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

3

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18

19

20 **Key Points:**

21 **Question:** What information should be included in a clinical trial protocol when a patient-reported
22 outcome (PRO) is a primary or key secondary outcome?

23 **Findings:** Following an international consensus development process using the Enhancing QUALity
24 and Transparency Of health Research (EQUATOR) methodology, sixteen PRO specific items are
25 recommended for inclusion in clinical trial protocols.

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

27

28 **Revision:** 18 December 2017

29 **Word Count:** 3941

30 **ABSTRACT (338/350 words)**

31

32 **Importance**

33 Patient-reported outcome (PRO) data from clinical trials can provide valuable evidence to inform
34 shared-decision making, labelling claims, clinical guidelines, and health policy; however, the PRO
35 content of clinical trial protocols is often suboptimal. The SPIRIT (Standard Protocol Items:
36 Recommendations for Interventional Trials) Statement was published in 2013 and aims to improve the
37 completeness of trial protocols by providing evidence-based recommendations for the minimum set of
38 items to be addressed, but does not provide PRO-specific guidance.

39

40 **Objective**

41 To develop international, consensus-based, PRO-specific protocol guidance: the SPIRIT-PRO
42 extension.

43

44 **Design, Setting, and Participants**

45 The SPIRIT-PRO Extension was developed following the Enhancing QUALity and Transparency Of
46 health Research (EQUATOR) Network's methodological framework for guideline development. This
47 included: (i) a systematic review of existing PRO-specific protocol guidance to generate a list of
48 candidate PRO-specific protocol items (published 2014); (ii) refinements to the list and removal of
49 duplicate items by the International Society for Quality of Life Research (ISOQOL) PROtocol Checklist
50 Taskforce; (iii) an international stakeholder survey of: clinical trial research personnel, PRO
51 methodologists, health economists, psychometricians, patient advocates, funders, industry
52 representatives, journal editors, policy makers, ethicists and researchers responsible for evidence
53 synthesis (distributed by 38 international partner organizations, October 2016); (iv) an international
54 Delphi exercise (n=137 invited; October 2016 to February 2017)and consensus meeting (n=30
55 invited; May 2017). Prior to voting, consensus meeting participants were informed of the results of the
56 Delphi exercise and given data from structured reviews evaluating the PRO protocol content of three
57 defined samples of trial protocols.

58

59 **Results**

60 The systematic review identified 162 PRO-specific protocol recommendations from 54 sources. The
61 ISOQOL Taskforce (n=21) reduced this to 56 items, which were considered by 138 international
62 stakeholders and 99 Delphi panelists. The final wording of the SPIRIT-PRO Extension was agreed at
63 a consensus meeting (n=29 participants) and reviewed by external stakeholders during a consultation
64 period. Eleven extensions and five elaborations to the SPIRIT 2013 checklist are recommended for
65 inclusion in clinical trial protocols where PROs are a primary or key secondary outcome. Extension
66 items focused on PRO specific issues relating to the: trial rationale, objectives, eligibility criteria,
67 concepts used to evaluate the intervention, timepoints for assessment, PRO instrument selection and
68 measurement properties, data collection plan, translation to other languages, proxy completion,
69 strategies to minimise missing data and whether PRO data will be monitored during the study to
70 inform clinical care.

71

72 **Conclusions and relevance**

73 These guidelines provide recommendations for items that should be addressed and included in
74 clinical trial protocols in which PROs are a primary or key secondary outcome. Improved design of
75 clinical trials including PROs could help ensure high-quality data that may inform patient-centered
76 care.

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85 **INTRODUCTION**

86 Clinical trial protocols are essential documents that describe the study design and conduct. A
87 protocol should provide sufficient detail to enable funders, reviewers and ethics committees to
88 appraise the trial's scientific, methodological and ethical rigor and for the research team to deliver a
89 high quality study.^{1,2} Although they serve as the foundation for study planning, conduct, reporting, and
90 appraisal, trial protocols vary greatly in content and quality.^{1,2} To address this issue, the SPIRIT
91 (Standard Protocol Items: Recommendations for Interventional Trials) Statement was published in
92 2013.^{1,2} SPIRIT provides an evidence-based list of items recommended for inclusion in trial protocols.
93 It does not, however, provide specific guidance on protocol content relating to patient-reported
94 outcomes (PROs), such as health-related quality of life (HRQOL) or patient-reported symptoms.

