Supplement 2 Key research evidence (Round 2 Delphi survey results and systematic review data) presented to meeting participants.

Report prepared for the SPIRIT-PRO Consensus meeting, 11-12 May 2017

by the SPIRIT-PRO Operations Group:
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for the SPIRIT PRO Group

Executive Summary

Thank you for agreeing to participate in the SPIRIT-PRO Consensus meeting on 11th/12th May 2017 at the University of Birmingham, UK; your input is invaluable.

Meeting Aims:

- The primary aim of the meeting is to reach consensus on which items should be included in patient-reported outcome (PRO) specific guidance for protocol writers; an official SPIRIT-PRO extension.

- The secondary aim is to produce preliminary recommendations about the inclusion of PRO information in documents that complement the protocol, e.g. guidance/training for trial staff, information/guidance for study participants, statistical analysis plans, etc.

For the primary aim, items may be included in the guidance as a SPIRIT-PRO extension or an elaboration. We propose that the SPIRIT-PRO Extensions or SPIRIT Elaborations will apply to randomised clinical trials where PROs are a primary or key secondary outcome as defined below:

Definitions:

SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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

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

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

Secondary Outcomes / Endpoint(s)
These are outcomes pre-specified in the protocol to assess additional effects of the intervention. Some PROs may be identified as important or key secondary outcomes.

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

SPIRIT-PRO Extension primary publication
The brief (approx. 4000 words) peer-review manuscript presenting the final SPIRIT-PRO checklist, including extension and elaboration items.

Supporting explanatory publication
A longer (approx. 10,000 words) supplementary peer-review manuscript explaining the SPIRIT-PRO in detail and illustrating how items may be addressed in a trial protocol.

Information about voting during the SPIRIT-PRO Consensus Meeting

RE Primary Aim: to reach consensus on which items should be included in the SPIRIT-PRO extension

Voting options: we propose that for each item we consider the following voting options:

1. Include as a SPIRIT-PRO extension item (or elaboration where indicated)
2. Exclude
3. Further discussion required.

Voting at the meeting will be informed by several pieces of evidence/information:

1. Whether the item in question was supported for inclusion in the Delphi and Stakeholder Survey (appendix 1)
2. Whether the item was adjudged by the SPIRIT-PRO Operations Group (MC, DK, RMB, AS, MK) as captured by the existing SPIRIT guidance (appendix 2).
3. How well the item is currently addressed in clinical trial protocols based on evidence from our systematic review of NIHR HTA protocols[1] and confidential preliminary results from the EPiC study[2].
4. Other key pieces of supportive evidence identified by the SPIRIT-PRO Operations Team.

The above evidence/information is summarised in Table 1. We have made a recommendation for each item based on this information and using the following decision rules (also outlined in Fig. 1).

- Recommendations for a SPIRIT-PRO **Extension** were based on the following criteria:

  - ≥70% of round 2 Delphi participants scored the proposed item as 'critical' (7-9) for inclusion in a trial protocol, whilst ≤15% scored the item as not important (1-3) [where PROs are included in a trial as a primary outcome].*

  AND

  - The item was adjudged by the Operations Group as **either**:
    (A) **not** captured by the existing SPIRIT guidance, **OR**
    (B) only **partially** captured by SPIRIT with important detail omitted and **rarely/inconsistently** addressed in practice (based on evidence from our HTA/EPiC review of trial protocols, note: we interpreted 'rarely' as <30% of protocols including item details and 'inconsistently' as between 31% and 70% inclusion).

- Recommendations for a SPIRIT-PRO **Elaboration** were based on the following criteria:

  - ≥70% of round 2 Delphi participants scored the proposed item as 'critical' (7-9) for inclusion in a trial protocol, whilst ≤15% scored the item as not important (1-3) [where PROs are included in a trial as a primary outcome].*

  AND

  - The item was adjudged by the operation team as: (C) covered by SPIRIT but rarely/inconsistently addressed in practice.

Inclusion of PRO Information in clinical trial protocols: key studies

There follows a brief summary of the key evidence the SPIRIT-PRO Operations Group drew upon when attempting to determine whether each of the candidate SPIRIT-PRO items was routinely addressed in clinical trial protocols.

EPiC Study (nearing completion, intended submission for publication July 2017)

Aim: to evaluate the standards of PRO-specific content in NIHR portfolio cancer trial protocols and their arising publications (completed studies between 2001 and 2014, all cancer specialties/age groups). The NIHR portfolio includes UK-led international/national trials, supported by a range of funders, adjudged as high-quality clinical research studies.

