SPIRIT-PRO Extension Information

This document includes key definitions of some of the terminology used in the survey on page 1 and the list of candidate items for the SPIRIT-PRO Extension checklist on page 2.

Key definitions

Some key definitions are provided below for your convenience. We recommend consulting the ISOQOL Dictionary of Quality of Life and Health Outcomes Measurement for clarification of any terms not listed below.

Hypothesis: a supposition made on the basis of limited prior evidence for further investigation.

The ISOQOL Dictionary distinguishes between two types of hypotheses:

> **Explanatory hypothesis**: In the context of a study on the efficacy or effectiveness of an intervention, some of the data collection would inform (explain) the process underlying in achieving the outcome. Inclusion and testing of these explanatory hypotheses would not affect the power of the study to test the main effect (confirmatory hypothesis). [1]
>
> **Exploratory hypothesis**: In the context of a study on the efficacy or effectiveness of an intervention, some of the data collection would inform the impact of the intervention on other outcomes that may be collateral or downstream from the main outcome. Inclusion and testing of these exploratory hypotheses would not affect the power of the study to test the main effect (confirmatory hypothesis).[1]

Endpoint: In the context of the evaluation of an intervention, it is the outcome for which the efficacy or effectiveness will be judged; in an intervention trial, endpoints have been distinguished as primary, key secondary or exploratory.[1]

Mode of administration: refers to the different methods or mediums for administering questionnaires (paper, electronic, etc.) or delivering questionnaires to respondents (in person, telephone, email) and how the questionnaire is completed (self-complete, interview administered).[2]

Objective: a statement on the specific aims or outcomes of the study, or how the research question will be answered by the outcome measures. Unlike hypotheses, objectives should not indicate the expected outcomes of the study. [3]

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." [4]

PRO measure (PROM): the questionnaire used to assess the target patient-reported outcome(s)

Proxy assessment: In some health populations self-reported assessment of quality of life or other health outcomes may not be possible (for example, in the cognitively impaired, or in very young children). A 'proxy', such as a caregiver or health professional may, in such cases, report on the patient's health status.[5]

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[1] ISOQOL, (2015). Dictionary of Quality of Life and Health Outcomes Measurement. 1st Ed. Ed NE Mayo. Milwaukee, WI.
[2] Bowling A. (2005). Mode of questionnaire administration can have serious effects on data quality. Journal of Public Health, 27(3) 281–291.
[3] Farrugia et al. (2010). Research questions, hypotheses and objectives. Cancer Surgery journal, 53 (4). 278-281.
[4] Food and Drug Administration (FDA). (2009) Guidance for Industry. Patient-reported outcome measures: Use in medical product development to support labelling claims. http://www.fda.gov/downloads/Drugs/.../Guidances/UCM193282.pdf p.6.
[5] Pickard AS and Knight SJ. (2005). Proxy Evaluation of Health-Related Quality of Life: A Conceptual Framework for Understanding Multiple Proxy Perspectives. Med Care. 43(5): 493–499.

SPIRIT-PRO Extension Checklist Candidate Items

ADMINISTRATIVE INFORMATION	
	Roles & Responsibilities of PRO Personnel
1	List personnel responsible for PRO components of trial protocol
INTRODUCTION	
Background, Rationale & Objectives	
	Background PRO-specific information
2	Describe what is currently known about PROs in this area and explain the gaps in literature
	PRO-specific rationale
3	Provide a rationale for the inclusion of PROs as appropriate to the study population, intervention, context, objectives and setting
	PRO-specific hypotheses/objectives
4	State the PRO study objective in relation to PRO domain/s, patient population and timeframe
5	State the PRO hypothesis and corresponding null hypothesis and to which outcome(s) the hypothesis relates
METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES	
	PRO study setting
6	If PROs will be collected in a subset of the study population or in specific centres, include a description/rationale for the sampling method
	PRO eligibility criteria
7	State the inclusion/exclusion criteria for PRO endpoint(s) (e.g., language/reading requirements)
8	Specify if PRO completion is pre-randomisation eligibility requirement
	PRO endpoint specification
9	Identify the PRO endpoint as the primary, secondary (and if so - whether a key/important secondary), or an exploratory endpoint
10	Describe the PRO constructs used to evaluate the intervention e.g. overall QOL, specific domain, specific symptom
11	Specify the timepoint(s) for PRO analysis (including the principle timepoint of interest) and provide the rationale for these
	Timing of PRO assessments
12	Include PRO assessments in the main protocol schedule of assessments, specifying which PRO measures (PROMs) will be used at each assessment
13	Specify if baseline PRO assessment should be completed before randomisation
14	Specify the targeted time and acceptable time windows for each PRO assessment
15	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)
	Justification for timing of PRO assessments
16	Justify the timing of PRO assessments. Scheduled 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
	PRO sample size
17	If PRO is the primary endpoint, state the required PRO sample size, otherwise discuss the power of the PRO analysis
METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS	
METHODS: DATA COLLECTION	