95
96 The importance of PROs has been recognized by major international health policy and regulatory
97 authorities and patients.³⁻⁵ PRO trial results, if captured in a scientifically rigorous way, may inform
98 clinical decision-making⁶, pharmaceutical labelling claims⁴⁻⁵, product reimbursement and influence
99 healthcare policy.⁶ Despite this, the quality of PRO content in many protocols is often suboptimal,
100 regardless of the degree of adherence to SPIRIT.⁷⁻⁹ Because PROs are intrinsically subjective and
101 require completion by patients within a specific time-frame, they present a range of scientific and
102 logistical challenges for researchers and data collection staff.¹⁰⁻¹² Comprehensive planning and
103 instruction in the protocol can mitigate many PRO-specific issues through trial conduct, and
104 subsequent analysis and reporting. Protocol developers, particularly those not familiar with PRO
105 methodology, may benefit from explanation of PRO-specific aspects to facilitate improvements in
106 content.

107
108 The aim of this international project was to develop an evidence-based extension of the SPIRIT 2013
109 statement, identifying additional PRO items recommended for inclusion in clinical trial protocols
110 (extensions) and to elaborate on the existing SPIRIT 2013 statement specifically as applied to PROs
111 (elaborations).¹³ This article describes the methods used to gain consensus on each additional
112 SPIRIT-PRO extension/elaboration, provides a brief explanatory rationale, and includes PRO specific
113 items that may be included in supplemental trial documents.

114
115

116 **SPIRIT-PRO DEVELOPMENT METHODS**

117 The SPIRIT-PRO Extension was developed according to the Enhancing QUALity and Transparency Of
118 health Research (EQUATOR) Network's methodological framework for guideline development
119 (eFigure 1 in Supplement 1).¹⁴ This included: a systematic review of existing PRO-specific protocol
120 guidance¹⁵; an international stakeholder survey; Delphi exercise and consensus meeting; followed by
121 consultation on the final SPIRIT-PRO Extension.¹⁴ The systematic review comprised a search of
122 MEDLINE, EMBASE, CINHAL and Cochrane Library databases (inception to February 2013) using
123 the key words 'Patient-Reported Outcomes' or 'Health-Related Quality of Life' in combination with
124 'Guidance', 'Guidelines' or 'Checklist'. Further guidance documents were identified via Google,
125 Google scholar, requests to members of the UK Clinical Research Collaboration registered clinical
126 trials units, international experts and through citation and reference searches of included articles.
127 Papers were deemed eligible if they contained guidance and/or a checklist on PRO related trial
128 protocol content.¹⁵

129 eFigure 1 summarizes the methods and participants involved in the development of SPIRIT-PRO, the
130 numbers of candidate items considered at each step, and the flow towards the final set of items
131 included in SPIRIT PRO. eTable 1 in Supplement 1 outlines the participant characteristics. Patient
132 partners contributed to the co-design of the research, grant application, have provided input
133 throughout the study and are coauthors.

134

135 ***Ethical Review of Study***

136 Ethical approval was provided by The University of Birmingham Ethical Review Board (Reference:
137 ERN_16-0819). Participant information was provided to potential participants prior to survey
138 completion and in advance of the consensus meeting. Survey participants provided electronic
139 informed consent and written consent was provided by the consensus meeting participants.

140

141 ***Systematic review of existing PRO-specific protocol guidance and development of the Delphi
142 and Stakeholder Survey***

143 Our systematic review of existing PRO protocol guidance identified 162 PRO-specific protocol
144 recommendations from 54 sources¹⁵. The International Society for Quality of Life Research (ISOQOL)
145 PROtocol Checklist Taskforce comprising international experts in PROs research and clinical trials

146 (eTable 1 and Acknowledgments, Supplement 1) reduced this list to 56 candidate items by removing
147 or merging duplicate items, meaning 56 items were included in the subsequent identical Stakeholder
148 and Delphi surveys. Survey participants were asked to rate the importance of including each of the 56
149 candidate items in the final SPIRIT-PRO Extension using a 9-point scale: 'not important' (1-3),
150 'important but not critical' (4-6) and 'critical' (7-9). Respondents provided separate ratings according to
151 whether a PRO was included as a primary versus secondary outcome in a trial.

152

153 ***International stakeholder survey***

154 In 2016, 38 international partner organizations (detailed in Supplement 1) invited their members with
155 relevant expertise to complete an online survey. From these organizations, a total 138 participants
156 provided anonymized survey results which informed round 2 of the Delphi panel exercise.