Methods: two independent investigators screened the portfolio trial database, retrieved the most up-to-date trial protocol (final ethically approved version) and arising publications for review, extracted demographic trial data, and reviewed: (i) the general quality/completeness of protocols/publications using the SPIRIT and CONSORT checklists respectively; and (ii) the PRO-specific aspects using a PRO protocol checklist and the CONSORT-PRO Extension.

Preliminary Results (Confidential): n=251 trials were included and n=106 protocols and n=157 publications were sourced. Preliminary data based on n=79 protocols matched to their corresponding publication(s) suggests general protocol quality/completeness was above average (adjusted mean SPIRIT score (max 50) = 30.96 (64.65%)), but PRO-specific content was frequently omitted (adjusted mean PRO protocol checklist score (max 33) = 9.96 (31.53%)). A similar picture was seen across the included trial publications (adjusted mean CONSORT score (max 37) = 23.43 (66.17%); adjusted mean CONSORT PRO score (max 14) = 3.14 (23.92%)). Worryingly, n=36 of 98 (36.7%) trials we have reviewed thus far **failed to report PRO results in either a primary or secondary publication**, meaning that **26,057** participants provided QoL data that was not subsequently made available to future patients.

HTA Study (Published in PLOS One in 2013, link to manuscript here)

Aim: to evaluate the PRO content of n=75 clinical trial protocols drawn from the UK National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (2012/13). The sample represented a broad range of clinical areas.

Methods: as per EPiC, but wholly focused on reviewing the general quality/completeness of protocols only using SPIRIT and the PRO protocol checklist.

Results: protocols included a mean of 63% SPIRIT recommendations and 33% PRO protocol checklist items. PRO protocol content was not associated with general protocol completeness; thus, protocols judged as relatively 'complete' using SPIRIT were still likely to have omitted a large proportion of PRO checklist items.

Note: EPIC and HTA studies used the same 33-item PRO protocol checklist (the precursor to SPIRIT-PRO) to judge the completeness of the PRO components of the included protocols. This checklist was developed in 2013, following a systematic review of PRO guidance for protocol developers published in PLOS One: link to manuscript. Where possible we have extracted item level data from both the EPiC and HTA studies into the summary table appearing in this document, however, the 33-item checklist does not map directly to all 56 candidate SPIRIT-PRO items meaning there are some missing data fields. For transparency, we have highlighted these in the table using a dash.

