelli F, Mitchell SA, Musoro J, O'Connor D, Oliver K, Piau-Louis E, Piccart M, Quinten C, Reijneveld JC, Schürmann C, Smith AW, Soltys KM, Taphoorn M, Velikova G, Bottomley A. International standards for the analysis of quality-of-life and patient-reported outcome endpoints in cancer randomised controlled trials: recommendations of the SISAQOL Consortium. *The Lancet Oncology* 2020;21(2):e83-e96.

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

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

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

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3 Coens C. Analysing data from patient-reported outcome and quality of life endpoints for
4 cancer clinical trials: a start in setting international standards. *The Lancet Oncology*.
5 2016;17(11):e510-e4.
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7
8

9 **Other resources**

10
11 Cappelleri JC, Zou KH, Bushmakina AG, Alvir JM, Alemayehu D, Symonds T. *Patient-*
12 *Reported Outcomes: Measurement, Implementation and Interpretation*. Boca Raton, Florida:
13 Chapman & Hall/CRC; 2013.
14

15 de Vet HCW, Terwee CB, Mokkink LB, Knol DL. *Measurement in Medicine*. Cambridge, UK:
16 Cambridge University Press; 2011.
17

18 Fairclough DL. *Design and Analysis of Quality of Life Studies in Clinical Trials*. 2nd ed. Boca
19 Raton, Florida: Chapman & Hall/CRC; 2010.
20

21 Fayers FM, Machin D. *Quality of Life: The Assessment, Analysis and Interpretation of Patient-*
22 *reported Outcomes*. 3rd ed. Chichester, England: John Wiley & Sons Ltd.; 2016.
23

24 Streiner DL, Norman GR, Cairney J. *Health Measurement Scales: A Practical Guide to Their*
25 *Development and Use*. 5th ed. New York, NY: Oxford University Press; 2015.
26
27

28 **Missing Data**

29
30 Mercieca-Bebber R, Palmer MJ, Brundage M, Calvert M, Stockler MR, King MT. Design,
31 implementation and reporting strategies to reduce the instance and impact of missing patient-
32 reported outcome (PRO) data: a systematic review. *BMJ Open*. 2016;6(6):e010938.
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35 Little RJ, D'Agostino R, Cohen ML, et al. The Prevention and Treatment of Missing Data in
36 Clinical Trials. *New England Journal of Medicine* 2012;367(14):1355-60.
37

38 Little RJ, Cohen ML, Dickersin K, et al. The design and conduct of clinical trials to limit
39 missing data. *Stat Med* 2012;31(28):3433-43. doi: 10.1002/sim.5519
40
41

42 **Patient Public Involvement (PPI) and Patient Experience**

43
44 Kluetz PG, O'Connor DJ, Soltys K. Incorporating the patient experience into regulatory
45 decision making in the USA, Europe, and Canada. *The Lancet Oncology*. 2018;19(5):e267-
46 e74.
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Title page

PRO content author:

Affiliation(s), telephone:

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

Explanation: Providing information (e.g. name, affiliation, contact details) on who wrote the PRO-specific aspects of the trial protocol promotes transparency and accountability and identifies the appropriate point of contact for resolution of any PRO specific queries. When patients have actively contributed to this process, this should be documented as per recent guidance for the reporting of patient and public involvement.⁷

Additional notes: *The PRO author should be part of the protocol writing committee. The trial study coordinator should ensure that PROs are harmonized with all the other clinical endpoints.*

1. Protocol Summary

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

1.3. Schedule of Activities (SoA)

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

Additional notes: *The PRO schedule of assessments should be summarised in a table alongside all other trial assessments to provide trial staff with a single point of reference. Ideally PRO assessments should appear in the table in the order which assessments will take place. If more than one PRO measure is being used, each may be specified on a separate line if they are administered at different time points.*

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

2. Introduction

2.1. Study Rationale

2.1.1. Summary of PRO-specific rationale

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

Additional note: As with other clinical information, the PRO-specific rationale should be summarized here and detailed information including summary of PRO findings in relevant studies should be provided in Section 4.2. Scientific Rationale for Study Design or in the PRO-specific section 8.1.

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

3. Objectives and Endpoints

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

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

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

Specify the PRO endpoint: the concepts/domains used to evaluate the intervention (e.g., overall health-related quality of life, specific domain, specific symptom) and, for each one, the analysis metric (e.g., change from baseline, final value, time to event) and the principal time point or period of interest. (SPIRIT-12-PRO Extension)

Additional note: Utility measures (e.g. EQ-5D) that inform cost-utility evaluations should also be included here.

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

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

4. Study Design

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

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

Additional notes: Detailed information should be provided here. Information not provided in Section 2.1.1. Summary of PRO-specific rationale should be presented here. Indicate how PRO evaluation aligns with the overall trial design, so it addresses the research objectives.

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

5. Study Population

Specify any PRO-specific eligibility criteria (e.g., language/reading requirements or pre-randomization¹ completion of PRO). (SPIRIT-10-PRO Extension)

If PROs will not be collected from the entire study sample, provide a rationale and describe the method for obtaining the PRO subsample. (SPIRIT-10-PRO Extension)

Additional notes: Efforts should be made to provide translated PRO versions where needed to promote inclusivity in PRO completion. Specify reasons if translated versions are not provided and certain populations are excluded. PRO-specific eligibility criteria should be included alongside other eligibility criteria to ensure research personnel have a single point of information.

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

6. Study Intervention

6.1. PRO capture method involving a medical device

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

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

7.1. Discontinuation of Study Intervention

Describe the process of PRO assessment for participants who discontinue or deviate from the assigned intervention protocol. (SPIRIT-18b (ii)-PRO Elaboration)

Additional note: Participants who withdraw from the study should be provided pre-paid packaging to return PRO assessments and ePRO devices if applicable.

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

8. Study Assessments and Procedures

8.1. Efficacy Assessments

8.1.1. Patient Reported Outcomes

Specify the PRO Hypotheses (SPIRIT-7-PRO Extension)

Additional note: Also specify whether the objective is to support superiority, equivalence or non-inferiority.

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

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

Additional note: Interpretation guidelines should include reference to pre-defined clinical relevance thresholds, preferably specific to the PRO population.

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

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

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

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

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Include a data collection plan outlining the permitted mode(s) of administration (e.g., paper, telephone, electronic, other) and setting (e.g., clinic, home, other). (SPIRIT-18a (ii)-PRO Extension)

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

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

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

Additional notes: Signpost to statistical analysis plan (SAP) as required. Collect reasons for missed PRO assessments during the trial. These could be documented in the case report forms (CRF). SISAQOL, CONSORT-PRO Extension and PROTEUS may be consulted for further guidance on missing data.^{2 4 5}

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

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

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

When the trial context requires someone other than a trial participant to answer on his or her behalf (a proxy-reported outcome), state and justify the use of a proxy respondent. Provide or cite evidence of the validity of proxy assessment if available. (SPIRIT-18a (iv)-PRO Extension)

Additional note: If a proxy reporting is used, this should ideally be the same person throughout the trial.

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

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3 down their actual answers). Clear justification and specification of proxy reporting in the
4 protocol allows external reviewers to assess potential bias and facilitates trial reporting in
5 accordance with CONSORT-PRO.²
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10 8.2. Safety Assessments

11 8.2.1 Monitoring of PRO data

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15 **State whether or not PRO data will be monitored during the study to inform the clinical**
16 **care of individual trial participants and, if so, how this will be managed in a**
17 **standardized way. Describe how this process will be explained to participants; e.g., in**
18 **the participant information sheet and consent form. (SPIRIT-22-PRO Extension)**

19 ***Additional note:*** *If PROs are used in place of or as an add-on to standard solicited AE*
20 *recording (at visits/phone calls the investigators asks if there have been any problems since*
21 *last visit) they should be recognised as part of the safety monitoring procedures of the trial.*
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24 ***Explanation:*** Evidence suggests that monitoring and management of PRO alerts
25 (psychological distress or physical symptoms evident from PRO responses that may require
26 an immediate response) vary across and within trials.^{13 18 20} To protect the interests of trial
27 participants and minimize potential bias, it is important to specify plans for monitoring.²¹ If
28 monitoring is not planned (e.g., in a low-risk study in which alerts are not anticipated), this
29 should also be briefly stated in the protocol, the participant information sheet, and the
30 consent form. Alternative support mechanisms for participants should be outlined.⁶
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33 9. Statistical considerations

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36 **When a PRO is the primary end point, state the required sample size (and how it was**
37 **determined) and recruitment target (accounting for expected loss to follow-up). If**
38 **sample size is not established based on the PRO end point, then discuss the power of**
39 **the principal PRO analyses. (SPIRIT-14-PRO Elaboration)**

40 ***Additional note:*** *Enough information on secondary, tertiary and even exploratory PRO*
41 *endpoints should be provided to justify their inclusion.*
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44 ***Explanation:*** In studies in which PROs are the primary outcome or end point, the target
45 sample size will generally be based on an a priori sample size calculation for that end point.⁹
46 Ideally, the criteria for clinical significance (e.g., minimal important difference, responder
47 definition) should be specified when known.^{22 23} If PROs are a secondary end point,
48 researchers should specify whether the sample size provides sufficient power to test the
49 principal PRO hypotheses.⁹
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9.1. Statistical analyses

State PRO analysis methods, including any plans for addressing multiplicity/type I (α) error. (SPIRIT-20a-PRO Elaboration)

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

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

9.1.1. Missing PRO data

State how missing data will be described and outline the methods for handling missing items or entire assessments (e.g., approach to imputation and sensitivity analyses). (SPIRIT-20c-PRO Elaboration)

Additional notes: *State whether PRO data is missing at the item level or at entire PRO assessment level and whether intermittent or lost to follow-up. In addition, state how missing PRO data is recorded and categorised. SISAQOL recommendations may be consulted for further guidance on missing data.⁴*

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

9.1.2. Other Analyse(s)

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

10. Supporting Documentation and Operational Considerations

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

10.1.1. Publication Policy

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

Note: *Whilst not a formal recommendation in the SPIRIT-PRO guidance, it is regarded as good practice to include, depending on the mode of administration, paper copies of PRO or screenshots of ePRO instruments.*

All copyrights and version information should be clearly showing in the appended PRO instruments with due acknowledgment for PROs requiring permission for use.

10.2. Appendix Copies of PROs

Glossary

Concept: “The specific measurement goal (i.e., the thing that is to be measured by a PRO instrument). In clinical trials, a PRO instrument can be used to measure the effect of a medical intervention on one or more concepts. PRO concepts represent aspects of how patients function or feel related to a health condition or its treatment.”²⁴

Domain: “A sub concept represented by a score of an instrument that measures a larger concept comprised of multiple domains. For example, psychological function is a larger concept with multiple domains (emotional and cognitive function) that are measured by relevant items.”²⁴

Endpoint*: the variable to be analysed. It is a precisely defined variable intended to reflect an outcome of interest that is statistically analysed to address a particular research question. A precise definition of an endpoint typically specifies the type of assessments made, the timing of those assessments, the assessment tools used, and possibly other details, as applicable, such as how multiple assessments within an individual are to be combined²⁵ (e.g. change from baseline at 6 weeks in mean fatigue score).²⁶

Health-related quality of life: “a multidimensional concept that usually includes self-report of the way in which physical, emotional, social, or other domains of well-being are affected by a disease or its treatment”²⁷

Important or key secondary PROs/end points: Some PRO measures (particularly health-related quality-of-life measures) are multidimensional, producing several domain-specific outcome scales; e.g., pain, fatigue, physical function, psychological distress. For any particular trial, it is likely that a particular PRO or PRO domain(s) will be more relevant than others, reflecting the expected effect(s) of the trial intervention(s) in the target patient population. These relevant PRO(s) and/or domain(s) may additionally constitute the important or key secondary PROs (identified a priori and specified as such in the trial protocol and statistical analysis plan) and will be the focus of hypothesis testing. In a regulatory environment, these outcomes may support a labelling claim. Because these outcomes are linked with hypotheses (CONSORT PRO Extension 2b),²⁷ they may be subject to P-value adjustment (or “ α spending”). Beyond efficacy/effectiveness, PROs may also be used to capture and provide evidence of safety and tolerability (e.g. using the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™))²⁸

Instrument: “A means to capture data (e.g., a questionnaire) plus all the information and documentation that supports its use. Generally, that includes clearly defined methods and instructions for administration or responding, a standard format for data collection, and well-documented methods for scoring, analysis, and interpretation of results in the target patient population.”²⁴

Intervention/treatment: A process or action that is the focus of a clinical study. Interventions include drugs, medical devices, procedures, vaccines, and other products that are either investigational or already available. Interventions can also include non-invasive approaches, such as education or modifying diet and exercise.²⁹

Item: “an individual question, statement, or task (and its standardized response options) that is evaluated by the patient to address a particular concept”²⁴

Observer-reported outcome: “a measurement based on a report of observable signs, events or behaviours related to a patient’s health condition by someone other than the patient or a health care professional”.³⁰

Outcome*: the variable to be measured. It is the measurable characteristic that is influenced or affected by an individual’s baseline state or an intervention as in a clinical trial or other exposure²⁵ (e.g. a fatigue score).

Patient-reported outcome (PRO): A PRO is any report of the status of a patient’s health condition that comes directly from the patient, without interpretation of the patient’s response by a clinician or anyone else and may include patient assessments of health status, quality

of life, or symptoms.^{24 27} PROs are assessed by self-reported questionnaires, referred to as PRO measures (PROMs) or instruments.²⁵

Primary outcome: the most important outcome in a trial, pre-specified in the protocol, providing the most clinically relevant evidence directly related to the primary objective of the trial.

Proxy-reported outcome: “a measurement based on a report by someone other than the patient reporting as if he or she is the patient”²⁴

Secondary outcomes: outcomes pre-specified in the protocol to assess additional effects of the intervention; some PROs may be identified as important or key secondary outcomes

SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials.^{31 32}

SPIRIT Elaboration item: an elaboration of an existing SPIRIT item as applied to a specific context; in this instance, as applied to clinical trials assessing PROs

SPIRIT-PRO Extension item: an additional checklist item describing PRO protocol content to address an aspect of PRO assessment that is not adequately covered by SPIRIT, as judged by available evidence and expert opinion

Time window: a predefined time frame before and after the protocol-specified PRO assessment time point whereby the result would still be deemed to be clinically relevant.³³

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

List of Abbreviations

CONSORT – Consolidated Standards of Reporting Trials

CRF – case report form

ePRO – electronic patient-reported outcome

PPI – Patient Public Involvement

PRO – patient-reported outcome

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

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

RS – recommendation statement

SAP – statistical analysis plan

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

SoA – Schedule of Activities

SPIRIT – Standard Protocol Items: Recommendations for Interventional Trials

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Supplement 1

Protocol evidence per final SPIRIT-PRO item.

SPIRIT PRO Item number and description	SPIRIT-PRO wording prior to finalisation	% HTA protocols including item	% EPiC protocols including item	% international ovarian cancer protocols including item
(5a) Specify the individual(s) responsible for the PRO content of the trial protocol		6.67%	22.78%	23.1%
(6a) Describe the PRO-specific research question and rationale for PRO assessment and summarise PRO findings in relevant studies	Describe what is currently known about PROs in this area and explain the gaps in the literature	49.33%	32.91%	42.3%
	Provide a rationale for the inclusion of PROs as appropriate to the study population, intervention, context, objectives and setting	8.00%	33.54%	57.7%
(7) State specific PRO objectives or hypotheses (including relevant PRO concepts/domains)	State the PRO study objective in relation to PRO domain/s, patient population and timeframe	77.33%	73.42% (17.09% in relation to dimension, population or timeframe)	30.8%
	State the PRO hypothesis and corresponding null hypothesis and to which outcome(s) the hypothesis relates	18.67%	-	PRO hypothesis provided 19.2%
(10) Specify any PRO-specific eligibility criteria (e.g. language/reading requirements or prerandomisation completion of PRO). If PROs will not be collected from the entire study sample, provide a rationale and describe the methods for obtaining the PRO subsample	If PROs will be collected in a subset of the study population or in specific centres, include a description/rationale for the sampling method	0.00%	10.76%	11.5%
	State the inclusion/exclusion criteria for PRO endpoint(s) (e.g., language/reading requirements)	45.33%	50.00%	7.7%

1		Specify if PRO completion is pre-randomisation eligibility requirement	-	-	7.7%
2					
3	(12) Specify the PRO concepts/domains used to evaluate the intervention (e.g. overall health-related quality of life, specific domain, specific symptom) and for each one, the analysis metric (e.g. change from baseline, final value, time to event) and the principal time point or period of interest	Describe the PRO constructs used to evaluate the intervention e.g. overall QOL, specific domain, specific symptom	-	-	73.1%
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14	(13) Include a schedule of PRO assessments, providing a rationale for the time points, and justifying if the initial assessment is not prerandomisation. Specify time windows, whether PRO collection is prior to clinical assessments, and, if using multiple questionnaires, whether order of administration will be standardised	Specify the timepoint(s) for PRO analysis (including the principle timepoint of interest) and provide the rationale for these	Timing specified 97.33%	Timing specified 83.54%	42.3%
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19		Include PRO assessments in the main protocol schedule of assessments, specifying which PRO measures (PROMs) will be used at each assessment	-	-	96.2%
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25		Specify if baseline PRO assessment should be completed before randomisation	-	-	53.8%
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28		Specify the targeted time and acceptable time windows for each PRO assessment	-	-	26.9%
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32		If PROs are to be completed in the clinic: specify timing of PROM delivery in relation to clinical assessments (e.g. before/whilst/after seeing clinician and/or clinical assessments)	-	-	54%
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40		Justify the timing of PRO assessments. Scheduled	Timing justified 6.67%	Timing justified 12.03%	23.1%
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	PRO assessments should link to research questions, hypotheses, length of recall, disease/treatment natural history, planned analysis and time of comparison must be comparable for both arms			
(14) 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	If PRO is the primary endpoint, state the required PRO sample size, otherwise discuss the power of the PRO analysis	50.67%	25.95%	30.8%
(18a i) Justify the PRO instrument to be used and describe the domains, number of items, recall period, and instrument scaling and scoring (e.g. range and direction of scores indicating a good or poor outcome). Evidence of PRO instrument measurement properties, interpretation guidelines, and patient acceptability and burden should be provided or cited if available, ideally in the population of interest. State whether the measure will be used in accordance with any user manual and specify and justify deviations if planned	Describe the PROMs including, number of items/domains, instrument scaling/scoring, reliability, content and construct validity, responsiveness, sensitivity, acceptability, recall period. Provide references as appropriate	PROM identified 100%; Justification in relation to study hypotheses 41.33%; Justified in relation to measurement properties 37.33%; Justified in relation to acceptability/patient burden 14.67%	PROM identified 63.29%; Justification in relation to study hypotheses 36.71%; Justified in relation to measurement properties 46.84%; Justified in relation to acceptability/patient burden 29.11%	Justification for measure used 84.6%
(18a ii) Include a data collection plan outlining the permitted mode(s) of administration (e.g. paper, telephone, electronic, other)	Include a pre-specified data collection plan	84.00% included brief details of PRO data collection procedures but often omitted information surrounding mode of administration,	57.59%	46.2%

1 2 3 4	and setting (e.g. clinic, home, other)		setting and proxy reporting: 8.00% included PRO data collection guidelines/training information for trial personnel.		
5 6 7 8 9 10 11 12	(18a iii) Specify whether more than one language version will be used and state whether translated versions have been developed using currently recommended methods	Provide evidence of measurement equivalence across modes (i.e., when mixing modes of PRO data collection) and/or of cross cultural validity where different language versions of questionnaires are used	-	-	7.7%
13 14 15 16 17 18 19 20 21	(18a iv) 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		-	-	0.0%
22 23 24 25 26 27 28 29 30	(18b i) Specify PRO data collection and management strategies for minimising avoidable missing data	Specify procedures for data collection and management methods to minimise missing data. E.g. checking completed PROMs (including who will check forms and how will they deal with missing PROMs or missing items).	-	-	38.5%
31 32 33 34 35 36	(18b ii) Describe the process of PRO assessment for participants who discontinue or deviate from the assigned intervention protocol	Establish process for PRO assessment at (and beyond) withdrawal for patients who withdraw early from a study or who go 'off-study'/'off treatment'	-	-	34.6%
37 38 39 40	(20a) State PRO analysis methods, including any plans for addressing multiplicity/type I (a) error	Include an a priori description of all planned PRO analyses pertaining to the study hypotheses	PRO statistical analysis plan provided? 96.00%	PRO statistical analysis plan provided? 53.16%	61.5%

	Pre-specify sequence of testing/exploratory analyses to control for multiplicity or pre-specify domains (e.g. in a regulatory trial/labelling claim) (Common in pharma trials. Involves pre-specifying domains that alpha would be spent on, or ordering the domains in priority & alpha would be spent down the list)	Plans to address multiplicity of PRO data provided? 1.33%	10.13%	7.7%
(20c) State how missing data will be described and outline the methods for handling missing items or entire assessments (e.g. approach to imputation and sensitivity analyses)	State how missing data will be described	45.33%	30.38%	-
	Describe method for handling missing assessments (e.g. approach to imputation and sensitivity analyses)	45.33%	30.38%	-
	Describe methods for scoring endpoints. Where possible, reference scoring manuals for summated scales from PROM (domain-specific &/or total) & methods for handling missing items, and methodological papers for composite endpoints (e.g. QTWiST)	-	-	53.8%
(22) 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 standardised way. Describe how this process will be explained to participants; e.g. in the participant information sheet and consent form	Include an a priori plan for consistent/standardised management of PRO alerts (symptoms reported by patients that exceed a pre-defined level of severity) to be clearly communicated to all appropriate trial staff	10.67%	0.63%	0.0%
	Specify whether PRO forms will be used to	4.00%	3.80%	7.7%

	influence therapy or patient management (i.e. will the clinician use PRO responses to inform the patient's care?)			
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Supplement 2

Summary recommendations for inclusion* of PRO specific information in the trial protocol, supplementary documents or training for staff.