157

158 ***International Delphi exercise***

159 In parallel with the international stakeholder survey, key experts (n=114) from the ISOQOL PROtocol
160 Checklist Taskforce, international partner organizations and other experts known or recommended to
161 the SPIRIT-PRO Executive were invited to join an international, multidisciplinary expert Delphi Panel.
162 Delphi panelists were advised not to complete the stakeholder survey to avoid double counting of
163 results. Delphi panelists (n=99) completed 2 rounds of online surveys and results informed the
164 subsequent international consensus meeting. Data collected from the stakeholder and round 1 Delphi
165 surveys were anonymized and the item-level results were provided to the Delphi panel for
166 consideration prior to voting in Delphi round 2. Further details and the results of the Delphi and
167 stakeholder surveys are available on the study website.¹⁶

168

169 ***Consensus meeting***

170 Using the Stakeholder and Delphi survey results, the SPIRIT-PRO Operations Team (MC, DK, RMB,
171 AS, MK) mapped the 56 candidate SPIRIT-PRO items to corresponding SPIRIT-2013 items, revising
172 wording as needed to address stakeholder/Delphi panelist comments. For each candidate SPIRIT-
173 PRO item, the Operations Team presented the consensus meeting delegates with recommendations
174 for SPIRIT 'elaborations' and 'extensions' (see Box for definitions) based on a decision tree (eFigure
175 2 in Supplement 1), which incorporated information drawn from the Delphi survey and three separate

176 reviews of PRO protocol content (n= 207 protocols): protocols from the UK National Institute for
177 Health Research (NIHR) Health Technology Assessment (HTA) programme⁷; cancer trial protocols
178 from the NIHR⁸ and international ovarian cancer protocols⁹. Twenty-nine participants purposively
179 sampled from the Delphi panel attended the two-day consensus meeting hosted by the University of
180 Birmingham, England, in May 2017 (eTable 1). The meeting was designed to seek consensus on the
181 content of the SPIRIT-PRO Extension. Meeting participants were invited to consider the focus of the
182 guidance and agreed that it should apply to trials where PROs are a primary or key secondary
183 outcome (as defined in Glossary). Delegates anonymously voted using Turning point© (v5.1,
184 2012)/Responseware© software to either: include the candidate item as recommended; exclude the
185 item; or initiate further discussion. Key research evidence (Round 2 Delphi survey results and
186 systematic review data) presented to meeting participants is provided in Supplement 2. Consensus
187 meeting participants were also invited to review Delphi results for recommendation on where to
188 include each of the candidate items in addition to, or instead of, the trial protocol (eg,
189 guidance/training for trial staff, information/guidance for study participants, or the statistical analysis
190 plan (SAP).

191

192 ***Final consultation***

193 Following the consensus meeting, attendees commented on wording and agreed on the penultimate
194 SPIRIT-PRO Extension content. Broader feedback on the final guidance was sought from our Delphi
195 panel and international partners during a three week consultation period. Final edits in response to
196 feedback were made by the Operations Team and agreed by the SPIRIT-PRO Group.

197

198 **RESULTS**

199

200 ***SPIRIT-PRO Checklist Items and Explanation***

201 The final SPIRIT-PRO Extension recommends that, in conjunction with existing SPIRIT 2013 items,
202 16 items should be routinely addressed in all clinical trial protocols where PROs are a primary or key
203 secondary outcome (11 extensions; 5 elaborations). Further information regarding the SPIRIT 2013
204 items is detailed in references^{1,2}. Table 1 lists the items of the SPIRIT 2013 checklist (left column) and

205 the SPIRIT-PRO extensions/elaborations (right-hand column). The 11 extensions and 5 elaborations
206 incorporated 34 of the original 56 candidate items, as 27 items were merged by consensus. One new
207 item was generated through discussion (SPIRIT-18a-PRO Extension (iii)). Definitions of key terms are
208 contained in the Glossary (Box). Below we provide a brief explanation for each PRO
209 extension/elaboration, including references to supporting empirical evidence where available (items
210 6a through 22). Item 5a was not supported by empirical evidence but was supported by expert opinion
211 drawn from our systematic review of PRO protocol guidance¹⁵, and in line with the development of the
212 original SPIRIT statement^{1, 2}, was underpinned by a strong pragmatic rationale.