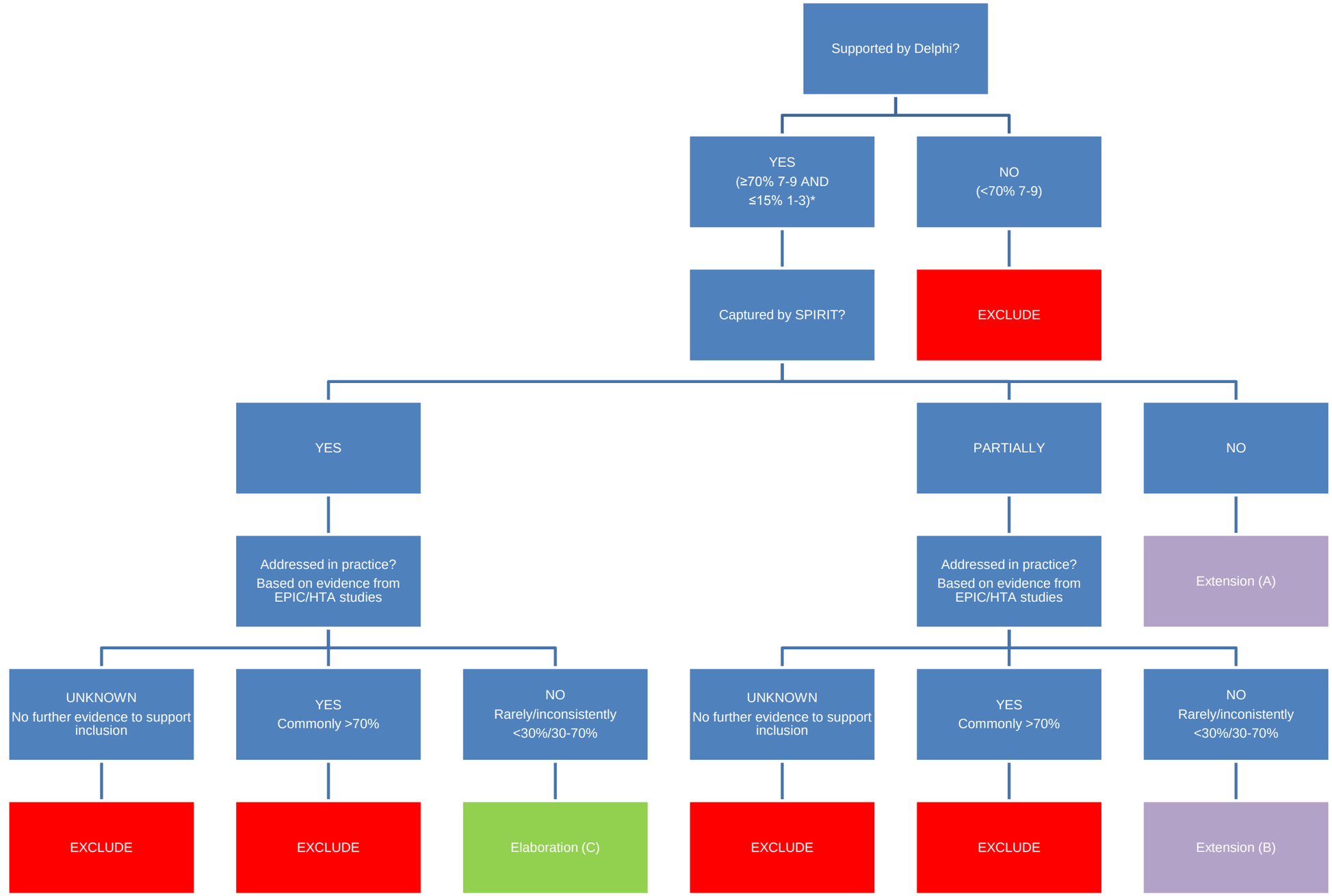

Figure 1. Proposed Decision Rules **Please note items which Delphi participants noted lacked clarity on wording and >60% scored 1-9 were also considered*

RE Secondary aim: Additional voting on PRO content of other trial documentation

Based on the Round 2 Delphi survey we have also highlighted where ≥50% of respondents recommended including PRO information in additional trial guidance e.g. Guidance/training for trial staff; Information/guidance for study participants; Statistical Analysis Plan (SAP); etc.

As part of the consensus meeting, attendees will be asked to vote on these suggestions to value-add to the meeting outputs in terms of recommendations for additional trial guidance about trial conduct and analysis to complement the trial protocol. It is our hope that a suitable suite of PRO-specific trial guidance will facilitate high-quality PRO evidence.

Final Thoughts

We would appreciate it if you would please review the table below prior to the meeting, as this will streamline the voting process on the day. Please note that since conducting Round 2 of the Delphi, we have merged and/or reworded some items based on respondent feedback. Where two or more items have been merged, we have reported the % of respondents who endorsed each item, if at least one of these items was endorsed by ≥50% or respondents.

If you have any questions regarding the process or information provided please get in touch.

We look forward to seeing you at the meeting.

Kind Regards

Prof Mel Calvert, Dr Derek Kyte, Rebecca Mercieca-Bebber, Dr Anita Slade and Prof Madeleine King on behalf of the SPIRIT-PRO Operations Group.

References

1. **Kyte D**, Duffy H, Fletcher B, Gheorghe A, Mercieca-Bebber R, King M, Draper H, Ives J, Brundage M, Blazeby J, Calvert M. (2014) Systematic Evaluation of the Patient-Reported Outcome (PRO) Content of Clinical Trial Protocols. PLoS ONE 9(10): e110229. doi: 10.1371/journal.pone.0110229.

2. Ahmed K, **Kyte D**, Keeley T, Efficace F, Armes J, Brown JM, Calman L, Copland C, Gavin A, Glaser A, Greenfield DM, Lanceley A, Taylor R, Velikova G, Brundage M, Mercieca-Bebber R, King MT, Calvert M. Systematic evaluation of patient-reported outcome (PRO) protocol content and reporting in UK cancer clinical trials: the EPiC study protocol. BMJ Open. 2016 Sep 21;6(9):e012863. doi: 10.1136/bmjopen-2016-012863.

Table 1 – Summary Data. '-' no EPiC or HTA data available for corresponding item.