SPIRIT PRO Item Description	SPIRIT 2013 / SPIRIT- PRO Item Number	Guidance/training for trial staff (eg, site initiation/face to face or online training/operations manual)	Information/guidance for participants (eg, participant information sheet)	Statistical Analysis Plan
Administrative information				
Specify the individual(s) responsible for the PRO content of the trial protocol	✓ SPIRIT-5a-PRO Elaboration	+		
Introduction				
Describe the PRO specific research question and rationale for PRO assessment, and summarize PRO findings in relevant studies.	✓ SPIRIT-6a-PRO Extension	✓	✓ ¹	
State specific PRO objectives or hypotheses (including relevant PRO concepts/domains).	✓ SPIRIT-7-PRO Extension			✓
Methods: Participants, interventions, and outcomes				
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.	✓ SPIRIT-10-PRO Extension	✓		✓
Identify the PRO endpoint as the primary, secondary (and if so - whether a key/important secondary), or an exploratory endpoint.	✓ SPIRIT-12			✓
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			
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	✓		✓
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			✓
Methods: Data collection, management, and analysis				

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46	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			✓ ²
	Provide evidence of measurement equivalence across modes (i.e. when mixing modes of PRO data collection) and/or of cross cultural validity where different language versions of questionnaires are used.				✓ ³
	Outline plans for evaluation of measurement properties, if appropriate (eg, if not previously validated in the population of interest).				✓ ⁴
	Specify the estimated time to complete each assessment, and discuss feasibility of assessment for the population.		✓	✓ ⁵	
	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	✓	✓	
	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	✓		
	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	✓		
	Specify who will administer the PROM (eg, a physician, nurse etc).		✓		
	If it is permissible for another person to help the study participant complete the PROM, describe what type and level of assistance is acceptable.		✓	✓	
	Include a plan for systematically training and contacting local site personnel to ensure that they understand the content and importance of collecting PRO data. Ideally coordinated by a lead data manager who monitors PRO completion rates in real time and communicates with sites if completion rates are suboptimal.		✓		
	Specify PRO data collection and management strategies for minimising avoidable missing data.	✓ SPIRIT-18b(i)- PRO Extension	✓		
	Include guidance on discussing importance of PROs with patient		✓		
	Describe the process of PRO assessment for participants who discontinue or deviate from their assigned intervention protocol.	✓ SPIRIT-18b(ii)- PRO Elaboration	✓		
	Specify that a named person/position at each centre (and/or centrally) be nominated to take responsibility for administration, collection and checking of PROM, specify whether this is the treating clinician or not.		✓ ⁶		
	Specify how an electronic PRO system/database will be maintained and how the investigator will meet regulatory requirements and ensure data integrity and security.	✓ SPIRIT-19	✓	✓ ⁷	
	Specify plan to monitor PRO compliance, including adherence to time windows.	✓ SPIRIT-19	✓	✓ ⁸	
	Include an overview of PRO administration (data collection), and data handling/transmission and storage procedures	✓ SPIRIT-19	✓	✓ ⁷	

1	Item 39: Include an a priori description of all planned PRO analyses pertaining to the study hypotheses. Item 44: Include a priori identified summary statistics (as appropriate).	✓ SPIRIT-20a			✓
2					
3	State the assumptions of PRO analyses.				✓
4					
5	Include an a priori estimation of PRO effect size.	✓ SPIRIT-14			✓
6					
7	Specify intention-to-treat or per-protocol PRO analyses.	✓ SPIRIT-20c			✓
8					
9	Specify the minimum PRO response rate and acceptable degree of timing deviation (i.e. acceptable time windows for each PRO assessment time point) before the PRO objective is compromised. Specify the minimum PRO response rate and acceptable degree of timing deviation (i.e. acceptable time windows for each PRO assessment time point) before the PRO objective is compromised.	✓ SPIRIT-14			✓
10					
11	Describe methods for scoring endpoints. Where possible, reference scoring manuals for summated scales from PROM (domain-specific and/or total) and methods for handling missing items, and methodological papers for composite endpoints (eg, QTWiST).	✓ SPIRIT-20a			✓
12					
13	State PRO analysis methods including any plans for addressing multiplicity/type 1 (α) error.	✓ SPIRIT-20a-PRO Elaboration			✓
14					
15	Specify the criteria for clinical significance (eg, state minimal [clinical] important difference and/or responder definition (size and duration of benefit)).	✓ SPIRIT-14			✓
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17	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			✓
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19	Monitoring				
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21	Describe the role of the Data Monitoring Committee and Quality Assurance for PROs.	✓ SPIRIT-21a			
22					
23	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	✓	✓ ⁷	
24					
25	Ethics and dissemination				
26					
27	Describe informed consent procedure for PRO assessment.		✓		
28					
29	Include detailed plans for regular feedback to participants via letter/newsletter on PRO aspect of study.		✓	✓	
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Footnotes: **Recommended for inclusion" indicates that >50% of the Delphi and Stakeholder Survey participants endorsed the item (or at least one item if two items were merged for the consensus meeting) for inclusion and/or the item was considered important for inclusion at the consensus meeting.

+Recommended by the Delphi panel but excluded following discussion at the consensus meeting.

¹ <50% of Delphi panellists voted to include this item, but item was included following discussion at the consensus meeting. It was felt important to include a brief rationale for PRO assessment in the PIS.

² Use of the PRO instrument in accordance with the user manual should be specified in the SAP.

³ Plans for dealing with different modes of administration should be specified in the SAP. This was not supported by the Delphi but was identified as important by the consensus panel.

⁴ If validation of the PRO instrument is planned as part of the trial then this should be pre-specified in the main trial SAP. If validation is planned as a separate sub-study, this should be specified a separate study protocol and SAP.

⁵ Estimation of time to complete each PRO assessment should be included in guidance and training for staff and in information for trial participants.

⁶ This should also be recorded in the delegation of duties log.

⁷ The participant information sheet should contain information regarding the storage and security of PRO data and provide information on who will access their PRO data and for what purpose.

⁸ If plans to monitor adherence to time windows, include reminders for participants eg. Via text or SMS, the relevant details should be specified in the information to participants.

BMJ Open

SPIRIT-PRO Extension explanation and elaboration: guidelines for inclusion of patient-reported outcomes in protocols of clinical trials

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Research Methods & Reporting

SPIRIT-PRO Extension explanation and elaboration: guidelines for inclusion of patient-reported outcomes in protocols of clinical trials

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Abstract

Patient reported outcomes (PROs) are used in clinical trials to provide valuable evidence on the impact of disease and treatment on patients' symptoms, function and quality of life. High-quality PRO data from trials can inform shared decision-making, regulatory and economic analyses, and health policy. Recent evidence suggests the PRO content of past trial protocols was often incomplete or unclear, leading to research waste. To address this issue, international, consensus-based, PRO-specific guidelines were developed: the SPIRIT-PRO Extension. The SPIRIT-PRO Extension is a sixteen-item checklist which aims to improve the content and quality of aspects of clinical trial protocols relating to PRO data collection to minimise research waste, and ultimately better inform patient-centred care.

This SPIRIT-PRO Explanation and Elaboration (E&E) paper provides information to promote understanding and facilitate uptake of the recommended checklist items, including a comprehensive protocol template. For each SPIRIT-PRO item, we provide a detailed description, one or more examples from existing trial protocols and supporting empirical evidence of the item's importance. We recommend this paper and protocol template be used alongside the SPIRIT 2013 and SPIRIT-PRO Extension paper to optimise the transparent development and review of trial protocols with PROs.

Article Summary

Strengths and limitations of this study

- The SPIRIT-PRO Extension aims to improve the completeness and transparency of trial protocols where patient-reported outcomes (PROs) are a primary or key secondary outcomes and was developed following EQUATOR Network Guidance.
- This Explanation and Elaboration paper provides information to promote understanding and facilitate uptake of the recommended PRO protocol SPIRIT-PRO checklist items for clinical trials.
- A comprehensive protocol template and selected examples from existing trial protocols are provided to facilitate implementation.
- The protocol template and explanation and elaboration paper were developed with multi-stakeholder international input including: trialists, PRO methodologists, psychometricians, patient partners, industry representatives, journal editors, regulators and ethicists.
- Although the guidance is limited in focus to clinical trials, many of the SPIRIT-PRO items may also provide useful prompts about PRO content for cohort studies and other non-randomised designs.

Background

Clinical trial protocols are essential documents intended to include the study rationale, intervention, trial design methods, study processes, outcomes, sample size, data collection procedures, proposed analyses and ethical considerations. Provision of sufficient detail is necessary to enable the research team to conduct a high-quality, reproducible study. It also facilitates external appraisal of the scientific, methodological, and ethical rigor of the trial by relevant stakeholders.^{1 2} Although trial protocols serve as the foundation for study planning, conduct, reporting, and appraisal, they vary greatly in content and quality.^{1 2} Appraisals of the patient reported outcome (PRO) content of over 350 past trial protocols revealed that many protocols lack specific information needed for high-quality PRO data collection and evidence generation (Supplement 1).³⁻⁵ As a result, research personnel and potential research participants may not appreciate the purpose of PRO data collection,⁶ and the need for standardised PRO assessment methods. This may result in high levels of missing data and poor-quality or non-reporting of PRO trial results, which may hinder the potential for PRO evidence to be used in regulatory decision-making, health policy and clinical care.⁶⁻⁸ For example, a recent review of cancer portfolio trials illustrates this point; recommended PRO protocol content was frequently not addressed and PRO data from 61 trials, including 49 568 participants, was unpublished.⁹ Another trial also cited poor PRO completion rates as the reason for not publishing PRO data – and the corresponding trial protocol included only sparse guidance related to the PRO study.⁷

In 2013, core protocol guidelines applicable to all types of trials was published based on expert consensus and research evidence, in the form of the SPIRIT 2013 Statement (Standard Protocol Items: Recommendations for Interventional Trials). Its corresponding SPIRIT 2013 Explanation and Elaboration (E&E) paper provides important information to promote full understanding of, and assist protocol writers to implement, the 33 checklist recommendations.^{1 2} However, SPIRIT 2013 does not provide specific recommendations about PRO endpoints. PROs can provide valuable information on the risks, benefits and tolerability of an intervention. PRO data are intrinsically subjective, requiring completion by patient-participants within a specific time frame and, as a result, present a range of scientific and logistical challenges for researchers which should be addressed in the trial protocol.^{6 10-12}

To address this issue, international stakeholders worked to develop the SPIRIT-PRO Extension, with the aim of improving PRO content of trial protocols and supporting documents, for use in conjunction with SPIRIT 2013 Guidelines and E&E papers.^{1 2} The SPIRIT-PRO Extension was published in 2018 and comprises 11 extensions (new, PRO-specific items) and 5 elaborations (an elaboration of an existing SPIRIT 2013 item as applied to clinical trials assessing PROs) recommended for inclusion in clinical trial protocols that have PROs as primary or key secondary outcomes (Table 1).¹⁰ The SPIRIT-PRO Extension paper reports the 16 items and describes the methods used to develop the checklist, but does not provide detailed implementation instructions or examples. This SPIRIT-PRO E&E paper aims to promote understanding of the guidelines, provide real examples of SPIRIT-PRO items being addressed from a range of different trials and facilitate uptake of the recommended checklist items. A table of contents detailing where to find an example and explanation of each item is provided in Table 2. In addition, we describe the

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3 development of a new PRO protocol template for use in protocol development.
4 Additional information and resources regarding the SPIRIT Initiative are available on
5 the SPIRIT website (www.spirit-statement.org).
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8 **Table 1. SPIRIT 2013 and SPIRIT-PRO Extension checklist: Recommended**
9 **Items to Address in a Clinical Trial Protocol**
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For peer review only

SPIRIT Section	SPIRIT Item No.	SPIRIT Item Description	SPIRIT-PRO Item No.	SPIRIT-PRO Extension or Elaboration Item Description	Please specify which page(s) of the protocol this item is addressed on.
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	SPIRIT5a-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, end-point 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	SPIRIT6a-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	SPIRIT7-PRO Extension	State specific PRO objectives or hypotheses (including relevant PRO concepts/domains).	
Trial design	8	Description of trial design, including type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, noninferiority, exploratory)			
Methods: Participants, Interventions, and Outcomes					

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Study setting	9	Description of study settings (e.g., 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 (e.g., surgeons, psychotherapists)	SPIRIT10-PRO Extension	Specify any PRO-specific eligibility criteria (e.g., language/reading requirements or pre-randomisation 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.	
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 (e.g., 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 (e.g., 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 (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome; explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	SPIRIT12-PRO Extension	Specify the PRO concepts/domains used to evaluate the intervention (e.g., overall health-related quality of life, specific domain, specific symptom) and, for each one, the analysis metric (e.g., change from baseline, final value, time to event) and the principal time point or period of interest.	
Participant timeline	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 in Chan et al) ^{1 2}	SPIRIT13-PRO Extension	Include a schedule of PRO assessments, providing a rationale for the time points, and justifying if the initial assessment is not pre-randomisation. 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	SPIRIT14-PRO Elaboration	When a PRO is the primary end point, state the required sample size (and how it was	

		determined, including clinical and statistical assumptions supporting any sample size calculations		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 enrolment to reach target sample size			
Methods: Assignment of Interventions (for Clinical Trials)					
Allocation					
Sequence generation	16a	Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., 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 (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned			

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1 2 3 4 5 6 7	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions			
8 9 10 11 12 13 14 15 16 17 18 19	Blinding (masking)	17a	Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts) and how			
20		17b	If blinded, circumstances under which unblinding is permissible and procedure for revealing a participant's allocated intervention during the trial			
21	Methods: Data Collection, Management, and Analysis					
22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known; reference to where data collection forms can be found, if not in the protocol	SPIRIT-18a (i)-PRO Extension	Justify the PRO instrument to be used and describe domains, number of items, recall period, and instrument scaling and scoring (e.g., range and direction of scores indicating a good or poor outcome). Evidence of PRO instrument measurement properties, interpretation guidelines, and patient acceptability and burden should be provided or cited if available, ideally in the population of interest. State whether the measure will be used in accordance with any	

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				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 (e.g., paper, telephone, electronic, other) and setting (e.g., clinic, home, other).	
			SPIRIT-18a (iii)-PRO Extension	Specify whether more than 1 language version will be used and state whether translated versions have been developed using currently recommended methods.	
			SPIRIT-18a (iv)-PRO Extension	When the trial context requires someone other than a trial participant to answer on his or her behalf (a proxy-reported outcome), state and justify the use of a proxy respondent. Provide or cite evidence of the validity of proxy assessment 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 (e.g., 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	SPIRIT20a-PRO Elaboration	State PRO analysis methods, including any plans for addressing multiplicity/type I (α) error.	
	20b	Methods for any additional analyses (e.g., subgroup and adjusted analyses)			
	20c	Definition of analysis population relating to protocol nonadherence (e.g., as randomized analysis) and any statistical methods to handle missing data (e.g., multiple imputation)	SPIRIT20c-PRO Elaboration	State how missing data will be described and outline the methods for handling missing items or entire assessments (e.g., approach to imputation and sensitivity analyses).	
Methods: Monitoring					
	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			

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		(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			
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	SPIRIT22-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)			
Ethics and Dissemination					
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board approval			
Protocol amendments	25	Plans for communicating important protocol modifications (e.g., changes to eligibility criteria,			

		outcomes, analyses) to relevant parties (e.g., 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 post-trial care	30	Provisions, if any, for ancillary and post-trial care and for			

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		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			
Appendixes					
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			

SPIRIT-PRO Item No.	Item title	SPIRIT-PRO Extension or Elaboration Item Description	Page number of example/explanation
5a	SPIRIT5a- PRO Elaboration	Specify the individual(s) responsible for the PRO content of the trial protocol.	To be added in proof
6a	SPIRIT6a- PRO Extension	Describe the PRO-specific research question and rationale for PRO assessment and summarize PRO findings in relevant studies.	To be added in proof
7	SPIRIT7-PRO Extension	State specific PRO objectives or hypotheses (including relevant PRO concepts/domains).	To be added in proof
10	SPIRIT10- PRO Extension	Specify any PRO-specific eligibility criteria (e.g., language/reading requirements or pre-randomisation 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.	To be added in proof
12	SPIRIT12- PRO Extension	Specify the PRO concepts/domains used to evaluate the intervention (e.g., overall health-related quality of life, specific domain, specific symptom) and, for each one, the analysis metric (e.g., change from baseline, final value, time to event) and the principal time point or period of interest.	To be added in proof
13	SPIRIT13-	Include a schedule of	To be added in

Table 2 Table of contents and resources

	PRO Extension	PRO assessments, providing a rationale for the time points, and justifying if the initial assessment is not pre-randomisation. Specify time windows, whether PRO collection is prior to clinical assessments, and, if using multiple questionnaires, whether order of administration will be standardized.	proof
14	SPIRIT14- 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.	To be added in proof
18a	SPIRIT-18a (i)-PRO Extension	Justify the PRO instrument to be used and describe domains, number of items, recall period, and instrument scaling and scoring (e.g., range and direction of scores indicating a good or poor outcome). Evidence of PRO instrument measurement properties, interpretation guidelines, and patient acceptability and burden should be provided or cited if available, ideally in the population of interest. State whether the measure will be used in	To be added in proof

		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 (e.g., paper, telephone, electronic, other) and setting (e.g., clinic, home, other).	To be added in proof
	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.	To be added in proof
	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.	To be added in proof
18b	SPIRIT-18b (i)-PRO Extension	Specify PRO data collection and management strategies for minimizing avoidable missing data.	To be added in proof
	SPIRIT-18b (ii)-PRO Elaboration	Describe the process of PRO assessment for participants who discontinue or deviate from the assigned intervention protocol.	To be added in proof
20a	SPIRIT20a-PRO Elaboration	State PRO analysis methods, including any plans for addressing multiplicity/type I (α) error.	To be added in proof
20c	SPIRIT20c-PRO Elaboration	State how missing data will be described and outline the methods for	To be added in proof

		handling missing items or entire assessments (e.g., approach to imputation and sensitivity analyses).	
22	SPIRIT22-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.	To be added in proof
Additional Resources			
Table 1. SPIRIT 2013 and SPIRIT-PRO Extension checklist: Recommended Items to Address in a Clinical Trial Protocol			To be added in proof
Glossary of terms			To be added in proof
Protocol template			Add link in proof

The development of the SPIRIT-PRO Extension followed the Enhancing Quality and Transparency of Health Research (EQUATOR) Network's methodological framework for guideline development,¹³ and has been published elsewhere.¹⁰ Ethical approval was provided by the University of Birmingham Ethical Review Board (ERN_16-0819). Briefly, these methods included:

- 1) a systematic review of existing PRO-specific protocol guidelines to generate the list of potential PRO-specific protocol items¹⁴;
- 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 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 organisations);
- 4) an international Delphi exercise;
- 5) a consensus meeting in May 2017 to finalise the guidelines and implementation strategy.

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3 International stakeholders provided feedback on the final wording of the SPIRIT-
4 PRO Extension during a final three-week consultation period. Following minor edits,
5 the guidelines were finalised and agreed by the SPIRIT-PRO Group.¹⁰
6
7

8 **Development of the PRO protocol template**

9
10 A PRO protocol template was developed to support implementation of the SPIRIT-
11 PRO guidance (ethical approval ERN_19-0939). The draft template was reviewed by
12 members of the project team and broader SPIRIT-PRO Group, including patient
13 partners. In addition, an international advisory group (IAG), comprising of global
14 PRO leads from major pharmaceutical companies, regulators and academics, was
15 convened to review and provide additional feedback on the template.

