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				

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]	

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			✓
State the assumptions of PRO analyses.				✓
Include an a priori estimation of PRO effect size.	✓ SPIRIT-14			✓
Specify intention-to-treat or per-protocol PRO analyses.	✓ SPIRIT-20c			✓
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			✓
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			✓
State PRO analysis methods including any plans for addressing multiplicity/type 1 (α) error.	✓ SPIRIT-20a-PRO Elaboration			✓
Specify the criteria for clinical significance (eg, state minimal [clinical] important difference and/or responder definition (size and duration of benefit)).	✓ SPIRIT-14			✓
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			✓
Monitoring				
Describe the role of the Data Monitoring Committee and Quality Assurance for PROs.	✓ SPIRIT-21a			
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]	
Ethics and dissemination				
Describe informed consent procedure for PRO assessment.		✓		
Include detailed plans for regular feedback to participants via letter/newsletter on PRO aspect of study.		✓	✓	

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.