Item No	SPIRIT-PRO Item Delphi Wording	Relevant SPIRIT 2013 Item	SPIRIT-PRO Extension proposal (Extension or Elaboration or Exclude)	Proposed SPIRIT-PRO Extension // Elaboration wording	% of Delphi panel rating item: 'Critical'	% of Delphi panel rating item: 'Not important'	Notes/ Key Comments from Stakeholder and Delphi Panel Survey participants (further detail in Summary Report)	% HTA protocols including item	% EPIC protocols including item	DECISION RULE	Guidance or training for trial staff	Information or guidance for study participants	Statistical Analysis Plan (SAP)	Other trial docs
1	List personnel responsible for PRO components of trial	(5a) Names, affiliations, and roles of protocol contributors	**SPIRIT-5a-PRO Elaboration**	**Specify the individual(s) responsible for the PRO content of the trial protocol**	65.7*	8.1	*1. Original wording unclear; 2. Refers to the person who wrote the PRO content of the protocol (often a co-I); 3. Some respondents felt that this level of detail was not required whilst others felt that this was important in terms of accountability to ensure quality of data collection. 4. note whether patients coproduced the protocol (Ops Team note this is an important issue but more general than PROs).	6.67%	22.78%	**C** Borderline support from Delphi (*note confusion over wording). Captured by SPIRIT 5a. Rarely addressed in practice.	✓ (72.7%)			
2	Describe what is currently known about PROs in this area and explain the gaps in literature	(6a) Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	**SPIRIT-6a-PRO Extension** **Merge items 2 & 3**	**Description of PRO specific research question, rationale for including PROs in the trial, and summary of PRO findings in relevant studies.**	84.8	3.0	1. 'Justifies time taken by patients to complete the questionnaires' 2. Brief description -same as other endpoints. 3. Helps ensure team are 'on the same page'/provides context for team and patients. 4. Fundamental step in making a sound scientific case for PROs.	49.33%	32.91%	**B** Strongly supported by Delphi evidence. Partially captured by SPIRIT 6a. Rarely/inconsistently addressed in practice (especially rationale).	✓ (42.4% (item 2) /55.6% (item 3))			
3	Provide a rationale for the inclusion of PROs as appropriate to the study population, intervention, context, objectives and setting				87.8	2.0	1. Needs to be concise; 2. Merge with previous question; 3. Justification needed from a 'scientific and ethical perspective'; 4. 'Study participants should not be expected to complete PRO assessments that are not well considered, justified for their condition and the study.'; 5. 'without this interpretation will be potentially flawed and it will become challenging to draw conclusions.'	8.00%	33.54%					

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4	State the PRO study objective in relation to PRO domain/s, patient population and timeframe	(7) Specific objectives or hypotheses	**SPIRIT-7-PRO Elaboration** **Merge items 4 & 5**	**State specific PRO objectives or hypotheses in relation to key PRO domain(s) and timeframes.**	92.8	1.0	1. The majority of respondents felt that this was crucial. 2. Others felt too much detail/may not apply to all study designs	77.33%	73.42% (17.09 in relation to dimension, population or timeframe)	**C** Strongly supported by Delphi evidence. Captured by SPIRIT 7. Hypotheses (Item 5) not routinely included in practice.			✓ (34.3%/ 55.6%)	
5	State the PRO hypothesis and corresponding null hypothesis and to which outcome(s) the hypothesis relates				82.8	4.0	1. Stating the hypothesis (or null) may not be needed; 2. Can be merged with the previous item(s)	18.67%	-					
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	(10) Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions	**SPIRIT-10-PRO Extension** **Merge items 6, 7 & 8**	**Specify if PRO specific inclusion/exclusion criteria (e.g., language/reading requirements or pre-randomisation completion of PRO) Detail if PROs will be collected in a subset of the study population or in specific centres, include a description/rationale for the sampling method.**	86.5	2.1	1. 'Why would PROs be done in a subset?' 2. 'Clear description is absolutely necessary.' 3. Description required but not rationale.	0.00%	10.76%	**B** Strongly supported by Delphi evidence. Partially captured by SPIRIT 10. Information rarely/inconsistently included in practice.	Although the survey results not support this for Item 6, the Ops Team recommend voting on its inclusion here.		✓ (50.5%)	
7	State the inclusion/exclusion criteria for PRO endpoint(s) (e.g., language/reading requirements)				84.8	2.0	1. 'These are general requirements for research endpoints'; 2. 'This is critical to evaluate the risk of bias'; 3. 'Conclusions could be undermined if exclude disadvantaged groups.'	45.33%	50.00%		✓ (60.6%/63.6%)			

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8	Specify if PRO completion is pre-randomisation eligibility requirement				80.8	4.0	1'Eligibility requirements must always be specified. PROs are not an exception.' Please note the ops team felt that this was a specific strategy for addressing missing data and could be used as an example under item 31.	-	-					
9	Identify the PRO endpoint as the primary, secondary (and if so - whether a key/important secondary), or an exploratory endpoint	(12) Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	**Exclude** **Captured by SPIRIT 12**	Exclude	97.0	1.0	1. 'From a regulatory perspective this is crucial.' 2. 'No brainer.' 3. Captured by SPIRIT/applied to all endpoints. Ops team noted that this item is captured by SPIRIT but viewed as extremely important and often unclear for PROs - therefore suggest elaboration.	97.33%	90.51%	Covered by SPIRIT 12. Commonly addressed in practice.			✓ (53.5%/ 38.4%)	
10	Describe the PRO constructs used to evaluate the intervention e.g. overall QOL, specific domain, specific symptom		**SPIRIT-12-PRO Extension**	Describe the PRO constructs used to evaluate the intervention e.g. overall QOL, specific domain, specific symptom	87.9	2.0	1. Clarification required - describe the PRO constructs themselves or list which constructs to use? 2. Respondents generally support the latter. 3. Too much detail for checklist? Duplication - covered by hypothesis?	-	-	**A** Strongly supported by Delphi. Not covered by SPIRIT 12.				