16
17 Teleconference meetings were held with members of the SPIRIT-PRO Group and
18 the IAG to discuss the feedback received. Based on the feedback the template was
19 revised and sent to all for final comments. After a final consultation period the PRO
20 protocol template was revised and finalised.
21

22 **Patient and Public Involvement**

23 Patient partners were involved in the design, conduct, reporting, and dissemination
24 plans of our research, including development of the SPIRIT-PRO Extension, the E&E
25 paper, protocol template, tools to support implementation by patient partners, and
26 are included as coauthors.
27
28

29 **Glossary**

30
31 **Concept:** “The specific measurement goal (i.e., the thing that is to be measured by a
32 PRO instrument). In clinical trials, a PRO instrument can be used to measure the
33 effect of a medical intervention on one or more concepts. PRO concepts represent
34 aspects of how patients function or feel related to a health condition or its
35 treatment.”¹⁵
36

37 **Domain:** “A sub concept represented by a score of an instrument that measures a
38 larger concept comprised of multiple domains. For example, psychological function is
39 a larger concept with multiple domains (emotional and cognitive function) that are
40 measured by relevant items.”¹⁵
41

42 **Endpoint*:** the variable to be analysed. It is a precisely defined variable intended to
43 reflect an outcome of interest that is statistically analysed to address a particular
44 research question. A precise definition of an endpoint typically specifies the type of
45 assessments made, the timing of those assessments, the assessment tools used,
46 and possibly other details, as applicable, such as how multiple assessments within
47 an individual are to be combined¹⁶ (e.g. change from baseline at 6 weeks in mean
48 fatigue score).¹⁷
49

50 **Health-related quality of life:** “a multidimensional concept that usually includes self-
51 report of the way in which physical, emotional, social, or other domains of well-being
52 are affected by a disease or its treatment”.¹⁸
53

54 **Important or key secondary PROs/end points:** Some PRO measures (particularly
55 health-related quality-of-life measures) are multidimensional, producing several
56 domain-specific outcome scales; e.g., pain, fatigue, physical function, psychological
57 distress. For any particular trial, it is likely that a particular PRO or PRO domain(s)
58 will be more relevant than others, reflecting the expected effect(s) of the trial
59 intervention(s) in the target patient population. These relevant PRO(s) and/or
60 domain(s) may additionally constitute the important or key secondary PROs

(identified a priori and specified as such in the trial protocol and statistical analysis plan) and will be the focus of hypothesis testing. In a regulatory environment, these outcomes may support a labelling claim. Because these outcomes are linked with hypotheses (CONSORT PRO Extension 2b),¹⁸ they may be subject to P-value adjustment (or “ α spending”). Beyond efficacy/effectiveness, PROs may also be used to capture and provide evidence of safety and tolerability (e.g. using the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™)).¹⁹

Instrument: “A means to capture data (e.g., a questionnaire) plus all the information and documentation that supports its use. Generally, that includes clearly defined methods and instructions for administration or responding, a standard format for data collection, and well-documented methods for scoring, analysis, and interpretation of results in the target patient population.”¹⁵

Intervention/treatment: A process or action that is the focus of a clinical study. Interventions include drugs, medical devices, procedures, vaccines, and other products that are either investigational or already available. Interventions can also include non-invasive approaches, such as education or modifying diet and exercise.²⁰

Item: “an individual question, statement, or task (and its standardized response options) that is evaluated by the patient to address a particular concept”.¹⁵

Observer-reported outcome: “a measurement based on a report of observable signs, events or behaviours related to a patient’s health condition by someone other than the patient or a health care professional”.²¹

Outcome*: the variable to be measured. It is the measurable characteristic that is influenced or affected by an individual’s baseline state or an intervention as in a clinical trial or other exposure¹⁶ (e.g. a fatigue score).

Patient-reported outcome (PRO): A PRO is any report of the status of a patient’s health condition that comes directly from the patient, without interpretation of the patient’s response by a clinician or anyone else and may include patient assessments of health status, quality of life, or symptoms.^{15 18} PROs are assessed by self-reported questionnaires, referred to as PRO measures (PROMs) or instruments.¹⁶

Primary outcome: the most important outcome in a trial, pre-specified in the protocol, providing the most clinically relevant evidence directly related to the primary objective of the trial.

Proxy-reported outcome: “a measurement based on a report by someone other than the patient reporting as if he or she is the patient”.¹⁵

Secondary outcomes: outcomes pre-specified in the protocol to assess additional effects of the intervention; some PROs may be identified as important or key secondary outcomes.

SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials.^{1 2}

SPIRIT Elaboration item: an elaboration of an existing SPIRIT item as applied to a specific context; in this instance, as applied to clinical trials assessing PROs.

SPIRIT-PRO Extension item: an additional checklist item describing PRO protocol content to address an aspect of PRO assessment that is not adequately covered by SPIRIT, as judged by available evidence and expert opinion.

Time window: a predefined time frame before and after the protocol-specified PRO assessment time point whereby the result would still be deemed to be clinically relevant.²²

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3 * The terms outcome and endpoint are often used interchangeably, although this is not always consistent with the range of
4 definitions available. For the definitions included in this glossary, an endpoint is defined from PRO data (i.e. the outcome) by
5 fully specifying four components: measurement variable (e.g. fatigue “in the past week” as measured by the QLQ-C30),
6 analysis metric (e.g., change in fatigue from baseline, final fatigue value, time to clinically important increase in fatigue (and
7 “event”), method of aggregation (e.g., median fatigue, proportion of patients with severe fatigue, proportion of patients with
8 clinically important change in fatigue), and time point. Note that using these definitions, several endpoints can be defined from
9 the same outcome source data, revealing the distinction and relationship between “outcome” and “endpoint” for PROs.
10
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12 **Purpose and Development of the Explanation and Elaboration paper and PRO** 13 **Protocol Template** 14

15 The SPIRIT-PRO Extension, this Explanation and Elaboration and the included PRO
16 protocol template are intended to guide the development of trial protocols for ethical
17 review where PROs are a primary or key secondary outcome, including single and
18 multi-arm trials. We recommend that authors also consider inclusion of checklist
19 items when PROs are exploratory in nature, as appropriate. Protocols may be
20 formatted in accordance with local requirements, however they need to address the
21 SPIRIT-PRO items completely and transparently. The examples provided in this E&E
22 document and protocol template are not intended to be prescriptive about how
23 information is included in protocols, nor how trials be conducted. Trialists may, for
24 example, wish to include a PRO specific, dedicated section in the protocol with
25 content informed by the SPIRIT-PRO checklist, whilst others may wish to add PRO
26 content to existing sections of the protocol.
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32 Modelled after other reporting guidelines,^{2 23 24} this E&E paper presents each
33 checklist item with at least one example from a trial protocol, followed by an
34 explanation of the rationale and main issues to address, to facilitate understanding
35 and usage. The guidelines are intended to be used in conjunction with the SPIRIT-
36 PRO Extension, SPIRIT 2013 Statement and E&E paper and other relevant
37 extensions.^{1 2 10 25} Empirical data and references to support each SPIRIT-PRO item
38 are provided. Real-world examples for each SPIRIT-PRO item, quoted verbatim, are
39 presented to reflect how key elements could be appropriately described in a trial
40 protocol. These examples were obtained from E&E paper authors, public websites,
41 journals, trial investigators, and industry sponsors. Some examples illustrate a
42 specific component of a checklist item, while others encompass all key
43 recommendations for an item. Reference numbers cited in the original quoted text
44 are denoted by [Reference] to distinguish them from references cited in this E&E
45 paper. Health-related quality of life (HRQL) has been used consistently to replace
46 terms for quality of life in examples.
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Administrative Information

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

Example

Trial name: Multicenter Randomized Controlled Trial of Conventional Versus Laparoscopic Surgery for Colorectal Cancer Within an Enhanced Recovery Programme (EnROL)

PRO endpoints: 1°, 2°

“EnROL Trial Management Group

Chief Investigator/Clinical Coordinator

RK, [address, telephone]

Co-Investigator

DK, [address, telephone]

Deputy Clinical Coordinator

TR, [address, telephone]

Trial Management/QA

SP, [address, telephone]; *JB*, [address, telephone], *LD*, [address, telephone]; *AF*, [address, telephone]

Nurse Advisor

SB, [address, telephone]

Statistics

SD, [address, telephone]

Health Economics

PF, [address, telephone]

Quality of Life

JMB, [address, telephone]

Translational Science Advisor

PQ, [address, telephone]

Collaborating Surgeons

HW, [address, telephone]; *MG*, [address, telephone]²⁶

Explanation

For trials assessing PROs, input from a person with expertise in PRO methodology early in the development phase of the protocol will improve its completeness and quality.¹⁰ Providing names and contact details of those contributing to the PRO-specific aspects of the protocol provides recognition, accountability and transparency. It aids identification of competing interests and prevents ghost authorship. It also provides a named point of contact to resolve any PRO-specific queries from other research team members, protocol reviewers, and sites (during trial start-up and conduct). Acknowledgements of PRO protocol input from patient-partners as per guidelines for the reporting of patient and public involvement is also recommended.²⁷ Patient and public involvement in all aspects of trial design, including but not limited to: selection of outcomes and measures, timepoints, mode of assessment, and reporting, can help minimise burden and ensure that data collected is patient-centred and relevant to participants and to the future patients who will benefit from the research.

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3 Only 7 of 75 (9%) protocols that included PROs from the United Kingdom (UK)
4 National Institute for Health Research (NIHR) Health Technology Assessment
5 programme explicitly described who was responsible for the PRO component
6 (Supplement 1).³

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

10 11 12 13 **Example**

14
15 **Trial name: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the**
16 **Efficacy and Safety of Idelalisib (GS-1101) in Combination with Rituximab for Previously**
17 **Treated Chronic Lymphocytic Leukemia**

18
19 **PRO endpoints: 2°**

20 21 **“3.5. Endpoint Selection Rationale**

22 23 3.5.2.2. Health-Related Quality of Life (HRQL)

24 Direct patient reporting of outcomes using standardized methods has become an increasingly
25 important component of therapeutic assessment. Evaluation of patient-reported outcomes
26 (PROs) is particularly relevant in patients who cannot be cured of disease [Reference].

27 PRO questionnaires have been previously used in CLL [chronic lymphocytic leukaemia] to understand
28 how patients differ from the general population in terms of health concerns [References], to
29 understand differences in perceptions of well-being in younger vs older patients [References], to
30 determine how treatment affects HRQL [References], and to assess the pharmacoeconomic cost of
31 improvements in HRQL [Reference].

32
33 Patients with CLL have overtly impaired well-being relative to comparable controls
34 [References]. Fatigue is cited as a common complaint, being present in the substantial majority of
35 patients. Impairment of HRQL prior to any treatment is apparent in those with B symptoms or in
36 patients with anemia, supporting the concept of initiating treatment when patients experience
37 symptomatic disease. Factors associated with lower overall HRQL have included older age, greater
38 fatigue, severity of co-morbid health conditions, advanced stage, and ongoing treatment for CLL
39 [Reference]. Younger patients appear to have worse emotional and social well-being but older
40 patients experience worse physical HRQL [Reference]. In comparative evaluation of
41 chemotherapy-containing regimens, differences in HRQL between therapies (eg, fludarabine
42 vs fludarabine-cyclophosphamide vs chlorambucil) reflected differences in toxicity while
43 greater efficacy was associated with improved HRQL [References].

44 In this Phase 3 study of GS-1101 and rituximab, it is postulated that incremental
45 GS-1101-mediated tumor control will be correlated with greater positive changes in HRQL
46 and that assessments of the drug’s safety profile will be supported by HRQL evaluations.”²⁸

47 48 49 **Explanation**

50
51 A summary of available PRO evidence and a clearly defined PRO question is
52 required in the background section of the protocol, or a dedicated PRO section if
53 appropriate. Researchers should demonstrate the need for the research and identify
54 the PRO specific research question to demonstrate the scientific approach and
55 integrity of the PRO study. This should include a review of existing PRO evidence
56 from relevant trials and observational studies (e.g. same/similar target population or
57 intervention). This will avoid duplication of research, establish the burden of disease
58 from the patient perspective, identify likely effects of treatment, and inform
59

objectives, hypotheses, selection of measures, endpoint definition and analyses (covered by subsequent SPIRIT-PRO items).

Many protocols include PROs without specifying the PRO-specific research question and without a rationale or any reference to PROs in related studies.^{3 4 9}

Provision of this information can inform and motivate research personnel to take note of PRO assessment methods and adhere to standardisation of PRO assessment (e.g. when, where, how and who of PRO assessment, as outlined in the protocol under subsequent SPIRIT-PRO items).^{6 11} Staff who understand the importance of PROs in a trial are able to share this understanding with participants. The combined effect of motivated and co-operative staff and participants may help reduce missing PRO data rates.²⁹ This information is also relevant to research ethics committees/IRBs and funders responsible for reviewing the scientific integrity and ethical aspects of the trial.

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

Examples

Trial group name: Trans Tasman Radiation Oncology Group (TROG)

Trial name: A randomised phase III trial of high dose palliative radiotherapy (HDPRT) versus concurrent chemotherapy + HDPRT (C-HDPRT) in patients with good performance status, locally advanced or metastatic NSCLC with symptoms predominantly due to intrathoracic disease who are not suitable for radical chemo-radiotherapy (TROG 11.03 P-LUNG GP)

PRO endpoints: 1°, 2°

“Objectives-

The Primary objective is to compare, in this group of patients, high dose palliative radiotherapy (HDPRT) versus concurrent chemotherapy and HDPRT (C-HDPRT), with respect to

- The relief of dyspnoea, cough, haemoptysis and chest pain as assessed by change in total symptom burden from baseline to six weeks after the completion of treatment.
- Response for each component symptom separately (dyspnoea, cough, haemoptysis, chest pain)

The secondary objectives are to compare the two regimens in terms of; Dysphagia during treatment, Thoracic symptom response rate, Duration of thoracic symptom response, HRQL, Toxicity, Progression-free survival and Overall survival.

The exploratory/tertiary objectives are;

- to determine how much improvement in HRQL and symptom palliation would be necessary to make the inconvenience due to the longer duration of radiotherapy of C-HDPRT worthwhile, relative to HDPRT. This objective will be addressed in the Patient Preferences Substudy.
- Analyse serum protein glycosylation changes and exosomes to identify potential biomarkers of disease response and progression. Prospectively collect and bank tumour tissue and blood samples from this cohort of patients for future evaluation of potential biological markers”³⁰

Trial name: Evaluating different rate control therapies in permanent atrial fibrillation: A prospective, randomised, open-label, blinded endpoint trial comparing digoxin and beta-blockers as initial rate control therapy (RATE-AF)

PRO endpoints: 1°, 2°, exploratory

“3.1 Hypothesis

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3 Null Hypothesis for primary outcome: No difference in patient-reported quality of life (measured using
4 the physical functioning domain of the SF36 questionnaire) when comparing a strategy of digoxin
5 versus beta-blocker therapy for initial rate control in patients with permanent AF.

6 Alternative Hypothesis :Use of digoxin or beta-blocker therapy as initial rate control in patients with
7 permanent AF is superior based on patient reported quality of life (measured using the physical
8 functioning domain of the SF36 questionnaire).

9 3.2 Primary objective

- 10 - Patient-reported quality of life (HRQL), with a predefined focus on physical well-being using
11 the SF-36 physical component summary at six months.

12 3.3 Secondary objectives

- 13 - Generic and AF-specific patient-reported HRQL using the SF-36 global and domain-specific
14 scores, the AFEQT overall score and the EQ-5D-5L summary index and visual analogue
15 scale at six and twelve months.
- 16 - Echocardiographic left-ventricular ejection fraction (LVEF) and diastolic function (E/e' and
17 composite of diastolic indices) at twelve months.
- 18 - Functional assessment, including 6-minute walking distance achieved, change in European
19 Heart Rhythm Association (EHRA) class and cognitive function at six and twelve months.
- 20 - Change in B-type natriuretic peptide (BNP) levels as a surrogate for total cardiac strain at six
21 months.
- 22 - Change in heart rate from baseline and group comparison using 24-hour ambulatory ECG."³¹

23 24 Explanation

25
26 The PRO objectives should reflect the research question to be addressed in the trial
27 (SPIRIT-6a-PRO Extension) and be described in the context of the population,
28 intervention, comparator, outcome and time-point (PICOT) and the estimand
29 framework.³² Study objectives may focus on measuring treatment benefit
30 (superiority), non-inferiority, equivalence. Alternatively, or in addition to one of these
31 objectives, the trial may focus on assessing the safety and tolerability from the
32 patient perspective, or may be more exploratory in nature, where results are
33 presented but no comparative conclusions can be drawn. The PRO-specific study
34 objectives need to clearly align with the proposed analyses methods (SPIRIT-20a-
35 PRO Elaboration). Critically, as described in work by the SISAQOL Consortium,³³
36 four key attributes need to be considered *a priori* for each PRO domain:
37
38
39

- 40 1) Broad PRO research objective/research question;
- 41 2) Between-group PRO objective;
- 42 3) Within-treatment group PRO assumption for the treatment or control arm;
- 43 4) Within-patient/within-treatment PRO objective (please note this component of
44 the objective directly addresses the SPIRIT-12-PRO Extension).

45
46
47 More detailed information on how these can be applied are described in the
48 SISAQOL consensus recommendations.³³ Although the SISAQOL recommendations
49 were published for oncology trials, the principles apply more broadly. Pre-
50 specification of objectives and hypotheses encourages identification of key PRO
51 domains and time-points. This is particularly important because PRO data are
52 multidimensional in two important ways. First, there is often more than one relevant
53 PRO in a trial, particularly when the high-level outcome of interest is health-related
54 quality of life (HRQL). Many HRQL questionnaires yield separate scores for distinct
55 dimensions, such as physical, emotional and social functioning, as well as key
56 symptoms such as fatigue and pain. Second, PRO assessments are typically
57 scheduled at several time points during a trial, such as baseline, end of treatment,
58 then a series of longer-term follow-ups. Pre-specification of objectives and
59
60

1
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3 hypotheses – focussing on the most important PRO domains and time points – is a
4 good way to reduce multiple statistical testing and avoid selective reporting of PROs
5 based on statistically significant results. Exploratory, hypothesis generating,
6 analyses can also be undertaken but should be specified as such in the final trial
7 report.¹⁸ This links to the SPIRIT-20a-PRO Elaboration, which includes plans for
8 addressing multiplicity/type 1 (α) error. The objectives are generally phrased using
9 neutral wording (e.g. “to compare the effect of treatment A versus treatment B on
10 fatigue”) rather than in terms of a particular direction of effect.^{2 34} In contrast, the
11 PRO hypothesis states the predicted effect of the interventions on the trial outcomes
12 (e.g. “patients allocated to treatment A will have less fatigue than those allocated to
13 treatment B”).³⁵⁻³⁷
14
15

16
17 Despite the importance of clearly defined PRO objectives and hypotheses, a review
18 of trial protocols determined that 23% failed to include PRO-specific objectives and
19 81% were missing a clear PRO hypothesis.³
20
21

22 **Methods: Participants, Interventions, and Outcomes**

23
24 **SPIRIT-10-PRO Extension: Specify any PRO-specific eligibility criteria (e.g.**
25 **language/reading requirements or pre-randomisation completion of PRO).**²⁹ **If**
26 **PROs will not be collected from the entire study sample, provide a rationale**
27 **and describe the method for obtaining the PRO subsample.**
28
29

30 **Example**

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32
33 **Trial group name: South West Oncology Group (SWOG)**

34 **Trial name: Health Status and Quality of Life in Patients With Early Stage Hodgkin's Disease: A**
35 **Companion Study to SWOG-9133 (SWOG S9208)**
36

37 **PRO endpoints: 1°, 2°**
38

39 “Eligibility Criteria

40 Ages Eligible for Study: 18 Years and older (Adult, Older Adult)
41 Sexes Eligible for Study: All
42 Accepts Healthy Volunteers: No
43 Sampling Method: Non-Probability Sample

44 Study Population: Community Sample

45 Criteria: DISEASE CHARACTERISTICS: Patients must be eligible for and registered to SWOG-9133
46

47 PATIENT CHARACTERISTICS: Patients must be able to complete the questionnaires in English. If
48 they are not able to complete questionnaires in English, patients may be registered to SWOG-9133
49 without participating in SWOG-9208.”
50

51 The Symptom and Personal Information Questionnaire #1, the Cancer Rehabilitation Evaluation
52 System Short Form (CARES-SF) and Cover Sheet must be completed prior to registration and
53 randomization on SWOG-9133.³⁸
54
55

56 **Explanation**

57
58 Any eligibility criteria relevant to PRO assessment should be considered during the
59 trial design and clearly specified in the protocol for consistent use by research
60

1
2
3 personnel. In some trials, the baseline PRO assessment is required before
4 randomisation as an eligibility criterion.²⁹ This helps to ensure there will be a valid
5 baseline questionnaire from all patients, which is essential for calculation of change
6 scores, or inclusion as a covariate in modelling longitudinal PRO data. For unblinded
7 trials, this also ensures PRO data are collected before participants are aware of the
8 randomisation which may affect some aspects of the participant's response, e.g.
9 anxiety/emotional well-being.³⁹ In the absence of such an eligibility criterion, there is
10 a risk that the baseline assessment may be conducted after randomisation but
11 before the intervention is administered, resulting in detection bias. The maximum
12 time between this assessment and randomization should be defined and should not
13 be too long.
14
15

16
17 It may not always be possible to collect PROs from all study participants, e.g. due to
18 non-availability of questionnaires in appropriate languages (see SPIRIT-18a(iii)-PRO
19 Extension),⁹ literacy requirements or due to cognitive function (see SPIRIT-18a(iv)-
20 PRO Extension). These PRO-relevant exclusions typically should not preclude the
21 affected participants from enrolling in the trial, unless the PRO is the primary
22 outcome. Evidence suggests eligibility criteria as stated in trial protocols often differ
23 from what is finally reported in the trial publication,⁴⁰ and data on use of other
24 language or culturally appropriate PRO instruments is often missing from the
25 protocol.^{13 41}
26
27