213

214 **Administrative Information**

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

216 **Elaboration.** *Explanation:* Providing information (eg, name, affiliation, contact details) on who wrote
217 the PRO specific aspects of the trial protocol promotes transparency and accountability, and identifies
218 the appropriate point of contact for resolution of any PRO specific queries. Where patients have
219 actively contributed to this process, this should be documented as per recent guidance for the
220 reporting of patient and public involvement.¹⁷

221

222 **Describe the PRO specific research question and rationale for PRO assessment, and**

223 **summarize PRO findings in relevant studies: SPIRIT-6a-PRO Extension.** *Explanation:* Inclusion of
224 PROs in a trial requires careful consideration and planning. A clearly defined question helps with
225 selection of measures and specification of hypotheses and analyses. Evidence suggests that many
226 trials include PROs without specifying the PRO-specific research question, and without a rationale or
227 any reference to PROs in related studies.⁷⁻⁹ Consequently, staff and patients may not understand why
228 PROs are being assessed, and missing data may result.⁷⁻¹² When the PRO is a secondary outcome,
229 a brief rationale may be adequate.

230

231 **State specific PRO objectives or hypotheses (including relevant PRO concepts/domains):**

232 **SPIRIT-7-PRO Extension.** *Explanation:* PRO measures may be multidimensional (eg, HRQOL) or
233 unidimensional (eg, specific symptoms such as pain) and assessments may be scheduled at several
234 time points during a trial. Pre-specification of objectives and hypotheses encourages identification of

235 key PRO domains and time-points, reducing the risk of multiple statistical testing and selective
236 reporting of PROs based on statistically significant results (see also PRO elaboration 20a below).⁴

237

238 **Methods: Participants, interventions, and outcomes**

239 **Specify any PRO-specific eligibility criteria (eg, language/reading requirements or pre-**
240 **randomization¹⁸ completion of PRO). If PROs will not be collected in the entire study sample,**
241 **provide a rationale and describe the method for obtaining the PRO subsample: SPIRIT-10-PRO**
242 **Extension. Explanation:** Any PRO-specific eligibility criteria should be considered at the design stage
243 of the trial and clearly specified in the protocol. In large trials, sufficient power may be achieved by
244 collecting PROs from a representative subset of participants; whilst in some trials it may not be
245 possible to collect PROs in the entire population (eg, due to non-availability of validated
246 questionnaires in all languages)⁸; in such instances the rationale for the sampling method should be
247 described.

248

249 **Specify the PRO concepts/domains used to evaluate the intervention (eg, overall HRQOL,**
250 **specific domain, specific symptom) and, for each one, the analysis metric (eg, change from**
251 **baseline, final value, time to event) and the principal time point or period of interest: SPIRIT-**
252 **12-PRO Extension. Explanation:** The PRO concepts/domains and time points for assessment should
253 closely align with the trial objectives and hypotheses. Because of the risk of multiple statistical testing,
254 the domain(s) and principal time point(s) for analyses should be specified *a priori*.^{4,19}

255

256 **Include a schedule of PRO assessments, providing a rationale for the time points, and**
257 **justifying if the initial assessment is not pre-randomization. Specify: time windows; whether**
258 **PRO collection is prior to clinical assessments; and if using multiple questionnaires, whether**
259 **order of administration will be standardized: SPIRIT-13-PRO Extension. Explanation:** Provision of
260 an easy to follow schedule will assist staff and may help reduce missing data.¹⁸ Collecting PRO data
261 prior to randomization helps ensure an unbiased baseline assessment, and if specified as an eligibility
262 criterion, ensures data completeness. This is important as baseline PRO data are often used as a
263 covariate in analyses and is essential to calculating change from baseline. Completion of PROs prior
264 to clinical assessments (as these may influence patient responses) and standardization of the order of

265 questionnaire administration are advised to help reduce measurement error.²⁰ Allowable time
266 windows for each scheduled PRO assessment should be specified to ensure that PRO data collection
267 captures the impact of the clinical event(s) of interest.

268

269 **Where a PRO is the primary endpoint, state the required sample size (and how it was**
270 **determined) and recruitment target (accounting for expected loss to follow-up). If sample size**
271 **is not established based on PRO endpoint, then discuss the power of the principal PRO**

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

278

279 ***Methods: Data collection, management, and analysis***

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

286 selection of PROs to be used in a clinical trial requires careful consideration. Ideally the measure
287 should be validated in the target population.²³ Consideration should be given to the number of
288 questionnaires to be used, acceptability of the questions, and the likely patient burden (eg, time taken
289 for completion and cognitive and/or emotional burden). Justification for the measures selected will
290 help trial personnel understand why specific measures are being used.¹⁰ Questionnaires should be
291 used in accordance with any existing user manuals to promote data quality and ensure standardized
292 scoring, and any deviations should be described.