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11	Specify the timepoint(s) for PRO analysis (including the principle timepoint of interest) and provide the rationale for these	(13) Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see fig 1])	**SPIRIT-13-PRO Extension** **Merge items 11/12/13/14/15/16** **Propose split into two parts a and b.**	**a) Specify and justify the timepoint(s) for PRO data collection and analyses (including the principal timepoint of interest and whether initial assessment is pre-randomisation) and provide the rationale for these.** b) **Include a schedule of assessments detailing which PRO will be used at which timepoint (and details regarding time windows and whether PRO collection is prior to clinical assessments, where applicable).**	91.7	0.0	1. Suggested rewording 2. 'Critical to state the timepoint but not the rationale.'	Timing specified 97.33%	Timing specified 83.54%	**B** Very strongly supported by Delphi evidence. Partially captured by SPIRIT 13. Time points are specified but further detail is often omitted (e.g. justification of timing <15%).	✓ (51.5%; 53.5%;61.6%;64.7%;69.7% - items 11-15)		✓ (Item 11= 50.5%)	
12	Include PRO assessments in the main protocol schedule of assessments, specifying which PRO measures (PROMs) will be used at each assessment				97.0	1.0	1. 'If the PRO assessment schedule is not included then there will be much confusion and ultimately the data will suffer.' 2. 'Key..' 3'. Patient burden could be significant depending on the number of measures.' [implication that this may be a useful overview to help assess this]	-	-					
13	Specify if baseline PRO assessment should be completed before randomisation				88.8	4.1	1. 'Critical.' 2. Default - baseline is prior to randomisation.	-	-					
14	Specify the targeted time and acceptable time windows for each PRO assessment				83.8	2.0	1. Not specific to PROs 2. Time windows viewed as excessive - could be detailed in the SAP.	-	-					

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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)				75.5	3.1	1.'Potentially has major impact on PRO results. 2. 'Necessity varies by study.'	-	-					
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				80.4	4.1	1. Complicated - covers to many aspects. 2. Covered by items 11 & 12	Timing justified 6.67%	Timing justified 12.03%					

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17	If PRO is the primary endpoint, state the required PRO sample size, otherwise discuss the power of the PRO analysis	(14) Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	**SPIRIT-14-PRO Elaboration** **Merge items 17 & 41**	**If PRO is the primary endpoint, state the required PRO sample size (and how it was determined) and recruitment target (accounting for expected loss to follow-up). Otherwise discuss the power of the PRO analysis.**	93.9	0.0	1. Covered by SPIRIT 2. 'Same rigour as other endpoints'.	50.67%	25.95%	**C** Strongly supported by Delphi. Captured by SPIRIT 14. Rarely/inconsistently addressed in practice.			✓ (62.6%; 63.6%)	
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	(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 a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms	**SPIRIT-18a-PRO Extension** **Merge items 18 & 19**	**Describe the PROs, where appropriate including: domains, number of items, recall period, instrument scaling/scoring, acceptability and measurement properties. Justify PRO choice and provide references as appropriate.**	77.8	2.0	1. 'Essential' 2. Some respondents felt there were too many items in the list.	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%	**B** Strongly supported by Delphi. Partially covered in general terms by the SPIRIT 18a wording but lacks important detail regarding elements. Inconsistently addressed in practice.			Not supported by survey, but Ops Team suggests that scoring info should be included in SAP	

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19	**Justify choice of PROM(s) by linking specific domains/items to cli**nical justifications and hypotheses	can be found, if not in the protocol			80.8	2.0	1. Overlap with previous items 2. Suggestion to omit clinical justification.							
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.		**Exclude**	**Exclude**	57.7	14.4	1. 'Evidence not always available' 2.'Overblown issue - meta-analyses suggest equivalence across modes.' 3. 'Not required in protocol	-	-	Not supported by Delphi.				
21	Outline plans for evaluation of measurement properties, if appropriate (e.g. if not previously validated in the population of interest)		**Exclude**	**Exclude**	61.1	10.5	1.'Should be a separate SAP/included in the SAP.' 2 'Additional research - but not part of the primary protocol.'	-	-	Not supported by Delphi.				