28
29 Where the needs of specific groups have been identified (e.g. not fluent in English)
30 but not accommodated in the study protocol (e.g. non-English language versions not
31 available, assistance with reading and writing English version not permitted), this
32 should be stated, and the rationale for the sampling method described and justified.
33 Trialists should aim to be as inclusive as possible. Given the significance of PROs,
34 the research community has a moral obligation to, where possible, to address gaps
35 in availability of culturally validated PRO instruments. In the meantime, the
36 implications for generalisability of findings should be discussed in subsequent
37 publications.¹⁸
38
39

40
41 **SPIRIT-12-PRO Extension: Specify the PRO concepts/domains used to**
42 **evaluate the intervention (e.g., overall health-related quality of life, specific**
43 **domain, specific symptom) and, for each one, the analysis metric (e.g., change**
44 **from baseline, final value, time to event) and the principal time point or period**
45 **of interest.**
46

47 Examples

48
49 **Trial name: Evaluating different rate control therapies in permanent atrial fibrillation: A**
50 **prospective, randomised, open-label, blinded endpoint trial comparing digoxin and beta-**
51 **blockers as initial rate control therapy (RATE-AF)**
52

53 **PRO endpoints: 1°, 2°, exploratory**

54 "12.1.1 Primary Outcome

55 Patient-reported quality of life (HRQL) - SF-36 physical component summary score at six months

56 12.1.2 Secondary Outcomes

57 Patient-reported HRQL:
58
59
60

- SF-36 global and domain-specific scores at 6 and 12 months
- EQ-5D-5L summary index and visual analogue scale at six and twelve months
- AFEQT overall score at six and twelve months³¹

Trial name: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Rituximab for Previously Treated Chronic Lymphocytic Leukemia

PRO endpoints: 2°

“Change in HRQL domain and symptom scores based on the Functional Assessment of Cancer Therapy: Leukemia (FACT-Leu)... defined as the change from baseline and the time to definitive increments or decrements of 10%, 20%, and 40% from baseline; time to definitive increment (better than baseline by the specified amount) is the interval from randomization to the first timepoint when the HRQL measure is consistently better than at baseline (including that timepoint as well as all the subsequent timepoints) in a subject whose last HRQL score is better than at baseline; and time to definitive HRQL decrement (worse than baseline by the specified amount) is the interval from randomization to the earliest of death or the first timepoint when the HRQL measure is consistently worse than at baseline (including that timepoint as well as all the subsequent timepoints) in a subject whose last performance status score is worse than at baseline.”²⁸

Explanation

For each outcome, including PROs, the trial protocol should define four components: the specific measurement variable, which corresponds to the data collected directly from trial participants (e.g., Beck Depression Inventory score, all cause mortality); the participant-level analysis metric, which corresponds to the format of the outcome data that will be used from each trial participant for analysis (e.g., change from baseline, final value, time to event); the method of aggregation, which refers to the summary measure format for each study group (e.g., mean, proportion with score > 2); and the specific measurement time point of interest for analysis.¹ Many PRO questionnaires are multidimensional, assessing multiple facets of the impact of a disease and its treatment and usually include multiple assessments over the course of the trial. The multidimensional nature of PROs is most apparent in HRQL questionnaires, which often include various aspects of functioning and symptoms, which are often scored as distinct ‘domains’. These domains may not be affected equally by the trial interventions. The SPIRIT-7-PRO Extension encourages protocol writers to identify the domains that are most likely to be affected in the trial objectives and hypotheses, drawing on previous evidence (SPIRIT-6a-PRO Extension). The SPIRIT-12-PRO Extension item reinforces the statement of these key domains, and also the most important time-points (i.e. where greatest impact of interventions are expected), and develops that concept further by encouraging protocol contributors to think about how these PRO domains and time-points will be analysed, i.e. the analysis metric.³³ To ensure transparency and credibility of the analysis, it is recommended that there is pre-specification of the PRO concepts/domains, analysis metric(s) and time-point(s) of interest, whether the PRO is a primary, secondary or exploratory outcome. These should closely align with the study hypotheses/objectives and the nature and trajectory of the disease or condition under investigation.^{33 42} The selected key domains, time-points, and analysis metric

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3 should be used to specify the PRO endpoints, integrated in the full endpoint model of
4 the trial.
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6
7 A clearly defined endpoint model, organizing all trial outcomes (PRO and non-PRO),
8 typically in primary, secondary and exploratory endpoints, allows rigorous control of
9 the evidence demonstration, especially the control of the statistical testing. Each
10 PRO endpoint in the model should explicitly specify a single domain and a single
11 time horizon. The endpoint model enables procedures for Type I error control (risk of
12 false positive finding) (see SPIRIT-20a-PRO Elaboration). Broadly, the concepts and
13 domains (sub concepts) measured by a PRO may be 'proximal' in nature, i.e. direct
14 impact of the disease and treatment (e.g. symptoms such as pain, fatigue, nausea,
15 rash and anxiety) or more distal, "knock-on" effects, (e.g. functional status and global
16 quality of life), as illustrated for ovarian cancer in (Figure 1, inspired by the Wilson
17 and Cleary model⁴³). Of note, the Food and Drug Administration (FDA) are
18 increasingly focused on the individual measurement of well-defined concepts that
19 impact on HRQL but are more proximal to a therapy's effect on the patient and the
20 patient's disease: symptomatic adverse events, physical function, and, where
21 appropriate, a measure of the key symptoms of the disease.⁴⁴

22
23 Common analysis metrics may include magnitude of event at time t , proportion of
24 responders at time t , overall PRO score over time or response patterns/profiles.
25 These should be pre-specified alongside the levels of statistical and clinical
26 significance for the study and any responder definition in use.¹⁵ Time-points for
27 analysis should be chosen to best address the research question, whilst taking into
28 account aspects such as the natural history of the disease/condition and its
29 treatment, the PRO measurement properties and recall period, and participant
30 completion burden.^{15 45}
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34 The example, Idelalisib and Rituximab Improve Progression-Free Survival Over
35 Rituximab Alone in Unfit Patients with Relapsed Chronic Lymphocytic Leukemia: A
36 Phase 3 Study, illustrates a 'time to event' PRO endpoint or analysis metric, where
37 the event is definitive improvement or definitive deterioration in a PRO. This
38 approach allows repeated PRO measurements to be converted to a single measure:
39 time to definitive increment or decrement. This requires quite complex and specific
40 criteria for degree and duration of change. Also, this particular example does not
41 specify any key domains of the FACT-Leu, but rather applies this analysis metric to
42 all HRQL domain and symptom scores. In contrast, the RATE-AF example identifies
43 a single score (the SF-36 physical component score), and a specific time-point (6
44 months) as the primary outcome, with other SF-36 domains, questionnaires and
45 time-points specified as secondary outcomes.
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53 **Figure 1 Proximal and distal effects of therapy on patient symptoms and**
54 **quality of life** adapted from Wilson and Cleary, 1995.⁴³
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12 **SPIRIT-13-PRO Extension: Include a schedule of PRO assessments, providing**
13 **a rationale for the time points, and justifying if the initial assessment is not**
14 **pre-randomisation. Specify time windows, whether PRO collection is prior to**
15 **clinical assessments, and, if using multiple questionnaires, whether order of**
16 **administration will be standardised.**
17
18

Examples

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22 **Trial group: TROG**

23 **Trial name: A randomised phase III trial of high dose palliative radiotherapy (HDPRT) versus**
24 **concurrent chemotherapy + HDPRT (C-HDPRT) in patients with good performance status,**
25 **locally advanced or metastatic NSCLC with symptoms predominantly due to intrathoracic**
26 **disease who are not suitable for radical chemo-radiotherapy (TROG 11.03 P-LUNG GP).³⁰**
27

28 **Figure 2 Example schedule of PRO assessments in the TROG 11.03 P-Lung GP**
29 **Trial**
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34 **Trial group: UK Medical Research Council Scottish Cancer Trials Breast Group in association**
35 **with: Breast International Group**

36 **Trial name: MRC phase III randomised trial to assess the role of adjuvant chest wall irradiation**
37 **in 'intermediate risk' operable breast cancer following mastectomy (MRC SUPREMO TRIAL**
38 **(BIG 2-04))**
39

40 **Figure 3 Example schedule of PRO assessments in the MRC SUPREMO TRIAL**
41 **(BIG 2-04)⁴⁶**
42

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46 **Figure 4 Flow diagram schedule of PRO assessments in the MRC SUPREMO**
47 **TRIAL (BIG 2-04)⁴⁶**
48

Explanation

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53 A clear and concise schedule of PRO assessments (Figures 2, 3 & 4) can: assist trial
54 staff to be organised and prepared for participant visits, inform study participants
55 about the methods and expectations of trial participation, and facilitate review of
56 participant burden by research ethics committees/IRBs.²⁹ The scheduled PRO
57 assessments should provide the data required to address the study's PRO
58 objectives. When selecting appropriate time-points for assessment, it is important to
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3 consider the natural history of disease/progression, the hypothesised impact of
4 therapy over time and practical considerations such as alignment of assessments
5 with clinic visits and recall period of PRO measures. PRO assessments should be
6 described in the protocol text and in the schedule of assessment table along with the
7 other clinical data collection activities, for ease of reference. This is recommended
8 whether the PRO is completed by the participant during study visits or outside of the
9 study visits (e.g. at home).
10
11

12 The timing of the baseline PRO assessment relative to other study-related events is
13 important and therefore should be specified in the schedule of assessments.
14 Collecting PRO data prior to randomisation helps ensure an unbiased baseline
15 assessment, and if specified as an eligibility criterion, can promote data
16 completeness (SPIRIT-10-PRO Extension). Baseline PRO data are often used as a
17 covariate in analyses and are essential to calculating change from baseline,
18 however, collecting data from enrolled patients prior to randomisation can be
19 logistically challenging. One approach is to have participants complete the baseline
20 PRO assessment immediately after providing consent, while the site staff obtain the
21 randomisation assignment from the study system. However, there may be scenarios
22 in which pre-randomisation PRO assessment is unnecessary or not possible, for
23 example, emergency surgery trials.
24
25
26

27 Stating the time-windows for each PRO assessment clearly in the protocol text and
28 schedule of assessments table or footnote will help staff adhere to them. Examples
29 of time-windows for PRO assessment are similar to time-windows for other types of
30 assessments, such as a study visit that may occur on Day 10-14 post-baseline, or on
31 Day 30 +/- 3 days post-surgery. Time-windows for each scheduled PRO assessment
32 require an unambiguous reference point, to ensure that PRO data collection
33 captures clinically relevant time points of interest. In deciding the size of the time-
34 window for a PRO assessment, consider the trade-off between a smaller, more
35 precise, time-window and a larger more feasible window. One approach is to specify
36 a time-window that is a little larger than the ideal and not allow exceptions; this
37 approach is more consistent than setting a smaller time-window and allowing
38 exceptions. Often PRO assessments that occur during active treatment, e.g.
39 chemotherapy, have a smaller time-window to capture acute toxicity that arise and
40 resolve relatively quickly, while those occurring many months or years after
41 treatment completion can have a larger window if the participant's outcomes are
42 expected to stabilise over time.
43
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47 When the PRO assessment occurs during a research or clinic visit, it is
48 recommended that PRO assessment is standardised to be completed prior to clinical
49 consultation, assessments or procedures. For example, if a PRO instrument
50 assesses participants' experiences of pain in the past 7 days, and the study visit
51 includes a bone marrow biopsy, the schedule of assessments should indicate that
52 the PRO assessment be completed prior to the biopsy. This will prevent the pain
53 assessment from capturing pain associated with the biopsy, reduce risk of missing
54 data as participants may not feel well enough to complete PROs following their
55 procedure, and offer a "routine" for study staff responsible for data collection.
56 When more than one PRO questionnaire is scheduled, it is recommended that the
57 order of questionnaires is standardised, with those higher in the endpoint hierarchy
58 being collected first.
59
60

These two forms of standardisation of PRO administration are examples of the more general principle in research methodology that standardisation of methods reduces unwanted sources of variation, whether random (i.e. no net effect on estimates of interest, such as the impact of interventions on PROs) or systematic (i.e. causing bias).

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.

Examples

Trial name: The chronic autoimmune thyroiditis quality of life selenium trial (CATALYST)

PRO endpoints: 1°

“The primary outcome is thyroid-related quality of life during 12 months’ intervention, as measured by a composite score from the ThyPRO questionnaire. Sample size estimation is based on this outcome. The trial should be sufficiently powered to identify a difference between the intervention and the control group of four points on the 0 to 100 ThyPRO composite scale, corresponding to a small to moderate effect. In previously obtained data, the standard deviation of ThyPRO-scores (sigma level) was 20 points. With a correlation between observations on the same participant of 0.50, and a power of 80% and a type I error probability (two-sided α level) of 0.05, a sample size of 236 experimental participants and 236 control participants is required. The sample size estimate is based on a design with five repeated measurements having a compound symmetry covariance structure.”⁴⁷

Trial name: Cosmesis and body image after single-port laparoscopic or conventional laparoscopic cholecystectomy: a multicenter double blinded randomised controlled trial (SPOCC-trial)

PRO endpoints: 1°, 2°

“The primary endpoint of the study concerns patient’s satisfaction with cosmesis and body image 12 weeks after surgery. This endpoint is assessed using a validated cosmesis and body image score (CBIS) that was previously used in surgery for Crohn’s disease and in donor nephrectomy. This score is calculated on an 8-item multiple choice type questionnaire . . . ranging between 8 and 48 points... A clinically relevant improvement of the cosmesis and body image score (CBIS) is defined as an improvement of 20% of the cosmesis score (8 points). Given the reported standard deviation of the CBIS between 4-6 and using (alpha = 0.05 and beta = 0.90), two groups of 49 patients are needed. This is based on a two-sided significance level (alpha) of 0.05 and a power of 0.90. Estimating a 10% dropout rate, which is common in randomized controlled trials, 55 patients will be randomized per arm.”⁴⁸

Trial group: TROG

Trial name: A randomised phase III study of radiation doses and fractionation schedules for ductal carcinoma in situ (DCIS) of the breast (BIG 3-07/TROG 07.01)

PRO endpoints: 2°

The sample size for this trial, based on the primary endpoint (time to local recurrence of invasive or intraductal breast cancer in the ipsilateral breast), was 1600 patients. The sample size for the PRO substudy was determined a priori, and was less than that required for the primary endpoint, as explained in the protocol excerpt below. Therefore, patients recruited after the PRO-specific target

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2
3 sample size was achieved did not complete PRO questionnaires, saving trial resources in data
4 collection and management.

5 “Sample size determination: For the quality of life study aiming to detect a difference between the
6 tumour bed boost and no boost groups of 0.2 standard deviations of a continuous scale such as
7 fatigue or physical symptoms, with 80% power at a two-sided alpha level of 5%, the required sample
8 size is 790 patients. To allow for attrition at a rate of 5% per year, 1020 patients are required to
9 participate in the quality of life study.”⁴⁹

10 **Explanation**

11
12 As with any primary endpoint, including those that focus on PRO, the criteria and
13 methods for estimating the necessary sample size should be specified, with
14 adjustments for expected discontinuation from the clinical study.⁴⁵ Ideally, the criteria
15 for clinical significance (e.g. minimal important difference, clinically meaningful
16 within-patient change threshold, responder definition) should be specified when
17 known.^{50 51} It is important to note that the FDA is more interested in what constitutes
18 a meaningful within-patient change in score from the patient perspective.¹⁵

19
20 In cases where the PRO is specified as a key secondary endpoint, the statistical
21 power based on the estimated sample size for the primary endpoint, should be
22 determined. If overpowered, specifying a smaller PRO-specific sample size will save
23 trial resources, as illustrated in the BIG 3-07/TROG 07.01 example. When sufficient
24 power may be achieved by collecting PROs from a representative subset of
25 participants, the sampling strategy should be clearly described.

26
27 Only 50.7% of NIHR Health Technology Assessment clinical trial protocols address
28 sample size and statistical power for PRO specified as secondary endpoints.³ If the
29 clinical trial is international in scope, the sampling across countries may be
30 influenced by availability of language translations.⁵² In addition, the variability of
31 measurement between countries may inflate type 2 error (reduces power).

32 **Methods: Data Collection, Management, and Analysis**

33
34 **SPIRIT-18a(i)-PRO Extension: Justify the PRO instrument to be used and
35 describe domains, number of items, recall period, instrument scaling and
36 scoring (e.g., range and direction of scores indicating a good or poor
37 outcome). Evidence of PRO instrument measurement properties, interpretation
38 guidelines, and patient acceptability and burden should be provided or cited if
39 available, ideally in the population of interest. State whether the measure will
40 be used in accordance with any user manual and specify and justify deviations
41 if planned.**

42 **Examples**

43
44 **Trial name: Impact of a multimodal support intervention after a "mild" stroke (YOU CALL- WE
45 CALL)**

46
47 **PRO endpoints: 1°, 2°**

48
49 “A number of quality of life tools were reviewed (e.g. SF-36, Stroke Impact Scale, Quality of Life
50 Index) and the tool chosen was a compromise between psychometric properties and adequacy of
51 content for mild stroke. The 32 item questionnaire Quality of Life Index (QLI) [Reference] which was
52 developed from Ferran’s conceptual model of quality of life and which has been used with a stroke
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3 clientele [Reference] was chosen as the primary outcome. Each item of the QLI as relating to four life
4 domains (health and functioning, socio-economic, psychological/spiritual and family), is evaluated in
5 terms of satisfaction and importance on a six-point scale. Scores for each domain and a global score
6 are expressed from 0-to-30, with a higher score indicating a better quality of life. These four life
7 domains relate well with the main issues covered through the WE CALL intervention. It has shown to
8 have adequate psychometric properties (concurrent validity, test-retest reliability and high internal
9 consistency: $\alpha = 0.90$) [Reference] and thus should be responsive to therapy-induced change
10 [References]. A one point difference was observed in the first six months post-stroke descriptive
11 follow-up ($n = 63$) for an effect size of 0.33 [References]. A two-point difference is considered a
12 clinically meaningful change leading to a moderate effect size of 0.66.⁵³

13
14 **Trial name: A randomised phase II/III multi-centre clinical trial of definitive chemoradiation,**
15 **with or without cetuximab, in carcinoma of the oesophagus (SCOPE 1: Study of**
16 **Chemoradiotherapy in Oesophageal Cancer Plus or Minus Erbitux)**

17
18 **PRO endpoints: 2°**

19 20 “HRQL instruments

21 Generic domains of HRQL will be assessed with the EORTC core Quality of Life Questionnaire, the
22 EORTC QLQ-C30 [Reference]. This instrument has been well validated in many international clinical
23 trials in oncology including oesophageal adenocarcinoma and squamous cell cancer. Disease specific
24 and CRT associated symptoms and side effects will be assessed with the oesophageal cancer
25 specific module, the EORTC QLQ-OES18 [Reference]. This has been validated and tested in patients
26 receiving definitive CRT. The module includes scales assessing dysphagia, eating restrictions, reflux,
27 dry mouth and problems with saliva and deglutition. The Dermatology Life Quality Index (DLQI) will
28 also be administered [Reference]. This is a well validated, easy to use index which assesses the
29 impact of dermatological conditions on patients' HRQL [Reference]. It has been included to accurately
30 assess the impact of the acneiform eruption commonly seen with cetuximab.⁵⁴

31 32 **Explanation**

33
34 The justification for the selection of PRO instrument(s) is required in the trial
35 protocol. This will help trial personnel and participants understand why specific
36 measures are being used and how they directly address the trial objectives and
37 stakeholder needs.¹¹ For example, regulatory agencies often focus on physical
38 symptoms and functioning to inform licensing and labelling claims, whereas patients
39 and health-policy makers may be more interested in broader aspects of HRQL, such
40 as engaging in social activities and emotional wellbeing.^{55 56} For regulatory trials, it is
41 prudent to seek regulatory advice at an early stage of trial development regarding
42 the acceptability of the instrument and the approach to PRO assessment.
43 Stakeholder-relevant PROs can be identified through patient involvement, qualitative
44 research, or core outcome sets,^{56 57} which alongside clinical outcomes, often include
45 outcomes such as symptom burden, functioning, and disease control, which can be
46 measured using PRO instruments.