293

294 **Include a data collection plan outlining the permitted mode(s) of administration (eg, paper,**
295 **telephone, electronic, other) and setting (eg, clinic, home, other): SPIRIT-18a(ii)-PRO**

296 **Extension.** *Explanation:* It is important that both research personnel and trial participants understand
297 how, when, and where PRO data will be collected in the study. Increasingly, electronic PRO
298 assessment is undertaken in trials, so evidence of equivalence between different modes of
299 administration should be considered.²⁴ If electronic PRO measures contain only minor modifications
300 with respect to the paper based versions, usability testing and cognitive debriefing may provide
301 sufficient evidence of equivalence.^{24,25} The setting for PRO data collection should be described and
302 standardized across trial arms and sites.

303

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

306 **Extension.** *Explanation:* Multinational trials, or national trials involving participants with different
307 languages, will require measures that have been translated, and culturally adapted where needed,
308 using appropriate methodology.^{11,26} This may influence the selection of measure to be used, since
309 inclusivity of participants can help ensure the generalizability of trial results. Plans to use translated
310 versions should be specified in the protocol, citing references where available.

311

312 **Where the trial context requires someone other than the trial participant to answer on their**
313 **behalf (a proxy reported outcome), state and justify this. Provide/cite evidence of the validity**
314 **of proxy assessment if available: SPIRIT-18a(iv)-PRO Extension.** *Explanation:* In some contexts,

315 eg, trials involving young children, or cognitively impaired participants, it may be necessary for
316 someone other than the trial participant to respond on their behalf. Clear justification and specification
317 of proxy reporting in the protocol will allow external reviewers to assess potential bias and will
318 facilitate trial reporting in accordance with CONSORT-PRO.²⁷ Evidence of the size and direction of
319 proxy bias is a key aspect of the validity of proxy versions of PRO measures, informing valid
320 interpretation and comparison of results. Note that the European Medicines Agency (EMA) state that
321 'in general proxy reporting should be avoided, unless the use of such proxy raters may be the only
322 effective means of obtaining information that might otherwise be lost'.⁵ The US Food and Drug

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

325

326 **Specify PRO data collection and management strategies for minimising avoidable missing**

327 **data: SPIRIT-18b(i)-PRO Extension.** *Explanation:* Missing data is a particular problem for PROs

328 since it is often those participants with the poorest outcomes in a trial that fail to complete planned

329 PRO assessments and data cannot be obtained retrospectively beyond the timeframe of interest or

330 from medical records. This is a potentially significant source of bias, and may reduce trial power.²⁸ It is

331 important to note that not all missing PRO data is avoidable: patients have the right to decide not to

332 complete questionnaires. Common reasons for avoidable missing PRO data are administrative errors,

333 lack of explanation of the importance of PRO data, and overly-burdensome questionnaires.

334 Addressing these in the protocol should help minimize avoidable missing data. A recent systematic

335 review provides a range of design, implementation and reporting strategies to help minimize and

336 address missing PRO data.¹⁸ Examples of protocol content include: ensuring PRO endpoints and

337 hypotheses are clearly defined and scientifically compelling, providing a rationale for PRO

338 assessment, clearly specifying the PRO assessment time points, defining acceptable PRO

339 assessment time windows, aligning PRO assessment time points to clinic visits (if clinically

340 informative), minimizing patient burden, and specifying the importance of complete PRO data.¹⁸

341

342 **Describe the process of PRO assessment for participants who discontinue or deviate from**

343 **their assigned intervention protocol: SPIRIT-18b(ii)-PRO Elaboration.** *Explanation:* A clear plan

344 for collection of PROs for trial participants who withdraw early from a study or who discontinue the

345 intervention will help minimise bias,²⁹ ensure staff collect all required PRO data in a standardized and

346 timely way, and may assist ethical appraisal of the study.