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22	Specify the estimated time to complete each assessment, and discuss feasibility of assessment for the population"		**Exclude**	**Exclude**	52.5	5.1	1. Details for REC/IRB to consider 2. Helps to understand participant burden 3. Feasibility is more important than time/vs agree to specifying time but not feasibility.	-	-	Not supported by Delphi.	✓ (62.6%)	Not supported by survey, but Ops Team feels this is important information for patients, and recommends voting on this,		
23	Include a pre-specified data collection plan		**SPIRIT-18a-PRO Extension** **Merge items 23-26**	**Include a data collection plan outlining the permitted mode of administration (e.g. pencil and paper, online, etc.); setting (e.g. clinic, home etc.) and conditions under which proxy assessment is allowed.**	81.3	3.1	1. Many respondents felt this item was too broad and vague.' 2. Captured by other, more specific, items	84.00% included brief details of PRO data collection procedures but often omitted information surrounding mode of administration, setting and proxy reporting: 8.00% included PRO data collection guidelines/training information for trial personnel.	57.59%	**B** Strongly supported by Delphi. Partially covered in general terms by the SPIRIT wording 18a but lacks important detail regarding elements. Inconsistently addressed in practice.	✓ (47.5%; 71.7%; 72.7%; 58.6%)	✓ (6%; 56.6%; 59.6%; 38%)		
24	Specify how PROM will be completed (e.g. pencil and paper, online, etc.)				75.8	3.0	1. Brief mention only 2. Important to consider back up plan for delivery.	-	-					
25	Specify where PROM will be completed (e.g. clinic, home, etc.)				71.7	4.0	1. Brief mention only 2. Important to consider back up plan for delivery.	-	-					

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26	Where applicable, justify use of proxies (define conditions under which proxy assessment is permissible)				76.3	4.1	1. Use the term observer 2.'Useful to distinguish type of help - family/clinicians/research personnel'. 3. 'Belongs in protocol and training'. 4. 'Not sure proxy completion should be allowed/use discouraged.'[This point should be picked up in the explanatory notes]	-	-					
27	Specify who will administer the PROM (e.g., a physician, nurse etc.)		**Exclude**	**Exclude**	58.2	8.2	1. 'May vary by centre.' 2. 'Micromanagement.'	-	-	Not supported by Delphi.	✓ (74.8%)			
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		**Exclude**	**Exclude**	63.6	9.1	1. Overlaps with #26. 2. This item is overcomplicated. Note– point of good practice to include in the paper linked to merged items 23-26.	-	-	Not supported by Delphi.	✓ (70.7%)	✓ (52.5%)		
29	If more than one PROM will be used, specify whether the order of administration will be standardised or randomised		**Exclude**	**Exclude**	54.5	12.1	1. Order is important and should be standardised 2. Often not stated as pre-printed books.	-	-	Not supported by Delphi.	✓ (58.6%)			

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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		**Exclude**	**Exclude**	64.3	12.2	1. Some felt this was critically important but 2. A number of respondents suggested not in the protocol. Note– point of good practice to include in the paper linked to merged items 23-26.	-	-	Not supported by Delphi.	✓ (71.7%)			

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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).	(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	**SPIRIT-19-PRO Extension**	**Specify procedures for data collection and management methods to minimise avoidable missing data. E.g. checking completed PROMs (including who will check forms and how will they deal with missing PROMs or missing items or whether PRO is a pre-randomisation eligibility requirement.**	72.7	6.1	1. Ops manual not protocol 2. Not so important with electronic data collection.	46.67%	31.01%	**B** Supported by the Delphi panel. Partially covered in general terms by the SPIRIT 19 wording but lacks important detail. Specifically: (1) The SPIRIT wording rather leans toward prevention of scoring errors. (2) Missing data is a major issue for PROs as evidenced by work of Fielding et al. Inconsistently addressed in practice.	✓ (70.7%)			Ops manual

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32	Include guidance on discussing importance of PROs with patient	(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 a 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	**Exclude**	**Exclude**	52.5	21.2	1. Not in a protocol 2. Include in training/PIS? 3. 'Depends on the nature of the PRO' 4. 'Brief mention of value might be useful in the protocol'.	-	-	Not supported by Delphi.	✓ (71.7%)			

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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'	(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	**Exclude** **Captured by SPIRIT 18b**	**Exclude**	75.8	5.1	1.'standard for all data items.' 2.'Captured by SPIRIT.' Ops Team noted that this is a major issue raised by Diane Fairclough in her book (based on her extensive experience dealing with missing PRO data), so may be worthy of Elaboration. Whether it is done consistently in protocols is yet to be assessed.	-	-	Supported by Delphi panel. Covered by SPIRIT 18b. No further evidence to support inclusion.	✓ (65.6%)			