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49 Appropriately developed and evaluated PRO instruments can provide more sensitive
50 and specific measurements of the effects of medical intervention, thereby increasing
51 the efficiency of clinical trials that attempt to measure the meaningful treatment
52 benefits of those therapies.⁵⁸⁻⁶⁰ Irrespective of whether the trial is conducted for
53 regulatory purposes, FDA guidance and ISOQOL guidance provide a useful
54 conceptual framework to assist in the selection of measures.^{15 61} Identifying and
55 selecting valid, reliable tools that are acceptable to patients from the target
56 population may prove challenging. The Consensus Based Standards for the
57 Selection of Health Measurement Instruments (COSMIN) initiative and the
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3 Evaluating the Measurement of Patient Reported Outcomes programme provide
4 useful guidance to support the review of measurement properties.^{56 62 63}
5 Ideally, the PRO instrument(s) will have been validated in the target population and
6 this evidence cited. This will help reviewers understand if claims being supported by
7 the PRO instrument can be substantiated by the evidence for using that instrument
8 in that, or a related, population. Further details on the domains, number of items,
9 recall period, instrument scaling and scoring (e.g. range and direction of scores
10 indicating a good or poor outcome) should be provided. This will assist trial
11 personnel in the collection and analysis of the PRO data. Questionnaires should be
12 used in accordance with user manuals to promote good data quality and ensure
13 standardized scoring. Deviations from user manuals or different ways of capturing
14 PRO data may invalidate the measure; therefore any deviations should be declared
15 and transparently reported.¹⁸

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19 If in the trial there are plans to use a questionnaire which has not been validated in
20 the trial's target population, or if a new instrument is being developed alongside the
21 trial, it is important to explain this in the protocol. Including an outline of any plans for
22 the evaluation of its measurement properties using the trial data, if this will be
23 undertaken, and if not why. This should be in accordance with established current
24 guidelines for PRO validation.⁶⁴

25
26
27 Although all the reviewed NIHR Health Technology Assessment clinical trial
28 protocols identified the PRO instrument to be used in the trial, few justified their use
29 in relation to the study hypotheses, PRO instrument measurement properties, or
30 expected participant burden (41.3%, 37.3% and 14.7% respectively).³
31 Patient partners involved in the design of the study can assist with the selection of
32 PRO instruments and provide feedback on the likely acceptability of the questions,
33 and participant burden (e.g., time taken for completion, cognitive burden, emotional
34 burden, repetition across questionnaires).⁶⁵ The number of PRO
35 instruments/questions to be assessed in a trial requires careful justification.
36 Minimising participant burden has been identified as a strategy to reduce risk of
37 missing PRO data, improve recruitment and retention.²⁹

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41 **SPIRIT-18a(ii)-PRO Extension: Include a data collection plan outlining the**
42 **permitted mode(s) of administration (e.g., paper, telephone, electronic, other)**
43 **and setting (e.g., clinic, home, other).**

44 45 46 Examples

47
48 **Trial name: Early surgery versus optimal current step-up practice for chronic pancreatitis: a**
49 **multi-centre randomised control trial (ESCAPE)**

50
51 **PRO endpoints: 1°, 2°**

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53
54 "The Izbicki pain score will be assessed every two weeks during a follow-up period of 18 months. For
55 this end, the Izbicki pain score will be assessed via a web questionnaire. Patients who do not have an
56 email will be given a folder with Izbicki pain score forms and return envelopes. Patients will be contacted
57 by telephone every two weeks and reminded to fill in the questionnaire and send it to the trial
58 coordinators. The Izbicki pain score is a one page questionnaire, easily completed in less than 3
59 minutes. The folder with the Izbicki score forms will be re-filled at every outpatient clinic visit
60 (scheduled every 6 months)."⁶⁶

Trial name: a randomised multi-stage phase II/III study of Sunitinib comparing temporary cessation with allowing continuation, at the time of maximal radiological response, in the first-line treatment of locally advanced/metastatic Renal Cancer (STAR)

PRO endpoints: 1°, 2°

Quality of life questionnaires during the first 6 months will be administered in clinic in order to support participant use before postal questionnaires are instituted after 6 months for the EQ-5DTM/EQ-VAS™ (FACT-G and FSKI will continued to be collected at clinic visits). Clinic staff should remind participants of the importance of the quality of life assessments at each clinic visit.

Due to the importance of HRQL data in this trial, measures will be taken to ensure maximum compliance of questionnaire completion. For the two-weekly questionnaires which participants complete at home from the 24-week time-point, where the participant consents to this, reminders for completion are sent by email or text message to the participant by the research team at CTRU: this is an optional part of the STAR Informed Consent Form. Where a HRQL questionnaire would be completed at a hospital clinic visit, but the local research team forget to give this to the participant, of the participant no longer attends clinic visits at hospital during their follow-up period, a questionnaire for the local research team will send this out by post to the participant's home after checking the participant's status and establishing it is appropriate to do so.^{67 68}

Explanation

Standardisation of all aspects of PRO administration is vital to PRO data quality. It is therefore critical that research personnel and trial participants understand how, when, and where PRO data will be collected in the study.¹⁰ The study protocol should specify the permitted mode(s), method(s) and setting(s) of PRO data collection, including the permitted "back-up" options and pre-planned reminders. For example, when PRO assessment is conducted in clinic via a tablet computer, paper forms could be permitted (and available) as a back-up option for instances when the tablet is not available or functioning properly. Offering alternative modes of completion may help improve response rates.²⁹ Of note, the FDA has previously recommended that there is a back-up plan for electronic PRO data collection (e.g., web-, phone-, or paper-based) implemented in case of malfunctions with electronic devices.⁶⁹

Electronic PRO assessment is increasingly available in trials, but traditional paper-based methods may still be useful or required in some situations. It is therefore important to know whether there are systematic differences induced by mode of administration. A recent meta-analysis that included 31 studies that randomised participants to different data collection modes found no evidence of bias associated with paper versus electronic administration.⁷⁰ These results support the use of multiple modes of administration within a research study, which may be a useful strategy for reducing missing PRO data. If evidence of equivalence between different modes of administration is available for the specific PRO questionnaires in a trial, it should be considered in determining the PRO administration plan. If electronic administration has not been attempted before for the trial PRO questionnaires, and only minor modifications to layout/presentation are needed with respect to the paper-based versions, it is advisable to pilot-test usability and conduct cognitive debriefing to assess equivalence.^{70 71} The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) provide useful guidance on key considerations for PRO data collection including multiple modes.^{71 72}

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3 The setting for PRO data collection, for example in clinic or at home (or clinic at
4 baseline, with follow up at home), should be described and standardized across trial
5 intervention groups and sites. Differential use of settings and modes of
6 administration by treatment arm should be avoided as these may lead to different
7 response rates and potentially biased results.¹¹
8
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10 The protocol should also specify the types of assistance trial staff can provide
11 patients for completing the PRO assessment. Respondents should be encouraged to
12 self-complete as far as possible. Some respondents may require some assistance,
13 however, the greater the degree of assistance, the greater the potential to influence
14 a respondent's responses. Assistance should therefore be limited, provided only by a
15 trained member of the research team, or a trained third party, the permissible types
16 of assistance should be clearly specified in the protocol and reviewed in staff
17 training. Allowable assistance might include instructions on how patients can input
18 their answer on the tablet, clarifying the response options, reading questions to the
19 participant, or recording the participants' answer on the form/tablet. This level of
20 assistance facilitates self-administration of the PRO instrument. Completion of a
21 PRO instrument with an interpreter, caregiver or family member should be avoided
22 as these individuals have not been trained, and may influence the individual's
23 responses, either directly by expressing opinions that influence the participant to
24 alter their answers, or indirectly, for example if the respondent seeks to avoid
25 embarrassment or to provide a more acceptable answer (social desirability bias).
26
27
28

29
30 Further, use of a human language interpreter should be avoided. When planning a
31 study, common languages spoken by patients attending the recruiting centres should
32 be considered so that validated language translations of chosen PRO instruments
33 can be obtained (see SPIRIT-18a(iii)-PRO Extension).
34

35 Interviewer administration of PRO instruments should be avoided, but where
36 necessary, should be clearly justified in the protocol. Interviewers should read
37 questions verbatim, ideally using a PRO instrument that has been validated in that
38 mode. Similarly, proxy or observer completion requires a proxy-validated/observer-
39 reported version of the PRO instrument (see SPIRIT-18a(iv)-PRO Extension).
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41

42 **SPIRIT-18a(iii)-PRO Extension: Specify whether more than one language**
43 **version will be used and state whether translated versions have been**
44 **developed using currently recommended methods.**
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46

47 **Example**

48
49 **Trial name: A Phase 3, Randomized, Open Label Trial of Lenalidomide/dexamethasone With or**
50 **Without Elotuzumab in Relapsed or Refractory Multiple Myeloma (ELOQUENT – 2)**
51

52 **PRO endpoints: 2°, exploratory**
53

54 **“5.8 Outcomes Research Assessments**

55 **5.8.1 HRQL Assessments**

56 To assess the impact of treatment, subject's quality of life will be measured using 3 validated HRQL
57 instruments: the European Organization for Research and Treatment of Cancer Quality of life
58 Questionnaire- Core (EORTC QLQ-C30), the myeloma-specific module (QLQ-MY20) and the Brief
59 Pain Inventory- Short Form (BPI-SF)...
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3 Non-English speaking subjects will complete the questionnaire using validated language transitions
4 developed and recommended for each instrument... The BPI-SF has demonstrated both reliability and
5 validity across cultures and languages, and has been used to study the effectiveness of pain
6 treatment.[Reference] A score of 6 on a scale of 0 to 10 on any single item is generally considered to
7 be clinically significant.[Reference] Pre-testing was carried out in the UK, Norway, Sweden, Denmark,
8 and Germany. Field testing of the module has been conducted in a range of Phase 3
9 trials.[Reference] The module has been validated in a large number of languages (see
10 www.eortc.be/home/qol).⁷³

11 Explanation

12
13 Trials involving participants with different language requirements require measures
14 that have been translated and culturally adapted using appropriate methodology.^{10 12}
15 ^{74 75} Providing culture- and language- appropriate PRO instruments for use in the
16 trial can lead to a reduction in missing data, ability to recruit people from ethnic
17 minority groups, lower attrition rates and improved generalizability of trial results.⁷⁶ If
18 the countries/languages are not known at the time of protocol writing then more
19 general protocol content may be appropriate:
20
21

22
23 “multiple language validated versions are available [provide references where these can be found]
24 and the correct language for this patient should be used”.

25
26 At present the extent to which this is happening is not clear. A review of protocols
27 and/or subsequent publications from cancer clinical trials with a PRO endpoint,
28 registered on the National Institute for Health Research portfolio examined reporting
29 of ethnically diverse recruitment and the use of culturally and linguistically validated
30 PRO instruments. The review found a lack of transparency around the use of
31 culturally and linguistically appropriate PRO instruments. Of the 88 studies reviewed
32 only 14(17%) reported any type of data on ethnic diversity. Although eight studies
33 were multicentre, multi-national cancer clinical trials, none identified if translated
34 versions of PRO instruments were being used.⁷⁷
35
36

37
38 There are clear guidelines for translating PRO instruments,^{74 78} and plans to use
39 translated versions, should be specified in the protocol, citing references when
40 available.¹⁰ Specification of use of translated versions in the protocol will help
41 reporting in accordance with CONSORT-PRO.^{18 74 75} It must not be assumed that
42 linguistic translation equates to cross cultural adaptation (preparing the instrument
43 for use in another setting). A number of studies^{79 80} have recommended that cross
44 cultural equivalence is also an important consideration.^{74 75 81}
45
46

47
48 Using different language versions of PRO instruments to collect data in a trial ideally
49 requires evidence to support the psychometric equivalence of data being reported,
50 especially if data are going to be pooled for clinical trial evaluation.^{52 82 83} Where
51 such evidence is unavailable, pre-specification in the statistical analysis plan (SAP)
52 of exploratory analyses to assess whether there are differences between PROs by
53 language group may be appropriate. The language in which each patient complete
54 the questionnaire should be recorded in the database to inform such analyses.⁵²
55

56 **SPIRIT-18a(iv)-PRO Extension: When the trial context requires someone other**
57 **than a trial participant to answer on his or her behalf (a proxy-reported**
58 **outcome), state and justify the use of a proxy respondent. Provide or cite**
59 **evidence of the validity of proxy assessment if available.**
60

Examples

Trial name: Cognitive Rehabilitation in Pediatric Acquired Brain Injury - a Randomized Controlled Trial (CORE-pABI)

PRO endpoints: 1°, 2°

“[Paediatric Acquired Brain Injury] constitutes a major disruption to child development and may affect cognitive, behavioural, emotional, social as well as academic function.

The primary outcome measure is the BRIEF, parent report.[*Reference*] BRIEF is an 86-item standardised questionnaire that captures parents perceptions of a child’s EF in his or her everyday environment. Each item’s frequency of occurrence is rated on a 3-point Likert scale from 1(never) to 3 (often). It has demonstrated good reliability, with high test-retest reliability (rs=0.88 for teachers, .82 for parents), internal consistency (Cronbach’s α s=0.80– 0.98), and moderate correlations have been detected between teacher and parent ratings (rs=0.32–0.34). The questionnaire has been applied to several clinical groups in Norway.”⁸⁴

Trial name: Evaluating the effectiveness and cost effectiveness of Dementia Care Mapping (DCM) to enable person-centred care for people with dementia and their carers: a cluster randomised controlled trial in care homes (DCM EPIC study 1.0)

PRO endpoints: 2°

“Relative/friend criteria

To be eligible to provide proxy data about a resident, relatives/friends must: Have visited the resident on a regular basis over the past month (i.e. at least once per week) Be willing to provide data at a time convenient to them Have sufficient proficiency in English to contribute to the data collection required for the research”⁸⁵

Explanation

In some contexts, such as trials involving young children or cognitively impaired participants or participants who are unable to reliably self-report for other reasons, it may be necessary for a proxy - someone other than a trial participant, to report the participant’s outcomes on their behalf as though they are the patient.^{10 86}

Proxy reports should be used only when necessary. 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.”^{15 42} The US FDA also discourages the use of proxy-reported outcomes to inform labelling claims, recommending observer reports for observable phenomenon only (e.g. vomiting, but not nausea) instead.

In contexts such as cancer, dementia or palliative care it is reasonable to anticipate the need for proxy response, throughout all or some of the trial. Previous studies have shown varying levels of agreement between participant and proxy ratings, dependant on the variable being measured, the quality, duration, and stability of the relationship between proxy and participant.^{87 88}

A trial protocol should indicate clearly who is eligible to provide the proxy report, with explicit administration guidelines for completion of proxy measures including how the report is to be captured, whether that same individual must be the “consistent rater” across all time-points of assessment (this is preferable, for consistency), or whether

1
2
3 varying proxy reports will be permissible. This information should also be provided
4 for observer-reported outcomes.
5

6 Just as the measurement properties of the PRO instrument should be specified, so
7 should the properties of measures to be used by proxy reporters.
8 Given known issues with patient and proxy reporter discordance,⁸⁸⁻⁹¹ while patient-
9 participants are still able to self-complete, collecting both participant and proxy-
10 reported data enables quantification of the size and direction of any bias, that may
11 later be adjusted for, if needed. Further data may be gathered about the proxy (e.g.
12 age, relationship to the patient, gender, proxy literacy, relationship and exposure to
13 the patient,⁹²) as these variables may guide interpretation of results and any
14 subgroup/sensitivity analyses. Whether proxy-reported data will be analysed
15 separately or pooled with participant-reported data should also be detailed. Any such
16 plans should be specified in the protocol and SAP. This information should also be
17 provided for observer-reported outcomes.
18
19
20
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22

23 **SPIRIT-18b(i)-PRO Extension: Specify PRO data collection and management** 24 **strategies for minimising avoidable missing data.** 25

26 **Examples** 27

28
29 **Trial group: National Cancer Institute, Naples**

30 **Trial name: Phase III randomized multicentre trial of Carboplatin + Liposomal Doxorubicin vs**
31 **Carboplatin + Paclitaxel in patients with ovarian cancer (MITO-2 (Multicentre Italian Trials in**
32 **Ovarian Cancer-2)**
33

34 **PRO endpoints: 2°**
35

36 “Operating procedure

- 37 • It is fundamental that the Researchers take great care when collecting the questionnaires, in
38 order to allow good compliance by the patients participating in the protocol.
- 39 • The quality of life form must be filled in by the patient herself.
- 40 • The quality of life form must be filled in before the clinical examination, and thus before the
41 discussion with the examining doctor which may provide favourable or unfavourable information
42 about the disease's status.
- 43 • When supplying the form to the patient, it is important to explain how to fill it in without going into
44 details about the contents of the questions.
- 45 • After the form has been returned, check that the patient has answered all the questions and ask
46 her to reply to any questions she has skipped.
- 47 • The quality of life questionnaires must be filled in using a black or blue pen.”⁹³
48

49 **Trial group: National Cancer Institute of Canada Clinical Trials Group (NCIC CTG)**

50 **Trial name: A double blind randomization to Letrozole or placebo for women previously**
51 **diagnosed with primary breast cancer completing five years of adjuvant aromatase inhibitor**
52 **either as initial therapy or after Tamoxifen (including those in the MA.17 Study) (NCIC CTG:**
53 **MA.17R)**
54

55 **PRO endpoints: 2°**
56

57 “4.9 Quality of Life

58 Mandatory for NCIC CTG centres and optional for centers within other cooperative groups:
59 Patient is able (i.e. sufficiently fluent) and willing to complete the two quality of life questionnaires in
60 either English or French. The baseline assessment must have been completed prior to randomization.

1
2
3 Inability (illiteracy in English or French, loss of sight, or other equivalent reason) to complete
4 questionnaires will not make the patient ineligible for the study. However ability but unwillingness to
5 complete the questionnaires will make the patient ineligible.”⁹⁴
6
7

8 **Explanation**

9

10 Missing PRO data are a particular problem because data cannot be obtained
11 retrospectively or from medical records. Missing PRO data may arise from different
12 sources⁹⁵ and, broadly speaking, missing data can be attributed to causes that are
13 unavoidable or avoidable. Unavoidable reasons may include if a participant has died
14 or become too unwell to self-complete PRO instruments. Avoidable reasons may
15 include some type of human error that could have been prevented. Examples of
16 avoidable missing data include: staff failing to hand out a scheduled questionnaire; a
17 participant not realising the questionnaire is double-sided so missing half of the
18 questions; an electronic PRO device not being charged; the internet or server being
19 down; or when the PRO assessment is overly burdensome on the patient (e.g. due
20 to the burden of multiple questionnaires at one time or repetitive scales) so the
21 patient decides not to complete it.
22
23
24

25 Although “unavoidable” types of missing data are more challenging for interpretation
26 because the missing data may be related to the measured outcome and it is
27 impossible to accurately calculate the extent of any associated bias,^{96 97} avoidable
28 types of missing data are also problematic.²⁹ Avoidable missing PRO data
29 compromise the interpretability, accuracy and value of PRO findings because study
30 power is reduced, which increases the risk of type 2 errors,⁹⁶ and because any
31 assumptions made during the analysis about missing PRO values are not
32 verifiable.⁹⁸
33
34

35 There are a range of design, implementation, and reporting strategies to help
36 minimise and address missing PRO data,²⁹ most of which can be addressed in the
37 trial protocol. Specific recommendations related to data collection and management
38 include: refraining from administering an excessive number of questionnaires to
39 participants (researchers should refrain from collecting more data than they really
40 need), using standardised and documented PRO administration procedures,
41 engaging and educating participants in the trial by providing updates or incentives,
42 maintaining participant records, employing active quality assurance measures (such
43 as real-time compliance/completion monitoring, sending reminders for upcoming or
44 missed assessments, checking completed questionnaires for missing items while the
45 participant is still present at clinic), appointing a dedicated staff member responsible
46 for PRO assessment at each centre, training staff about the importance of PROs as
47 well as procedures for assessment, offering an alternative mode of administration if
48 the participant is not able to complete the questionnaire via the primary mode (e.g.
49 completing the questionnaire over the phone if the hardcopy cannot be completed at
50 the clinic within the acceptable time window) and recording reasons for missed
51 assessments using standardised forms.²⁹ From a regulatory perspective, the FDA
52 encourages maintaining consistency in assessment methods, however, this should
53 be balanced with reduction of missing data. If different modes are used, they should
54 be justified and presented in the study documentation.⁹⁹ If different modes are used
55 “FDA will review the comparability of data obtained when using multiple data
56 collection methods or administration modes within a single clinical trial to determine
57
58
59
60

whether the treatment effect varies by method or mode”.⁶⁹ Additional strategies are described in the full review.²⁹

The MITO-2 and MA.17R examples above illustrate some of these strategies. MA.17R comes from the Canadian Cancer Trials Group (CCTG), a multi-centre cooperative oncology group that conducts clinical trials in cancer therapy, supportive care and prevention. The CCTG requires completion of the PRO questionnaire(s) as a pre-randomisation eligibility requirement (as per SPIRIT-10-PRO Extension). This flags the importance of PRO data to investigators and clinical research associates, indicating PROs are as important as other inclusion clinical criteria. It also helps to maximize compliance.

Our prior work suggests that few trials actively specify such procedures in their protocols; 46.7% HTA protocols³ and 38.5% of international ovarian cancer trials⁴ included strategies to minimise 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.

Examples

Trial name: A multi-centre, open-label, randomised, two-arm Phase III trial on the effect on progression free survival of bevacizumab plus chemotherapy versus chemotherapy alone in patients with platinum-resistant, epithelial ovarian, fallopian tube or primary peritoneal cancer (AURELIA)

PRO endpoints: 2°

AURELIA was a multi-centre, open-label, randomised, two-arm Phase III trial of bevacizumab plus chemotherapy versus chemotherapy alone in patients with platinum-resistant, epithelial ovarian, fallopian tube or primary peritoneal cancer [Reference]. The primary endpoint was progression-free survival (PFS); quality of life was a secondary endpoint. The protocol stated that:

“Upon clear evidence of disease progression (PD) or toxicity, study therapy should be discontinued permanently.”

The protocol also specified post-progression treatment options: women who had been on the chemotherapy alone arm would have the option of bevacizumab alone or standard of care, while those who had been on the chemotherapy plus bevacizumab arm would receive standard of care treatment. The protocol stated that:

“In case the patient decides to prematurely discontinue study treatment (“refuses treatment”), she should be asked if she can still be contacted for further information.” and that “After PD, patients will be followed for survival only.”