	PRO instrument description
18	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
	PRO instrument justification
19	Justify choice of PROM(s) by linking specific domains/items to clinical justifications and hypotheses
20	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
21	Outline plans for evaluation of measurement properties, if appropriate (e.g. if not previously validated in the population of interest)
22	Specify the estimated time to complete each assessment, and discuss feasibility of assessment for the population
	PRO data collection plan
23	Include a pre-specified data collection plan
24	Specify how PROM will be completed (e.g. pencil and paper, online, etc)
25	Specify where PROM will be completed (e.g. clinic, home, etc)
26	Where applicable, justify use of proxies (define conditions under which proxy assessment is permissible)
27	Specify who will administer the PROM (e.g., a physician, nurse etc)
28	If it is permissible for another person to help the study participant complete the PROM, describe what type and level of assistance is acceptable
29	If more than one PROM will be used, specify whether the order of administration will be standardised or randomised
	PRO data collection guidelines/training information
30	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
	Plans to avoid/minimise missing data
31	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).
32	Include guidance on discussing importance of PROs with patient
33	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	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 or is not the treating clinician
METHODS: DATA MANAGEMENT	
	PRO-specific Quality Assurance
35	Specify how an electronic PRO system/database will be maintained and how investigator will meet regulatory requirements and ensure data integrity and security
36	Specify plan to monitor PRO compliance, including adherence to time windows
37	Include an overview of PRO administration (data collection), and data handling/transmission and storage procedures
38	Ensure plans for administration of PROM(s) are consistent with each PROM's user manual

METHODS: DATA ANALYSIS	
	PRO Statistical Analysis
39	Include an a priori description of all planned PRO analyses pertaining to the study hypotheses
40	State the assumptions of PRO analyses
41	State the anticipated response rate and implications for the sample size
42	Include an a priori estimation of PRO effect size
43	Specify intention-to-treat or per-protocol PRO analyses.
44	Include a priori identified summary statistics (as appropriate)
45	Specify the minimum PRO response rate and acceptable degree of timing deviation (i.e acceptable time windows for each PRO assessment timepoint) before the PRO objective is compromised
46	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 (e.g. QTWiST)
	Plans to address multiplicity of PRO data
47	State statistical significance levels and include plans for multiplicity/controlling type 1 error
48	Pre-specify sequence of testing/exploratory analyses to control for multiplicity or pre-specify domains (e.g. in a regulatory trial/labelling claim)
	PRO clinical significance
49	Specify the criteria for clinical significance (e.g. state minimal [clinical] important difference and/or responder definition (size and duration of benefit))
	Statistical methods to deal with missing PRO data
50	State how missing data will be described
51	Describe method for handling missing assessments (e.g. approach to imputation and sensitivity analyses)
MONITORING	
	PRO data monitoring
52	Describe the role of the Data Monitoring Committee and Quality Assurance for PROs
	PRO alerts
53	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
ETHICS AND DISSEMINATION	
	PRO-specific consent information
54	Describe informed consent procedure for PRO assessment.
	PRO-specific confidentiality procedures
55	Specify whether PRO forms will be used to influence therapy or patient management (i.e. will the clinician use PRO responses to inform the patient's care?)
	PRO dissemination policy
56	Include detailed plans for regular feedback to participants via letter/newsletter on PRO aspect of study