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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		**Exclude**	**Exclude**	49.5	15.2	1. Infeasible 2.Management is highly variable	-	-	Not supported by Delphi.	✓ (68.7%)			
35	Specify how an electronic PRO system/database will be maintained and how investigator will meet regulatory requirements and ensure data integrity and security	(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	**Exclude**	**Exclude**	62.6	13.1	1. Not specific to PROs 2. Should be included in SOPs Note: This information can be described in relation to the prevention of avoidable missing data.	60.00%	15.82%	Not supported by Delphi.				SOPs

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36	Specify plan to monitor PRO compliance, including adherence to time windows		**Exclude**	**Exclude**	65.7	7.1	1. 'Too much for protocol' 2. Include in site training manuals	-	-	Not supported by Delphi.	✓ (54.6%)			Site manual
37	Include an overview of PRO administration (data collection), and data handling/transmission and storage procedures		**Exclude**	**Exclude**	51.5	14.1	1. Should be covered in SOP 2. IRB 3. Covered by SPIRIT(MC)	-	-	Not supported by Delphi.	✓ (54.6%)			SOPs/ethics

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38	Ensure plans for administration of PROM(s) are consistent with each PROM's user manual	(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 a 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	**Exclude**	**Exclude**	48.0	14.3	1. Implementation not protocol issue 2. PRO may not have user manual 3. Include site manual	-	-	Not supported by Delphi.				Site manual?

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39	Include an a priori description of all planned PRO analyses pertaining to the study hypotheses	(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	**Exclude** **Captured by SPIRIT 20a**	**Exclude**	83.5	5.2	1. Same as other outcomes 2. High level description in the protocol - rest in SAP 3. Captured by SPIRIT	PRO statistical analysis plan provided? 96.00%	PRO statistical analysis plan provided? 53.16%	Strongly supported by Delphi. Captured by SPIRIT 20a. Commonly collected in practice.			✓ (65.7%) merge with item 44?	
40	State the assumptions of PRO analyses		**Exclude**	**Exclude**	60.4	10.4	1. Wording is unclear/vague 2. Should be covered in SAP	-	-	Not supported by Delphi.			✓ (66.7%)	

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41	State the anticipated response rate and implications for the sample size	(14) Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	**SPIRIT-14-PRO Elaboration** **Merge items 17 & 41**	**See item 17**	80.4	3.1	1. Covered by SPIRIT-14 2.Conjecture in protocol	-	-	See item 17			✓ (63.7%)	
42	Include an a priori estimation of PRO effect size		**Exclude** **Captured by SPIRIT 14**	**Exclude**	74.0	3.1	1. Covered by item 17 2. Captured by SPIRIT (As part of Elaboration for SPIRIT 14 (merged Items 17 and 41), effect size can be mentioned as one way of specifying a priori smallest important clinical effect for sample size determination.)	-	-	Supported by Delphi. Captured by SPIRIT 14. No further evidence to support inclusion			✓ (64.6%)	

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43	Specify intention-to-treat or per-protocol PRO analyses.	(20c) Definition of analysis population relating to protocol non-adherence (e.g., as randomised analysis), and any statistical methods to handle missing data (e.g., multiple imputation)	**Exclude** **Captured by SPIRIT 20c**	**Exclude**	80.0	4.2	1. General requirement for all outcomes 2. Should be in SAP 3. Covered by SPIRIT	-	-	Strongly supported by Delphi. Captured by SPIRIT 20c. No further evidence to support inclusion.			✓ (65.7%)	
44	Include a priori identified summary statistics (as appropriate)	(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	**Exclude** **Captured by SPIRIT 20a**	**Exclude**	59.8	10.9	1. Wording is unclear/vague 2. Should be covered in SAP 3. May be useful to 'flag how PRO data will be used.' 4. Covered by Item 39	-	-	Not supported by Delphi.			✓ (65.7% merge with 39?)	

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45	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	(14) Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	**Exclude** **Captured by SPIRIT14.**	**Exclude**	55.3	10.6	1. SAP not protocol 2. Covered by item 14	-	-	Not supported by Delphi. .			✓ (58.6%)	
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)	(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	**Exclude** **Partially captured by SPIRIT 20a.**	**Exclude**	77.9	4.2	1. Briefly mention in the protocol (cite references) 2. Include in SAP/HE plan?	-	-	Supported by the Delphi panel. Partially captured by SPIRIT 20a. No further evidence to support inclusion.			✓ (67.7%)	
47	State statistical significance levels and include plans for multiplicity/controlling type 1 error		**SPIRIT-20a-PRO Extension** **Merge 47 & 48** Rationale: (1) This is partially covered by SPIRIT in the explanatory document but the	**State statistical significance levels and include plans for multiplicity/controlling type 1 error**	84.5	4.1	1. Should be covered in the SAP 2. Required by regulators (FDA) 3. Overlap with SPIRIT	1.33%	10.13%	Supported by the Delphi panel. Partially covered in general terms by the SPIRIT 20a wording but lacks important detail. Rarely addressed			✓ (71.7%; 64.7%)	