However, it lacked an explicit statement about PRO assessment post-progression, which may explain some inconsistency among sites, with some sites collecting PRO data post-progression, and other not.

As stated in the AURELIA PRO paper (*ref, p1310*), “Only questionnaires completed until PD were included in the main analyses. Questionnaires completed after PD were excluded based on the medical assumption that these patients were unlikely to be benefiting from their study treatment, may

1
2
3 have been receiving another treatment, and were therefore not relevant to the intended comparison of
4 chemotherapy alone versus bevacizumab plus chemotherapy. However, post hoc sensitivity analyses
5 were performed to determine the impact of questionnaires completed after PD.” The latter analyses
6 were consistent with the main analyses, but could perhaps have been avoided, and patients saved
7 unnecessary HRQL assessment burden, if the protocol has contained a clear statement that HRQL
8 assessments should cease at disease progression.¹⁰⁰
9

10
11
12 **Trial group: Australasian Leukaemia & Lymphoma Group (ALLG); Trial name: BLAM- A phase**
13 **IIb study of Blinatumomab + Cytarabine (AraC) and Methotrexate in adult B-precursor Acute**
14 **Lymphoblastic Leukaemia (ALLG ALL8)**
15

16 **PRO endpoints: 2°**

17
18 ALLG ALL8 is a BLAM-A phase IIb study of Blinatumomab + Cytarabine (AraC) and Methotrexate in
19 adult B-precursor Acute Lymphoblastic Leukaemia (B-ALL). It is a single-arm study which aims to
20 demonstrate preliminary evidence of the benefit of frontline Blinatumomab in combination with
21 Cytarabine and Methotrexate in adult B-ALL, and to demonstrate the ability of this combination to
22 attain deep (MRDnegative) remissions and hence to reduce the need for allogeneic stem cell
23 transplantation. The ALLG ALL8 protocol specifies that the decision for allogeneic stem cell
24 transplantation is left up to the investigator, and that patients who proceed to allogeneic stem cell
25 transplant discontinue the assigned intervention protocol. Being recommended for allogeneic stem
26 cell transplant is therefore a withdrawal criteria. However, patients do not have to withdraw – it is
27 optional, the patient’s choice. The trial team is in fact interested in the experience of patients who
28 proceed to allogeneic stem cell transplant. So the protocol states:
29

30 “Subjects who proceed to allogeneic stem cell transplant who have not withdrawn consent to the
31 study should have FACT-Leu (HRQL questionnaire) assessments performed 6-monthly.”
32

33 This provides the trial team with the opportunity to document the experience of patients who proceed
34 to allogeneic stem cell transplant in terms of the range of common symptoms and aspects of well-
35 being assessed by FACT-Leu.¹⁰¹
36

37 **Explanation**

38
39 A clear plan for collection of PROs for trial participants who withdraw early from a
40 study or who discontinue the intervention helps minimize bias,¹⁰² ensures that staff
41 collect all required PRO data in a standardized and timely way, and may assist
42 ethical appraisal of the study.^{10 102}
43

44
45 Often, participants can provide valuable PRO data even after stopping the assigned
46 intervention protocol, whether due to personal choice and/or clinical
47 recommendation, as illustrated in the one-arm phase II trial ALLG ALL8 trial.
48 However, this does not hold in all contexts (as illustrated in the AURELIA trial), a
49 randomised phase III trial, in which participants whose cancer had progressed on
50 their assigned treatments, were then often switched to alternative treatment.
51

52
53 Providing a clear description of the process of PRO assessment for participants who
54 discontinue or deviate from the assigned intervention protocol and how the data will
55 be used, enables all staff to follow a standardised procedure to collect the required
56 PRO data in timely way, and to avoid collecting data that will not contribute to
57 analysis.
58
59
60

Correspondingly, the SAP should be clear on how such data will be handled. In the case where post-discontinuation/deviation PRO data are useful, the SAP should state the study objective that these data will address and how they will be analysed. Participants should also be aware of this process, so a simple and clear description of whether or not they will be asked to continue to complete PRO questionnaires after stopping or changing the treatment they were initially allocated to should be included in the participant information sheet (PIS).

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

Example

Trial name: A phase 3, randomized double-blind, placebo-controlled study of the efficacy and safety of 2 doses of Tofacitinib (Cp-690,550) in subjects with active psoriatic arthritis and an inadequate response to at least one TNF inhibitor (OPAL BEYOND)

PRO endpoints: 1°, 2°, exploratory

9.2.1. Analysis of Primary Endpoint

There are two primary endpoints in A3921125 and two doses of tofacitinib each of which will be compared to placebo for each endpoint. In order to control for Type I error a step-wise testing procedure will be used. This implies that a given endpoint for a given dose can only achieve significance if the prior endpoint is significant. The order of the fixed sequence for testing against placebo is as follows: tofacitinib 10mg ACR20 response rate at 3 months, tofacitinib 5mg ACR20 response rate at 3 months, tofacitinib 10mg HAQ-DI at 3 months, tofacitinib 5mg HAQ-DI at 3 months. This gate-keeping or step-down approach strongly protects the Type I error rate at the 0.05 (2-sided) level...

9.2.1.1. ACR20 Response

For all comparative analyses, the normal approximation for the difference in binomial proportions will be used to test the superiority of each dose of tofacitinib to placebo and to generate confidence intervals for the differences. The primary analysis will be ACR20 response rate at Month 3. The ACR20 response rate will also be analysed at other time points as a secondary analysis. Missing values due to a subject dropping from the study for any reason (e.g., lack of efficacy or adverse event) will be handled by setting the ACR20 value to nonresponsive.

9.2.1.2. HAQ-DI

The HAQ-DI score will be expressed as a change from baseline. The primary timepoint will be at Month 3. The analysis will be done using a repeated measure model that includes fixed effects of treatment, visit (Week 2, Months 1, 2 and 3), treatment by visit interaction, geographic location and baseline value. The model will use and fit an unstructured variance-covariance matrix. Full details will be listed in the analysis plan.

Additional analyses of the HAQ-DI will include a responder analysis at Month 3 where subjects with a change of 0.3 will be considered responders and subjects who dropped from the study will be considered nonresponsive. Another responder analysis will be conducted using a change of 0.35 at the cutpoint for response [Reference]. The normal approximation for the difference in binomial proportions will be used for these responder analyses.

9.2.2. Analysis of Secondary and other Endpoints

1
2
3 Key secondary efficacy variables are as follows: PASI75, enthesitis score, dactylitis severity score,
4 physical function domain of SF-36, and FACIT-F at Month 3. In order to strongly protect the study-
5 wise Type I error rate with respect to these key secondary endpoints and the primary endpoints, these
6 endpoints will be tested only if all endpoints/doses for the primary endpoints are statistically
7 significant. The order of testing is as listed above; for each endpoint, tofacitinib 10mg will be tested vs
8 placebo first, followed by tofacitinib 5mg. Testing stops at the first instance in which statistical
9 significance is not achieved...

10
11 Methods for analysing all other endpoints will be enumerated in the statistical analysis plan. Briefly,
12 binary variables (e.g., remission rates) will follow the analyses described above for binary variables
13 (e.g., ACR20) and continuous endpoints will follow the same type of analyses described above for
14 continuous endpoints (e.g., HAQ-DI). Descriptive statistics may also be calculated and displayed."¹⁰³

15 16 **Explanation**

17
18 Statistical analysis of multiple domains^{10 104} and time-points implies multiple
19 hypothesis testing, which inflates the probability of false-positive results (type I
20 error).⁴⁵ This can be contained by pre-specifying the key PRO domain(s) or overall
21 score of interest and the principal time-point(s) which cross-reference to SPIRIT-7-
22 PRO Extension and SPIRIT-12-PRO Extension.

23
24
25 Any plans to address multiplicity, such as stepwise or sequential analyses, whereby
26 multiple end points are tested in a defined sequence that contains the overall type I
27 error to the desired level, or conventional non-hierarchical methods (e.g. Bonferroni
28 correction), should be specified *a priori*.¹⁵ There are many strategies and/or choices
29 of methods that may be appropriate.¹⁰⁵ Family-wise type I error should be
30 considered for all of the applicable endpoints of the trials together and not for the
31 PRO endpoints separately. Some clinical trials include PROs as exploratory
32 endpoints and no adjustment is made for multiplicity in subscale scores administered
33 at multiple study visits. These analyses may only provide limited information on the
34 tolerability of the intervention.

35
36 Protocols should make some reference to key considerations for the analysis of the
37 trial PROs (including any plans for addressing multiple testing), but the detail is often
38 more appropriately included in the SAP, usually developed after the protocol. If no
39 adjustments for type I error are to be made, then this should be clearly stated.
40 However, clinical trial protocols in which PROs are secondary outcomes rarely
41 include any information about PRO statistical analyses, beyond any that are pre-
42 specified as primary or key secondary endpoints or when the sponsor is interested in
43 achieving a product label claim. Our review of trial protocols found that fewer than
44 2% provided information on the statistical analysis plans to address multiplicity for
45 the PRO endpoints.³

SPIRIT-20c-PRO Elaboration: State how missing data will be described and outline the methods for handling missing items or entire assessments (e.g., approach to imputation and sensitivity analyses).

Example

Trial group: European Organisation for Research and Treatment of Cancer-Gynaecological Cancer Group, and Gynecologic Cancer Intergroup (EORTC-GCG and GCIG)

Trial name: A randomised, multicentre, phase III study of Erlotinib versus observation in patients with no evidence of disease progression after first line, platinum-based chemotherapy for high-risk ovarian epithelial, primary peritoneal, or fallopian tube cancer (EORTC 55041)

PRO endpoints: 2°

“10.3.2 Compliance

Missing data may hamper assessment of HRQL in clinical trials. This may occur because centers do not collect the questionnaires at the appropriate time (unit non-response), and also because patients may not reply to questions within the questionnaires (item non-response). The latter problem occurs less than 2% on average and should not be a problem. The former problem will be minimized by ensuring that participating centers are properly informed and motivated towards HRQL assessment. During the study, compliance with completing HRQL questionnaires will be investigated at each time point. The compliance of the HRQL assessments will also be reviewed twice a year and will be a part of the descriptive report by the Data Center for the Group's plenary sessions and, if possible, be presented by the EORTC Quality of Life Group's appointed liaison person.

The compliance rate between the two arms will be compared at each time point using a chi-square test. In order to adjust for the multiplicity of the tests, a Bonferroni adjustment will be made by which each test will be performed at the 0.01 significance level. Should follow-up compliance levels drop below 60% at subsequent bi-annual compliance reviews, then the Protocol Writing Committee would review this to either improve compliance or consider terminating the HRQL assessment in the trial...

10.4.3 Missing data

When performing HRQL analyses complications may arise due to large quantities of missing data. This issue has a bearing on whether a valid comparison of the treatment arms is being made. In HRQL research there are two main types of missing data: (1) item non-response, (2) unit nonresponse (the whole questionnaire is missing for a patient). As item non-response occurs less than 2% on average in the QLQ-C30 it is not such a major problem and thus the methods described in the EORTC QLQ-C30 scoring manual for handling item non-response will be used. For missing questionnaires, it is necessary to identify both the extent of missing questionnaires and the main process of missing data. Three different types of missing data processes may exist: missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR, informative dropout mechanism). These have distinct consequences for data analysis [Reference]. If the missing data process is considered to be non-ignorable (MNAR) then quality of life will be compared between groups using longitudinal data modeling techniques (i.e. Proc mixed in SAS with either selection models or pattern-mixture models) in combination with a logistic regression for the dropout process. If the missing data mechanism can be considered ignorable (MAR), then standard longitudinal data analysis will be used (proc mixed in SAS). If the data are MCAR then complete case analysis can be used without biasing the results.”¹⁰⁶

Explanation

Most clinical trials with PROs will have some missing PRO data,⁹⁸ yet a review of protocols found that less than half outlined statistical methods to deal with missing PRO data.³

There are two types of missing PRO data: 1) missing items, when the participant completes some but not all of the questions within a PRO instrument, and 2) missing

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3 assessments, when the participant does not complete a scheduled assessment at all
4 (i.e. there are no PRO data available for analysis from the participant at that
5 assessment time point). The latter type is more serious, as it potentially affects the
6 choice of analysis method and the interpretation and generalisability of the results.
7 The trial protocol should explain how both types of missing data will be handled in
8 the analysis.
9

10
11 1) Handling missing items: many PRO scoring manuals provide guidance for
12 handling missing items. A common approach is to impute the mean score of the
13 completed items, if less than one-half of items comprising the scale are missing.¹⁰⁷
14 ¹⁰⁸ This approach is possible for multi-item scales but it is not possible to impute
15 scores for single item scales. Always consult the scoring manual to determine how to
16 handle missing items, and cite the manual in the protocol. Missing items of PRO
17 instruments that are underpinned by modern psychometrics techniques (Item
18 Response Theory or Rasch Measurement Theory) are naturally handled without
19 requiring imputation.^{33 109}
20
21

22
23 2) Handling missed assessments: missing assessments present a major problem for
24 PRO analyses; lead to a loss of power and wider confidence intervals from a lack of
25 precision,^{110 111} and potentially to biased results. The risk of bias depends on the
26 underlying cause of why data are missing (called the “missing data mechanism”),
27 and this in turn should influence the choice of statistical analysis methods.
28 In order to gain insights into the mechanism of missing PRO data, it is helpful to
29 ascertain and record reasons for missed PRO assessments during trial conduct. The
30 protocol needs to describe how these reasons will be collected in a standardised
31 manner. Typically a standard form is used (which can be included in the Appendix
32 along with the PRO questionnaires). Also, the form can be used to collect additional
33 data (referred to as “auxiliary data”) related to “missingness” or the PRO,²⁹ which
34 should be specified in the protocol.
35
36

37
38 The trial protocol should also provide a summary of how missing data will be
39 described and handled in the analysis,¹⁰ and state that comprehensive details about
40 the planned analysis will be provided in a subsequent SAP.¹¹² The SISAQOL
41 consortium have developed a taxonomy of research objectives that can be matched
42 with appropriate statistical methods for PRO analysis, standardised statistical
43 terminology relating to missing data, and are determining appropriate ways to
44 manage missing data, currently focused in an oncology setting. A simulation study
45 was done to assess whether it was possible to have a threshold to define substantial
46 missing data.¹¹³ Although no agreement was reached for a threshold, the simulation
47 study showed that the effect of missing data rates on PRO findings depends on the
48 type of missing data (i.e., informative or non-informative missing data). It was
49 recommended that collecting reasons for missing data is key in assessing the effect
50 of missing data for PRO findings.³³ Additionally, SISAQOL is developing a set of
51 macros to describe patterns of missing data, and to evaluate imputation methods for
52 use in sensitivity analysis.^{33 35 37}
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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 standardised way. Describe how this process will be explained to participants; e.g., in the participant information sheet and consent form.

Example

Trial name: The use of an electronic Patient-Reported Outcome Measure in the Management of Patients with Advanced Chronic Kidney Disease (RePROM)

PRO endpoints: 2°

Protocol:

"If, when reviewing the completed EQ-5D-5L questionnaire, the research nurse becomes concerned for the wellbeing of the participant, they should discuss their concerns with the participant directly, working in partnership to determine the best course of action. With the participant's permission, the research nurse may need to consult with the PI and/or treating clinician to address these concerns. In exceptional circumstances, the research nurse may consult with the PI and/or treating clinician without the permission of the participant if they are concerned for the participant's safety."

Patient information sheet:

"If the study research nurse becomes concerned for your wellbeing during a study review, they will discuss their concerns with you, to determine the best course of action. With your permission, the research nurse may need to consult with a senior member of the study and/or your treating clinician to address these concerns. In exceptional circumstances, the research nurse may need to do this without your prior permission if they are concerned for your safety."

Consent form:

"I understand that if the study research nurse becomes concerned for my wellbeing during a study review, they will discuss their concerns with me to determine the best course of action. With my permission, the research nurse may need to consult with a senior member of the study and/or my treating clinician to address these concerns. In exceptional circumstances, the research nurse may need to do this without my prior permission if they are concerned for my safety."¹¹⁴

Explanation

To protect participant safety, PRO data may be monitored during a study for signs of psychological distress or physical symptoms that may require an immediate response: so-called 'PRO Alerts'.¹¹⁵ Examples of PRO data that may raise concern include signs of psychological distress, poor physical well-being, or high symptom burden presenting as extreme scores on questionnaires. Concerns can also arise when additional information is provided by the participant (for example, through free text report), or in discussions between the participant and research staff.¹¹⁵ The nature of some studies may mean that participants are more at risk than in others. In studies where prior risk assessment deems the probability of PRO alerts being generated by participants to be minimal, PRO data may not be reviewed until the end of the trial for pragmatic reasons, however, concerning PRO data, may still arise during the course of the study.^{11 116} If monitoring is not planned this should be stated. If monitoring is planned, steps for how PRO alerts will be dealt with should be included in the trial protocol, to provide immediate reassurance to concerned trial staff about how to proceed and promote appropriate clinical management and transparency considering professional obligations to patient care. Any arising

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3 interventions should be recorded. Evidence suggests the absence of such
4 information leads to inconsistent handling of concerning data including administration
5 of non–prespecified interventions to aid the trial participant which risks co-
6 intervention bias i.e., bias caused by “any intervention other than the experimental
7 maneuver that alters the frequency of a trial’s outcome of interest”.^{12 116 117} Identifying
8 participants at risk and in need of urgent attention through PRO monitoring is an
9 ethical issue as is acknowledging that information identified in the completion of a
10 PRO too may be shared with the clinical team when the need arises. Information
11 about how the trial staff will respond to concerns, or alternative support mechanisms
12 where monitoring is not taking place, should be provided to participants (in
13 participant information and consent documentation). This information provided in the
14 patient information sheet (PIS) will manage participant expectations and ensure
15 transparent and explicit communication about the intended use of PRO study data in
16 fulfilment of contemporary data protection laws, for example, the European Union
17 General Data Protection Regulation.¹¹⁸

21
22 There is no regulatory requirement from the US FDA that PRO data measuring
23 symptomatic side effects be monitored and alerts for these items created. However,
24 it is good practice to remind participants at each PRO assessment whether their data
25 is or is not being monitored in real time. In the case PRO data are not being
26 monitored, participants should be reminded to speak to clinical staff if they are
27 experiencing a specific problem, symptom or side effect.

30 **Box Regulatory/HTA perspective**

32 Regulatory agencies, such as the MHRA, EMA and FDA are placing more focus on
33 capturing the patient experience when developing drugs.^{15 42 55 119} However poorly
34 defined PRO objectives have hindered the utility of PROs in regulatory decisions.
35 Accurate and well-defined PRO methods can provide the patients’ perspective on
36 the impact of a treatment on disease-related symptoms and symptomatic adverse
37 events. Efforts to improve PRO clinical trial standards are welcomed and the SPIRIT-
38 PRO extension provides an additional resource for drug developers to consider in
39 their development programmes. Alongside these guidelines and other regulatory
40 guidance documents, the importance of seeking early scientific advice directly from
41 the regulatory authorities and health technology assessment bodies such as NICE
42 cannot be understated, where advice can be given on the acceptability of a particular
43 approach. Therefore, raising PRO standards is key to the successful integration of
44 PROs in drug development programmes, ensuring that the impact of medicines on a
45 disease can be captured from the patient’s perspectives.

51 **Box Patient perspective**

52
53 What is the question that doctors and nurses ask their patients more than any other?
54 “How are you feeling?” That is why we need PROs in clinical research. They allow
55 patients to answer that question in a systematic and measurable way, which will
56 benefit others and from which we may well benefit ourselves at some point.
57 For patients, including PROs in health and social care research studies is vital in
58 assessing whether or not our health and/or wellbeing are improving. Well-designed
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3 PRO instruments will help assess our general health and emotional mood, our ability
4 to complete our daily tasks, and our self-measured levels of pain and/or fatigue.
5 PROs are very different from the clinical measures used to assess the effectiveness
6 of new drugs or other treatments, yet for us, it is the PROs that measure “tolerability”
7 and thus the real-life “effectiveness” of the drug or intervention as a medicine or
8 treatment.
9

10
11 The ultimate measure of the performance of any health service must be in whether
12 or not it helps people recover from an acute illness, live well with a chronic condition,
13 and face the end of life with dignity—and people's own reports on their own condition
14 are the only valid way to gauge success. So if a drug or treatment is to be trialled for
15 use in health-care delivery, it is essential that PROs are included in the success
16 criteria.
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18
19 It is equally essential therefore that participants on the study understand the
20 importance of completing PRO assessments and to understand how and why the
21 data is collected. This should not be too onerous for researchers to explain to
22 patients. Patients who choose to participate in clinical trials do so because they wish
23 to benefit others and if possible, to benefit themselves. PROs are a means of doing
24 both – provided that the reporting and recording are not too much of a burden. ‘We
25 must do all that we can to make patient-reported outcome assessment feasible and
26 credible. If we fail in our task we will have left out the heart of all health-care
27 research: the patient.’¹²⁰
28
29

30
31 And when we do complete our PROs on your research study, please let us know
32 what happens to the study, what you know now that you didn't know before, and how
33 that will be used to help people. Because that's why we participate in research; it's to
34 help people like us.
35

36 **Protocol template**

37
38 The PRO protocol template [\[journal to link to template\]](#) aims to support protocol
39 writing for pharmaceutical companies, funders, clinicians and international trials
40 groups by providing PRO content that can be incorporated directly into the relevant
41 sections of existing clinical trial protocols or retained as a dedicated PRO section
42 within the protocol.
43
44

45 **Supplementary Trial Documents**

46
47 Supplement 2 outlines additional items recommended for inclusion in other trial
48 documentation, such as the SAP, participant information sheet, and training and
49 guidance documents for staff.^{10 121} This is not an exhaustive list and further PRO
50 content may be warranted in training materials and patient facing documents
51 dependant on the trial. We recommend input from PRO experts working in
52 conjunction with the clinical team, trials unit, or Contract Research Organisation
53 (CRO) and patient partners involved in the co-design of research with regulatory
54 input as required to optimise the protocol and supplementary resources.
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57 **Discussion**

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3 This paper provides a detailed rationale, implementation instructions and real-world
4 examples to assist investigators to develop the PRO-specific components of clinical
5 trial protocols, in accordance with the 16 items of the SPIRIT-PRO Extension. This
6 SPIRIT-PRO Extension E&E paper is recommended for use alongside the original
7 SPIRIT 2013 and SPIRIT-PRO guidelines.^{1 2 10} The mission of the SPIRIT-PRO
8 Group is to improve the design and standardisation of PRO components of clinical
9 trials and thereby ensure high-quality PRO data to inform patient-centered care. To
10 further facilitate uptake of the SPIRIT-PRO items, we have provided a PRO-specific
11 protocol template covering all the SPIRIT-PRO items. This can be used in two ways:
12 either incorporated item-by-item into relevant sections of existing clinical trial
13 protocols or retained whole as a dedicated PRO section within a trial protocol. The
14 use of a template should support investigators to address all required SPIRIT-PRO
15 checklist items comprehensively and meaningfully, in conjunction with the real-world
16 examples provided for each SPIRIT-PRO item in this manuscript.
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21 The overall aim of the SPIRIT-PRO Extension and E&E is to improve the
22 completeness, quality and transparency of PRO sections of clinical trial protocols,
23 where PROs are a primary or key secondary outcome. We also recommend use of
24 the guidelines to support development of protocols where PROs data are exploratory
25 in nature, including single-arm trials with PRO endpoints. Many of the SPIRIT-PRO
26 items may also provide useful prompts about PRO content for cohort studies and
27 other non-randomised designs. The SPIRIT-PRO guidelines,¹⁰ and E&E paper aim
28 to facilitate development of high quality PRO protocol content, which will ultimately
29 also facilitate the review of protocols by research ethics committees/IRBs, scientific
30 review groups, and funders. Improved PRO protocol content has been associated
31 with more complete reporting which will help facilitate the critical appraisal of final
32 trial reports and results³ and use of PRO data to inform patient-centered care.
33 Several SPIRIT-PRO items correspond to items on the CONSORT (Consolidated
34 Standards of Reporting Trials) -PRO checklist.^{10 18} This is particularly important since
35 reviews of PRO reporting indicate that, where published PRO trial data were
36 available, there was often considerable delay between publication of primary
37 outcomes and the PRO results and standards of reporting were poor.^{4 5 7 9 122-125}
38 Worryingly, a recent review of cancer trials suggested that 49,568 participants were
39 involved in studies that failed to publish their PRO data and that poor reporting was
40 associated with suboptimal PRO protocol content.⁹ This finding is consistent with
41 findings from Schandelmaier et al. which demonstrated that 52% of cancer trials
42 specified HRQL outcomes in their protocols, however, only 20% reported any HRQL
43 data in associated publications.¹²² Non-reporting of PRO findings is widespread,^{7 9}
44 ¹²²⁻¹³⁰ meaning patient-centred information may not be available to benefit patients,
45 clinicians, and regulators. Non-reporting of these important patient data is unethical
46 and is a waste of limited health-care research resources.¹³¹⁻¹³³ In the EU Clinical
47 Trials Regulation (536/2014) there will be a requirement for results of all primary
48 endpoint and patient relevant secondary endpoints to be reported within 12 months
49 of the end of the study.¹³⁴ The provision of a protocol template alongside example
50 excerpts from trial protocols will help facilitate protocol developers understand how to
51 write high quality PRO protocol content and support more complete reporting of
52 results.
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58 In a companion paper,¹³⁵ we also present tools for patient advocates involved in the
59 co-design of trial protocols or the review of protocols through roles on ethics
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3 committees or funding committees with PRO endpoints to further optimise study
4 design and facilitate patient involvement. It is essential that patients' experiences,
5 perspectives, needs, and priorities are captured and meaningfully incorporated. The
6 SPIRIT-PRO Group and regulatory agencies strongly support the early and
7 continued involvement of patients and members of the public in trial design and
8 conduct.^{119 136}
9

10
11 The next steps for the SPIRIT-PRO Initiative are to promote uptake and use of the
12 guidelines and implementation tools and development of ethical guidelines for
13 institutional review boards and ethics committees. The SPIRIT website (www.spirit-statement.org)
14 and PROlearn, a free resource on the optimal use of PROs in
15 research and routine practice (www.bham.ac.uk/prolearn) provides the latest
16 resources and information on the initiative, including a list of supporters. We invite
17 international stakeholders to assist in the evaluation of the SPIRIT Statement and
18 E&E paper by using the documents and providing feedback to inform future
19 revisions.
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22
23 SPIRIT-PRO forms part of a growing toolbox to promote the optimal use of PROs in
24 trials including guidance for the selection of measures,⁶¹ design (SPIRIT-PRO),¹⁰
25 analysis (SISAQOL),³³ reporting (CONSORT-PRO),¹³ and presentation of results
26 (Figure 5).¹³⁷⁻¹³⁹ These tools are currently being disseminated by the PROTEUS
27 Consortium (Patient-Reported Outcomes Tools: Engaging Users & Stakeholders)
28 who aim to partner with key patient, clinician, research, and regulatory groups
29 around the world to promote the uptake and use of these methodologic tools to
30 optimise the assessment and reporting of PROs in clinical trials
31 (<https://more.bham.ac.uk/proteus/>). Patient and public involvement in all of these
32 activities can help ensure that PRO selection, study implementation and application
33 is transparent, relevant, and acceptable. Consistent with this philosophy, patient
34 partners have been involved in all aspects of the development of the SPIRIT-PRO
35 Extension.^{10 140 141}
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38 **Figure 5 Resources to promote high quality PRO trial design, analysis and** 39 **dissemination**⁹ 40 41

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45 Through widespread uptake and support, the potential to improve the completeness
46 and quality of trial protocols and the efficiency of their review can be fully realised.
47 Ultimately, high-quality PRO results can help ensure that important patient-centred
48 evidence on the efficacy, safety and tolerability of interventions is available to inform
49 shared decision making, labelling claims, clinical guidelines, and health policy.
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In memory of Doug Altman (1948-2018), statistician, pioneer, luminary. “To maximise the benefit to society, you need to not just do research, but do it well”.

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Concept and design: MJ Calvert, MT King.

Acquisition, analysis, or interpretation of data: MJ Calvert, MT King, R Mercieca-Bebber, OL Aiyegbusi, D Kyte, A Slade, A-W Chan, E Basch, JA Bell, AV Bennett, V Bhatnagar, J Blazeby, A Bottomley, J Brown, M Brundage, L Campbell, JC Cappelleri, H Draper, A Dueck, C Ells, L Frank, RM Golub, I Griebisch, K Haywood, BL King-Kallimanis, L Martin, S Mitchell, T Morel, L Nelson, JM Norquist, D O’Connor, MJ Palmer, D Patrick, G Price, A Regnault, A Retzer, D Revicki, J Scott, R Stephens, G Turner, A Valakas, G Velikova, M von Hildebrand, A Walker, L Wenzel.

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Data sharing

References to protocols available in the public domain are provided. Permissions to access unpublished protocols may be sought via request to Melanie Calvert: m.calvert@bham.ac.uk. Requests will be forwarded to the relevant research team for consideration.

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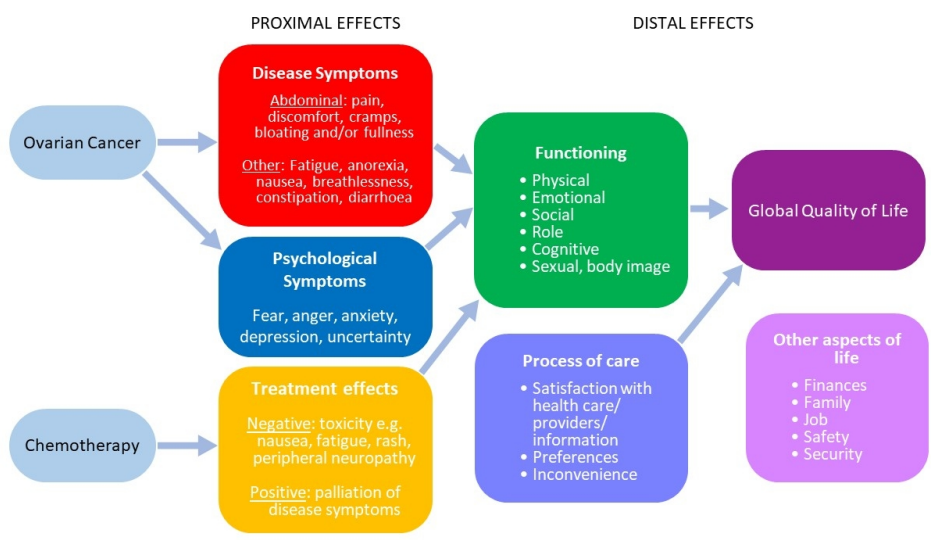


Figure 1 Proximal and distal effects of therapy on patient symptoms and quality of life adapted from Wilson and Cleary, 1995.

338x190mm (96 x 96 DPI)

PRO endpoints: 1°, 2°

Assessment Time Point	Beginning of Acceptable time limit	End of Acceptable time limit
1. Pre-Registration	Date of signing consent	Date patient made aware of treatment arm to which they have been assigned
2. Pre-Treatment	Date patient made aware of treatment arm to which they have been assigned	Date of first radiation dose
3. During Treatment	Day of treatment	Before next treatment (eg If patient given QOL form on Monday then QOL should be completed before treatment on Tuesday)
4. End of Treatment	Date of last treatment	Five days after last treatment
5. Two weeks after end of treatment	1 week after end of treatment	3 weeks after end of treatment
6. Six weeks after end of treatment	Five weeks after end of treatment	Eight weeks after end of treatment
7. Three months after end of treatment	Nine weeks after end of treatment	Eighteen weeks after end of treatment
8. Six months after end of treatment	Five months after end of treatment	Nine months after end of treatment

Figure 2 Example schedule of PRO assessments in the TROG 11.03 P-Lung GP Trial

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Visits(a)	Patients involved	Screening	Post (+/-) chemo pre (+/-) RT	Post (+/-) RT	1 yr	2 yr	3 yr	4 yr	5 yr	6 yr	7 yr	8 yr	9 yr	10 yr	Recurrence ²
					Baseline 1	2	3	4	5	6	7	8	9	10	11
Investigations															
Informed consent	All	X													
Medical history & examination (b)	All	X		X	X	X	X	X	X	X	X	X	X	X	X
Staging tests	All	X													
Contralateral mammography	All	X			A mammogram of the opposite breast, if appropriate, is recommended at least in alternate years for 10 years from the date of mastectomy										
Blood sampling	If consented to TRANS-SUPREMO	X													X
Tumour paraffin block from primary tumour ¹	All	X													
Tumour paraffin block at recurrence if available ²	All														X
Acute/ Late morbidity ³	All			X	X	X	X	X	X	X	X	X	X	X	X
Cardiac symptoms and examination	If consented to cardiac sub study	X	X ⁴	X	X				X					X	X
Blood sampling for BNP	If consented to cardiac sub study	X	X ⁴	X	X				X					X	X
Electrocardiogram	If consented to cardiac sub study	X			X ⁵				X ⁵					X	X ⁵
Echocardiogram (c)	If consented to cardiac sub study	X			X ⁵				X ⁵					X	X ⁵
QOL and EQ5D economic assessment (d)	If consented to QOL sub study	X			X	X			X					X	

(a) Patients in the control arm MUST follow the same follow up schedule as irradiated patients.
 (i) The only exception are patients in the cardiac sub study who receive chemotherapy. This is the only group of patients who must attend a post chemotherapy visit.
 (ii) For patients receiving chemotherapy, follow up will be on completion of radiotherapy or at 3 months after chemotherapy in non-irradiated patients.
 For patients not receiving chemotherapy follow up will be on completion of radiotherapy or at 3 months after surgery in non-irradiated patients.
 (b) Questioning for symptoms of recurrent breast cancer, examination of loco-regional area and other relevant clinical areas for evidence of recurrence depending on clinical features.
 (c) In centres where isotope ventriculography is the standard examination for patients requiring anthracycline containing chemotherapy, an echocardiogram will also be required at baseline. Echocardiography will be used for all subsequent time points in the study.
 (d) Baseline (pre randomisation) quality of life assessment will be conducted in the clinic. All subsequent quality of life assessment questionnaires will be mailed to the patient.

Final protocol version 29- 30th August 20

Figure 3 Example schedule of PRO assessments in the MRC SUPREMO TRIAL (BIG 2-04)

141x96mm (144 x 144 DPI)

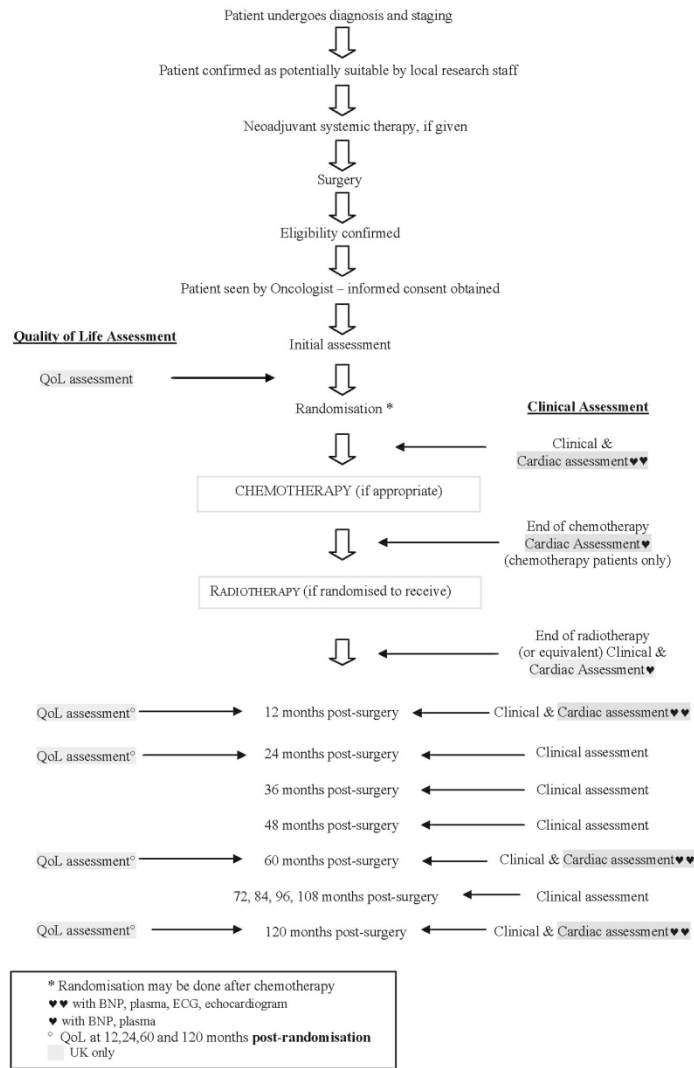


Figure 4 Flow diagram schedule of PRO assessments in the MRC SUPREMO TRIAL (BIG 2-04)

210x297mm (200 x 200 DPI)

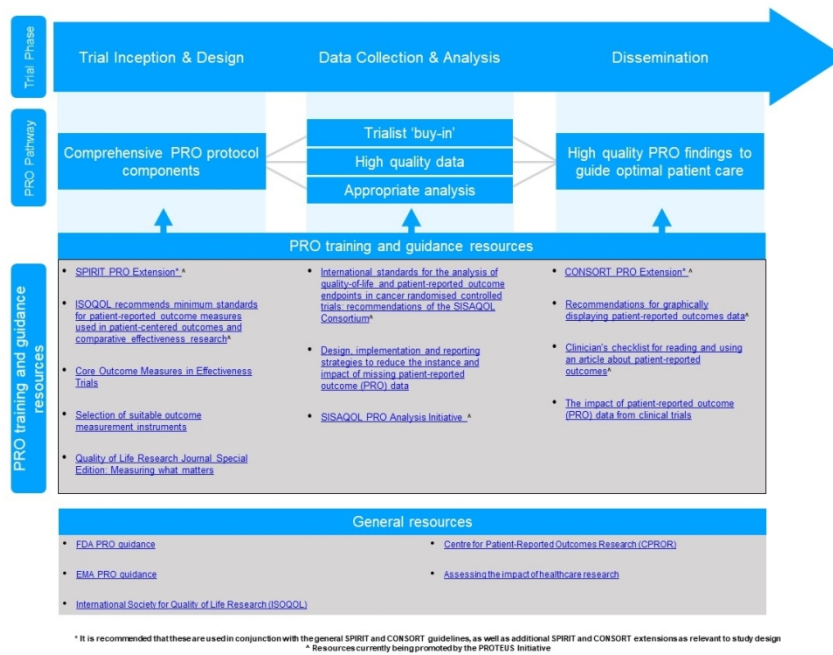


Figure 5 Resources to promote high quality PRO trial design, analysis and dissemination

361x270mm (96 x 96 DPI)

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8 **SPIRIT-PRO**
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11 **PROtocol Template**
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For peer review only

About this PROtocol Template

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

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

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

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

Journal to add E&E paper reference please

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

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

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

Protocol writers can confirm that they have successfully adhered to the SPIRIT-PRO guideline using the checklist available here:

<https://jamanetwork.com/journals/jama/article-abstract/2671472>

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

References and useful resources:

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

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200-207.

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

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

Estimands

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

E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). October 2017.
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Akacha M, Bretz F, Ruberg S. Estimands in clinical trials - broadening the perspective. *Stat Med*. 2017;36(1):5-19.

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

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

Patient Reported adverse events

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

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

Tolerability

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

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

Analysis

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

<https://event.eortc.org/sisaqol/>

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Title page

PRO content author:

Affiliation(s), telephone:

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

Explanation: Providing information (e.g. name, affiliation, contact details) on who wrote the PRO-specific aspects of the trial protocol promotes transparency and accountability and identifies the appropriate point of contact for resolution of any PRO specific queries. When patients have actively contributed to this process, this should be documented as per recent guidance for the reporting of patient and public involvement.⁷

Additional notes: The PRO author should be part of the protocol writing committee. The trial study coordinator should ensure that PROs are harmonized with all the other clinical endpoints.

1. Protocol Summary

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

1.3. Schedule of Activities (SoA)

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

Additional notes: *The PRO schedule of assessments should be summarised in a table alongside all other trial assessments to provide trial staff with a single point of reference. Ideally PRO assessments should appear in the table in the order which assessments will take place. If more than one PRO measure is being used, each may be specified on a separate line if they are administered at different time points.*

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

2. Introduction

2.1. Study Rationale

2.1.1. Summary of PRO-specific rationale

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

Additional note: As with other clinical information, the PRO-specific rationale should be summarized here and detailed information including summary of PRO findings in relevant studies should be provided in Section 4.2. Scientific Rationale for Study Design or in the PRO-specific section 8.1.

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

3. Objectives and Endpoints

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

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

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

Specify the PRO endpoint: the concepts/domains used to evaluate the intervention (e.g., overall health-related quality of life, specific domain, specific symptom) and, for each one, the analysis metric (e.g., change from baseline, final value, time to event) and the principal time point or period of interest. (SPIRIT-12-PRO Extension)

Additional note: Utility measures (e.g. EQ-5D) that inform cost-utility evaluations should also be included here.

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

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

4. Study Design

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

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

Additional notes: Detailed information should be provided here. Information not provided in Section 2.1.1. Summary of PRO-specific rationale should be presented here. Indicate how PRO evaluation aligns with the overall trial design, so it addresses the research objectives.

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

5. Study Population

Specify any PRO-specific eligibility criteria (e.g., language/reading requirements or pre-randomization¹ completion of PRO). (SPIRIT-10-PRO Extension)

If PROs will not be collected from the entire study sample, provide a rationale and describe the method for obtaining the PRO subsample. (SPIRIT-10-PRO Extension)

Additional notes: Efforts should be made to provide translated PRO versions where needed to promote inclusivity in PRO completion. Specify reasons if translated versions are not provided and certain populations are excluded. PRO-specific eligibility criteria should be included alongside other eligibility criteria to ensure research personnel have a single point of information.

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

6. Study Intervention

6.1. PRO capture method involving a medical device

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

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

7.1. Discontinuation of Study Intervention

Describe the process of PRO assessment for participants who discontinue or deviate from the assigned intervention protocol. (SPIRIT-18b (ii)-PRO Elaboration)

Additional note: Participants who withdraw from the study should be provided pre-paid packaging to return PRO assessments and ePRO devices if applicable.