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48	Pre-specify sequence of testing/exploratory analyses to control for multiplicity or pre-specify domains (e.g. in a regulatory trial/labelling claim)		item wording does not address multiplicity (2) This is a major issue for PROs because of potential number of analyses. (3) Required by regulators. (4) Hardly ever addressed in practice		65.3	12.6	1. Should be included in SAP 2. Redundant item as covered by 47			in practice.				
49	Specify the criteria for clinical significance (e.g. state minimal [clinical] important difference and/or responder definition (size and duration of benefit))	(14) Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	**Exclude**	**Exclude**	86.6	3.1	1. Should be included in the SAP/HE plan. 2. 'Very important issue' 3. 'very important and to link these to potential claims 4. Not always available/possible. (As part of Elaboration for SPIRIT 14 (merged Items 17 and 41), minimally important difference and responder definition can be mentioned as ways of specifying a priori smallest important clinical effect for sample size determination.)	-	-	Strongly supported by the Delphi panel. Captured by SPIRIT 14. No further evidence to support inclusion			✓ (67.7%)	
50	State how missing data will be described	(20c) Definition of analysis population relating to protocol non-adherence (e.g., as randomised analysis), and any statistical methods to handle missing data (e.g., multiple imputation)	**SPIRIT-20c-PRO Extension** **Merge items 50 and 51**	**State how missing data will be described and the methods for handling missing assessments/items (e.g. approach to imputation and sensitivity analyses)**	72.9	5.2	1. Should be included in the SAP 2. Wording requires clarification	45.33%	30.38%	**B** Supported by Delphi. Partially captured by SPIRIT 20c. Inconsistently addressed in practice.			✓ (66.7%)	

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51	Describe method for handling missing assessments (e.g. approach to imputation and sensitivity analyses)				78.6	5.1	1. Include in SAP 2. Covered by SPIRIT	45.33%	30.38%				✓ (68.7%)	
52	Describe the role of the Data Monitoring Committee and Quality Assurance for PROs	(21a) Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC not needed	**Exclude** **Captured by SPIRIT 21a**	**Exclude**	62.1	11.6	1. Overlaps with other QA items 2. Not specific to PROs	60.00%	0.63%	Not supported by Delphi.				Data monitoring charter

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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	(22) Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	**SPIRIT-22-PRO Extension** **Merge items 53 & 55**	**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. Specify whether PRO forms will be used to influence therapy or patient management. This information should also be provided in the PIS.**	68.8*	8.6	1. 'Critical but does the field have a sound approach towards this?' 2Include in training/SOPs	10.67%	0.63%	Inconclusive support from the Delphi panel – *note queries over whether the field has an approach to address this. Partially covered in general terms by the SPIRIT 22 wording but lacks important detail. Rarely addressed in practice. See http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0144658 for current management.	✓ (60.6%; 64.7%)	✓ (51.5%- item 55)		

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54	Describe informed consent procedure for PRO assessment	(26a) Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (26b) Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable. 32 Model consent form and other related documentation given to participants and authorized surrogates	**SPIRIT-26a/b-PRO Elaboration**		70.5	13.7	1. Should be included in the PIS in the appendix 2. Informed consent - not specific to PROs	1.33%	13.92%	**C** Supported by Delphi. Captured by SPIRIT items 26a/b Rarely addressed in practice.	✓ 67.7%;			

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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?)	(22) Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	**SPIRIT-22-PRO Extension** **Merge items 53 & 55**	**See 53 above**	78.4	6.2	1. Links to items 53/54 2. Not common for PROs to inform care in the trial [NOT TRUE BASED ON OUR EVIDENCE] 3. Should be in PIS 4. 'As this can introduce treatment variation and bias findings, it is important to note whether personnel are allowed to review, and alter treatment based on PRO.'	4.00%	3.80%	**See 53 above**				
56	Include detailed plans for regular feedback to participants via letter/newsletter on PRO aspect of study	(31a) Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	**Exclude** **Captured by SPIRIT 31a**	**Exclude**	40.2	21.6	1. Good research practice 2. Applies to overall study not just PROs 3. May help improve compliance at later time points 4. Potential for bias Matrix notes - should be informed by trials ops group including patients.	33.33%	0.63%	Not supported by Delphi.	✓ (55.6%)	✓ (54.6%)		