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

8. Study Assessments and Procedures

8.1. Efficacy Assessments

8.1.1. Patient Reported Outcomes

Specify the PRO Hypotheses (SPIRIT-7-PRO Extension)

Additional note: Also specify whether the objective is to support superiority, equivalence or non-inferiority.

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

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

Additional note: Interpretation guidelines should include reference to pre-defined clinical relevance thresholds, preferably specific to the PRO population.

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

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

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

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

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Include a data collection plan outlining the permitted mode(s) of administration (e.g., paper, telephone, electronic, other) and setting (e.g., clinic, home, other). (SPIRIT-18a (ii)-PRO Extension)

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

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

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

Additional notes: Signpost to statistical analysis plan (SAP) as required. Collect reasons for missed PRO assessments during the trial. These could be documented in the case report forms (CRF). SISAQOL, CONSORT-PRO Extension and PROTEUS may be consulted for further guidance on missing data.^{2 4 5}

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

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

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

When the trial context requires someone other than a trial participant to answer on his or her behalf (a proxy-reported outcome), state and justify the use of a proxy respondent. Provide or cite evidence of the validity of proxy assessment if available. (SPIRIT-18a (iv)-PRO Extension)

Additional note: If a proxy reporting is used, this should ideally be the same person throughout the trial.

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

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

8.2. Safety Assessments

8.2.1 Monitoring of PRO data

State whether or not PRO data will be monitored during the study to inform the clinical care of individual trial participants and, if so, how this will be managed in a standardized way. Describe how this process will be explained to participants; e.g., in the participant information sheet and consent form. (SPIRIT-22-PRO Extension)

Additional note: *If PROs are used in place of or as an add-on to standard solicited AE recording (at visits/phone calls the investigators asks if there have been any problems since last visit) they should be recognised as part of the safety monitoring procedures of the trial.*

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

9. Statistical considerations

When a PRO is the primary end point, state the required sample size (and how it was determined) and recruitment target (accounting for expected loss to follow-up). If sample size is not established based on the PRO end point, then discuss the power of the principal PRO analyses. (SPIRIT-14-PRO Elaboration)

Additional note: *Enough information on secondary, tertiary and even exploratory PRO endpoints should be provided to justify their inclusion.*

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

9.1. Statistical analyses

State PRO analysis methods, including any plans for addressing multiplicity/type I (α) error. (SPIRIT-20a-PRO Elaboration)

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

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

9.1.1. Missing PRO data

State how missing data will be described and outline the methods for handling missing items or entire assessments (e.g., approach to imputation and sensitivity analyses). (SPIRIT-20c-PRO Elaboration)

Additional notes: *State whether PRO data is missing at the item level or at entire PRO assessment level and whether intermittent or lost to follow-up. In addition, state how missing PRO data is recorded and categorised. SISAQOL recommendations may be consulted for further guidance on missing data.⁴*

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

9.1.2. Other Analyse(s)

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

10. Supporting Documentation and Operational Considerations

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

10.1.1. Publication Policy

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

Note: *Whilst not a formal recommendation in the SPIRIT-PRO guidance, it is regarded as good practice to include, depending on the mode of administration, paper copies of PRO or screenshots of ePRO instruments.*

All copyrights and version information should be clearly showing in the appended PRO instruments with due acknowledgment for PROs requiring permission for use.

10.2. Appendix Copies of PROs

Glossary

Concept: “The specific measurement goal (i.e., the thing that is to be measured by a PRO instrument). In clinical trials, a PRO instrument can be used to measure the effect of a medical intervention on one or more concepts. PRO concepts represent aspects of how patients function or feel related to a health condition or its treatment.”²⁴

Domain: “A sub concept represented by a score of an instrument that measures a larger concept comprised of multiple domains. For example, psychological function is a larger concept with multiple domains (emotional and cognitive function) that are measured by relevant items.”²⁴

Endpoint*: the variable to be analysed. It is a precisely defined variable intended to reflect an outcome of interest that is statistically analysed to address a particular research question. A precise definition of an endpoint typically specifies the type of assessments made, the timing of those assessments, the assessment tools used, and possibly other details, as applicable, such as how multiple assessments within an individual are to be combined²⁵ (e.g. change from baseline at 6 weeks in mean fatigue score).²⁶

Health-related quality of life: “a multidimensional concept that usually includes self-report of the way in which physical, emotional, social, or other domains of well-being are affected by a disease or its treatment”²⁷

Important or key secondary PROs/end points: Some PRO measures (particularly health-related quality-of-life measures) are multidimensional, producing several domain-specific outcome scales; e.g., pain, fatigue, physical function, psychological distress. For any particular trial, it is likely that a particular PRO or PRO domain(s) will be more relevant than others, reflecting the expected effect(s) of the trial intervention(s) in the target patient population. These relevant PRO(s) and/or domain(s) may additionally constitute the important or key secondary PROs (identified a priori and specified as such in the trial protocol and statistical analysis plan) and will be the focus of hypothesis testing. In a regulatory environment, these outcomes may support a labelling claim. Because these outcomes are linked with hypotheses (CONSORT PRO Extension 2b),²⁷ they may be subject to P-value adjustment (or “ α spending”). Beyond efficacy/effectiveness, PROs may also be used to capture and provide evidence of safety and tolerability (e.g. using the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™))²⁸

Instrument: “A means to capture data (e.g., a questionnaire) plus all the information and documentation that supports its use. Generally, that includes clearly defined methods and instructions for administration or responding, a standard format for data collection, and well-documented methods for scoring, analysis, and interpretation of results in the target patient population.”²⁴

Intervention/treatment: A process or action that is the focus of a clinical study. Interventions include drugs, medical devices, procedures, vaccines, and other products that are either investigational or already available. Interventions can also include non-invasive approaches, such as education or modifying diet and exercise.²⁹

Item: “an individual question, statement, or task (and its standardized response options) that is evaluated by the patient to address a particular concept”²⁴

Observer-reported outcome: “a measurement based on a report of observable signs, events or behaviours related to a patient’s health condition by someone other than the patient or a health care professional”.³⁰

Outcome*: the variable to be measured. It is the measurable characteristic that is influenced or affected by an individual’s baseline state or an intervention as in a clinical trial or other exposure²⁵ (e.g. a fatigue score).

Patient-reported outcome (PRO): A PRO is any report of the status of a patient’s health condition that comes directly from the patient, without interpretation of the patient’s response by a clinician or anyone else and may include patient assessments of health status, quality

of life, or symptoms.^{24 27} PROs are assessed by self-reported questionnaires, referred to as PRO measures (PROMs) or instruments.²⁵

Primary outcome: the most important outcome in a trial, pre-specified in the protocol, providing the most clinically relevant evidence directly related to the primary objective of the trial.

Proxy-reported outcome: “a measurement based on a report by someone other than the patient reporting as if he or she is the patient”²⁴

Secondary outcomes: outcomes pre-specified in the protocol to assess additional effects of the intervention; some PROs may be identified as important or key secondary outcomes

SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials.^{31 32}

SPIRIT Elaboration item: an elaboration of an existing SPIRIT item as applied to a specific context; in this instance, as applied to clinical trials assessing PROs

SPIRIT-PRO Extension item: an additional checklist item describing PRO protocol content to address an aspect of PRO assessment that is not adequately covered by SPIRIT, as judged by available evidence and expert opinion

Time window: a predefined time frame before and after the protocol-specified PRO assessment time point whereby the result would still be deemed to be clinically relevant.³³

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

List of Abbreviations

CONSORT – Consolidated Standards of Reporting Trials

CRF – case report form

ePRO – electronic patient-reported outcome

PPI – Patient Public Involvement

PRO – patient-reported outcome

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

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

RS – recommendation statement

SAP – statistical analysis plan

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

SoA – Schedule of Activities

SPIRIT – Standard Protocol Items: Recommendations for Interventional Trials

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Supplement 1

Protocol evidence per final SPIRIT-PRO item.

SPIRIT PRO Item number and description	SPIRIT-PRO wording prior to finalisation	% HTA protocols including item	% EPiC protocols including item	% international ovarian cancer protocols including item
(5a) Specify the individual(s) responsible for the PRO content of the trial protocol		6.67%	22.78%	23.1%
(6a) Describe the PRO-specific research question and rationale for PRO assessment and summarise PRO findings in relevant studies	Describe what is currently known about PROs in this area and explain the gaps in the literature	49.33%	32.91%	42.3%
	Provide a rationale for the inclusion of PROs as appropriate to the study population, intervention, context, objectives and setting	8.00%	33.54%	57.7%
(7) State specific PRO objectives or hypotheses (including relevant PRO concepts/domains)	State the PRO study objective in relation to PRO domain/s, patient population and timeframe	77.33%	73.42% (17.09% in relation to dimension, population or timeframe)	30.8%
	State the PRO hypothesis and corresponding null hypothesis and to which outcome(s) the hypothesis relates	18.67%	-	PRO hypothesis provided 19.2%
(10) Specify any PRO-specific eligibility criteria (e.g. language/reading requirements or prerandomisation completion of PRO). If PROs will not be collected from the entire study sample, provide a rationale and describe the methods for obtaining the PRO subsample	If PROs will be collected in a subset of the study population or in specific centres, include a description/rationale for the sampling method	0.00%	10.76%	11.5%
	State the inclusion/exclusion criteria for PRO endpoint(s) (e.g., language/reading requirements)	45.33%	50.00%	7.7%

1		Specify if PRO completion is pre-randomisation eligibility requirement	-	-	7.7%
2					
3	(12) Specify the PRO concepts/domains used to evaluate the intervention (e.g. overall health-related quality of life, specific domain, specific symptom) and for each one, the analysis metric (e.g. change from baseline, final value, time to event) and the principal time point or period of interest	Describe the PRO constructs used to evaluate the intervention e.g. overall QOL, specific domain, specific symptom	-	-	73.1%
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14	(13) Include a schedule of PRO assessments, providing a rationale for the time points, and justifying if the initial assessment is not prerandomisation. Specify time windows, whether PRO collection is prior to clinical assessments, and, if using multiple questionnaires, whether order of administration will be standardised	Specify the timepoint(s) for PRO analysis (including the principle timepoint of interest) and provide the rationale for these	Timing specified 97.33%	Timing specified 83.54%	42.3%
15		Include PRO assessments in the main protocol schedule of assessments, specifying which PRO measures (PROMs) will be used at each assessment	-	-	96.2%
16		Specify if baseline PRO assessment should be completed before randomisation	-	-	53.8%
17		Specify the targeted time and acceptable time windows for each PRO assessment	-	-	26.9%
18		If PROs are to be completed in the clinic: specify timing of PROM delivery in relation to clinical assessments (e.g. before/whilst/after seeing clinician and/or clinical assessments)	-	-	54%
19		Justify the timing of PRO assessments. Scheduled	Timing justified 6.67%	Timing justified 12.03%	23.1%
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	PRO assessments should link to research questions, hypotheses, length of recall, disease/treatment natural history, planned analysis and time of comparison must be comparable for both arms			
(14) 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	If PRO is the primary endpoint, state the required PRO sample size, otherwise discuss the power of the PRO analysis	50.67%	25.95%	30.8%
(18a i) Justify the PRO instrument to be used and describe the domains, number of items, recall period, and instrument scaling and scoring (e.g. range and direction of scores indicating a good or poor outcome). Evidence of PRO instrument measurement properties, interpretation guidelines, and patient acceptability and burden should be provided or cited if available, ideally in the population of interest. State whether the measure will be used in accordance with any user manual and specify and justify deviations if planned	Describe the PROMs including, number of items/domains, instrument scaling/scoring, reliability, content and construct validity, responsiveness, sensitivity, acceptability, recall period. Provide references as appropriate	PROM identified 100%; Justification in relation to study hypotheses 41.33%; Justified in relation to measurement properties 37.33%; Justified in relation to acceptability/patient burden 14.67%	PROM identified 63.29%; Justification in relation to study hypotheses 36.71%; Justified in relation to measurement properties 46.84%; Justified in relation to acceptability/patient burden 29.11%	Justification for measure used 84.6%
(18a ii) Include a data collection plan outlining the permitted mode(s) of administration (e.g. paper, telephone, electronic, other)	Include a pre-specified data collection plan	84.00% included brief details of PRO data collection procedures but often omitted information surrounding mode of administration,	57.59%	46.2%

1 2 3 4	and setting (e.g. clinic, home, other)		setting and proxy reporting: 8.00% included PRO data collection guidelines/training information for trial personnel.		
5 6 7 8 9 10 11 12	(18a iii) Specify whether more than one language version will be used and state whether translated versions have been developed using currently recommended methods	Provide evidence of measurement equivalence across modes (i.e., when mixing modes of PRO data collection) and/or of cross cultural validity where different language versions of questionnaires are used	-	-	7.7%
13 14 15 16 17 18 19 20 21 22	(18a iv) 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		-	-	0.0%
23 24 25 26 27 28 29 30	(18b i) Specify PRO data collection and management strategies for minimising avoidable missing data	Specify procedures for data collection and management methods to minimise missing data. E.g. checking completed PROMs (including who will check forms and how will they deal with missing PROMs or missing items).	-	-	38.5%
31 32 33 34 35 36	(18b ii) Describe the process of PRO assessment for participants who discontinue or deviate from the assigned intervention protocol	Establish process for PRO assessment at (and beyond) withdrawal for patients who withdraw early from a study or who go 'off-study'/'off treatment'	-	-	34.6%
37 38 39 40	(20a) State PRO analysis methods, including any plans for addressing multiplicity/type I (a) error	Include an a priori description of all planned PRO analyses pertaining to the study hypotheses	PRO statistical analysis plan provided? 96.00%	PRO statistical analysis plan provided? 53.16%	61.5%

	Pre-specify sequence of testing/exploratory analyses to control for multiplicity or pre-specify domains (e.g. in a regulatory trial/labelling claim) (Common in pharma trials. Involves pre-specifying domains that alpha would be spent on, or ordering the domains in priority & alpha would be spent down the list)	Plans to address multiplicity of PRO data provided? 1.33%	10.13%	7.7%
(20c) State how missing data will be described and outline the methods for handling missing items or entire assessments (e.g. approach to imputation and sensitivity analyses)	State how missing data will be described	45.33%	30.38%	-
	Describe method for handling missing assessments (e.g. approach to imputation and sensitivity analyses)	45.33%	30.38%	-
	Describe methods for scoring endpoints. Where possible, reference scoring manuals for summated scales from PROM (domain-specific &/or total) & methods for handling missing items, and methodological papers for composite endpoints (e.g. QTWiST)	-	-	53.8%
(22) 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 standardised way. Describe how this process will be explained to participants; e.g. in the participant information sheet and consent form	Include an a priori plan for consistent/standardised management of PRO alerts (symptoms reported by patients that exceed a pre-defined level of severity) to be clearly communicated to all appropriate trial staff	10.67%	0.63%	0.0%
	Specify whether PRO forms will be used to	4.00%	3.80%	7.7%

	influence therapy or patient management (i.e. will the clinician use PRO responses to inform the patient's care?)			
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Supplement 2

Summary recommendations for inclusion* of PRO specific information in the trial protocol, supplementary documents or training for staff.

SPIRIT PRO Item Description	SPIRIT 2013 / SPIRIT- PRO Item Number	Guidance/training for trial staff (eg, site initiation/face to face or online training/operations manual)	Information/guidance for participants (eg, participant information sheet)	Statistical Analysis Plan
Administrative information				
Specify the individual(s) responsible for the PRO content of the trial protocol	✓ SPIRIT-5a-PRO Elaboration	+		
Introduction				
Describe the PRO specific research question and rationale for PRO assessment, and summarize PRO findings in relevant studies.	✓ SPIRIT-6a-PRO Extension	✓	✓ ¹	
State specific PRO objectives or hypotheses (including relevant PRO concepts/domains).	✓ SPIRIT-7-PRO Extension			✓
Methods: Participants, interventions, and outcomes				
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.	✓ SPIRIT-10-PRO Extension	✓		✓
Identify the PRO endpoint as the primary, secondary (and if so - whether a key/important secondary), or an exploratory endpoint.	✓ SPIRIT-12			✓
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			
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	✓		✓
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			✓
Methods: Data collection, management, and analysis				

1	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			✓ ²
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4	Provide evidence of measurement equivalence across modes (i.e. when mixing modes of PRO data collection) and/or of cross cultural validity where different language versions of questionnaires are used.				✓ ³
5					
6	Outline plans for evaluation of measurement properties, if appropriate (eg, if not previously validated in the population of interest).				✓ ⁴
7					
8	Specify the estimated time to complete each assessment, and discuss feasibility of assessment for the population.		✓	✓ ⁵	
9					
10	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	✓	✓	
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13	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	✓		
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16	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	✓		
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19	Specify who will administer the PROM (eg, a physician, nurse etc).		✓		
20	If it is permissible for another person to help the study participant complete the PROM, describe what type and level of assistance is acceptable.		✓	✓	
21					
22	Include a plan for systematically training and contacting local site personnel to ensure that they understand the content and importance of collecting PRO data. Ideally coordinated by a lead data manager who monitors PRO completion rates in real time and communicates with sites if completion rates are suboptimal.		✓		
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26	Specify PRO data collection and management strategies for minimising avoidable missing data.	✓ SPIRIT-18b(i)- PRO Extension	✓		
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29	Include guidance on discussing importance of PROs with patient		✓		
30	Describe the process of PRO assessment for participants who discontinue or deviate from their assigned intervention protocol.	✓ SPIRIT-18b(ii)- PRO Elaboration	✓		
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33	Specify that a named person/position at each centre (and/or centrally) be nominated to take responsibility for administration, collection and checking of PROM, specify whether this is the treating clinician or not.		✓ ⁶		
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36	Specify how an electronic PRO system/database will be maintained and how the investigator will meet regulatory requirements and ensure data integrity and security.	✓ SPIRIT-19	✓	✓ ⁷	
37					
38	Specify plan to monitor PRO compliance, including adherence to time windows.	✓ SPIRIT-19	✓	✓ ⁸	
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40	Include an overview of PRO administration (data collection), and data handling/transmission and storage procedures	✓ SPIRIT-19	✓	✓ ⁷	
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1	Item 39: Include an a priori description of all planned PRO analyses pertaining to the study hypotheses. Item 44: Include a priori identified summary statistics (as appropriate).	✓ SPIRIT-20a			✓
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3	State the assumptions of PRO analyses.				✓
4					
5	Include an a priori estimation of PRO effect size.	✓ SPIRIT-14			✓
6					
7	Specify intention-to-treat or per-protocol PRO analyses.	✓ SPIRIT-20c			✓
8					
9	Specify the minimum PRO response rate and acceptable degree of timing deviation (i.e. acceptable time windows for each PRO assessment time point) before the PRO objective is compromised. Specify the minimum PRO response rate and acceptable degree of timing deviation (i.e. acceptable time windows for each PRO assessment time point) before the PRO objective is compromised.	✓ SPIRIT-14			✓
10					
11	Describe methods for scoring endpoints. Where possible, reference scoring manuals for summated scales from PROM (domain-specific and/or total) and methods for handling missing items, and methodological papers for composite endpoints (eg, QTWiST).	✓ SPIRIT-20a			✓
12					
13	State PRO analysis methods including any plans for addressing multiplicity/type 1 (α) error.	✓ SPIRIT-20a-PRO Elaboration			✓
14					
15	Specify the criteria for clinical significance (eg, state minimal [clinical] important difference and/or responder definition (size and duration of benefit)).	✓ SPIRIT-14			✓
16					
17	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			✓
18					
19	Monitoring				
20					
21	Describe the role of the Data Monitoring Committee and Quality Assurance for PROs.	✓ SPIRIT-21a			
22					
23	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	✓	✓ ⁷	
24					
25	Ethics and dissemination				
26					
27	Describe informed consent procedure for PRO assessment.		✓		
28					
29	Include detailed plans for regular feedback to participants via letter/newsletter on PRO aspect of study.		✓	✓	
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Footnotes: "Recommended for inclusion" indicates that >50% of the Delphi and Stakeholder Survey participants endorsed the item (or at least one item if two items were merged for the consensus meeting) for inclusion and/or the item was considered important for inclusion at the consensus meeting.

+Recommended by the Delphi panel but excluded following discussion at the consensus meeting.

¹ <50% of Delphi panellists voted to include this item, but item was included following discussion at the consensus meeting. It was felt important to include a brief rationale for PRO assessment in the PIS.

² Use of the PRO instrument in accordance with the user manual should be specified in the SAP.

³ Plans for dealing with different modes of administration should be specified in the SAP. This was not supported by the Delphi but was identified as important by the consensus panel.

⁴ If validation of the PRO instrument is planned as part of the trial then this should be pre-specified in the main trial SAP. If validation is planned as a separate sub-study, this should be specified a separate study protocol and SAP.

⁵ Estimation of time to complete each PRO assessment should be included in guidance and training for staff and in information for trial participants.

⁶ This should also be recorded in the delegation of duties log.

⁷ The participant information sheet should contain information regarding the storage and security of PRO data and provide information on who will access their PRO data and for what purpose.

⁸ If plans to monitor adherence to time windows, include reminders for participants eg. Via text or SMS, the relevant details should be specified in the information to participants.