347

348 **State PRO analysis methods including any plans for addressing multiplicity/type 1 (α) error:**

349 **SPIRIT-20a-PRO Elaboration.** *Explanation:* Many questionnaires, such as HRQOL measures, are

350 multidimensional and therefore may yield several summary scores (eg, multiple domains and an

351 overall score). Further, PROs are usually assessed at multiple time points. Statistical analysis of all

352 domains and timepoints implies multiple hypothesis testing, which inflates the probability of false

353 positives (type 1 error, or 'alpha').¹⁹ This can be contained by pre-specifying the key PRO domain(s)
354 or overall score of interest, and the principal time point(s). Any plans to address multiplicity, such as
355 step-wise or sequential analyses, whereby multiple endpoints are tested in a defined sequence that
356 contains the overall type 1 error to the desired level, or conventional non-hierarchical methods (eg,
357 Bonferroni correction), should be specified *a priori*.⁴ The protocol should either fully address these
358 issues, or provide a summary, with reference to where full details can be found (eg, in the statistical
359 analysis plan (SAP)).

360

361 **State how missing data will be described and outline the methods for handling missing items**
362 **or entire assessments (eg, approach to imputation and sensitivity analyses): SPIRIT-20c-PRO**

363 **Elaboration.** *Explanation:* There are two levels of missing PRO data: 1) patient completion of some,
364 but not all items within an instrument; 2) absence of the entire PRO assessment. Whether and how
365 missing items should be imputed is usually specified in an instrument's scoring algorithm. When entire
366 PRO assessments are missed, analysis requires assumptions about why those data were missing (ie,
367 the missing data mechanism). There are a range of statistical approaches, each with specific
368 assumptions. Inappropriate method selection may lead to potentially biased and misleading
369 results.^{18,29} Common methods include complete case analysis, imputation (various approaches), a
370 range of maximum likelihood modelling approaches, and sensitivity analysis.²⁹ The protocol should
371 acknowledge these issues, and address them in summary, with full detail provided in the SAP.

372

373 **Methods: Monitoring**

374 **State whether or not PRO data will be monitored during the study to inform the clinical care of**
375 **individual trial participants and, if so, how this will be managed in a standardized way.**

376 **Describe how this process will be explained to participants, eg, in the participant information**
377 **sheet and consent form: SPIRIT-22-PRO Extension.** *Explanation:* Evidence suggests the

378 monitoring and management of 'PRO-alerts' (psychological distress or physical symptoms evident
379 from PRO responses that may require an immediate response) varies across and within trials.^{10,11,30}

380 In order to protect the interests of trial participants and minimize potential bias, it is important to

381 specify plans for monitoring.³¹ If monitoring is not planned (for example in a low risk study where

382 alerts are not anticipated) then this should also be briefly stated in the protocol, the participant
383 information sheet and consent form. Alternative support mechanisms for patients should be outlined.

384

385 **Supplementary trial documents**

386 Supplement 3 outlines additional items recommended for inclusion in other trial documentation such
387 as the SAP, participant information sheet or in training/guidance documents for staff.

388

389 **DISCUSSION**

390 The SPIRIT-PRO Extension provides international consensus-based guidance on PRO-specific
391 information that should be included in clinical trial protocols. It comprises 16 items: 5 elaborations to
392 existing SPIRIT 2013 items in the context of PROs, and 11 new extensions, for use alongside the
393 existing SPIRIT 2013 guidance.^{1,2} It is important to note that these are minimum requirements, and
394 that there may be value in including additional items in the protocol and/or in supplementary trial
395 documents, as outlined in Supplement 3. While this guidance has been developed for trials where
396 PROs are a primary or key secondary outcome we encourage protocol writers to consider use of this
397 guidance in all trials or clinical research studies where PROs are collected, including if PROs are
398 exploratory endpoints. The guidance does not aim to be prescriptive regarding how information
399 should be included, as this may vary depending on the research setting and local requirements.
400 Further details of empirical evidence underpinning the SPIRIT-PRO items and examples for
401 implementation will be provided in a future explanatory publication on the PROlearn³² and SPIRIT
402 Initiative³³ websites and will be facilitated through further development of the SPIRIT 2013
403 implementation tool SEPTRE³³ (SPIRIT Electronic Protocol Tool and Resource) and through
404 dissemination via our international partners (see Supplement 1). Inclusion of PRO-specific protocol
405 content will facilitate appraisal of the PRO elements by funders, reviewers, research ethics
406 committees, and patient partners. The SPIRIT-PRO Extension is intended to encourage and facilitate
407 careful planning of PRO components of trials, and thereby improve PRO trial design. Consequently,
408 this is expected to help staff and patients understand the rationale for PRO assessment, improve
409 PRO data completeness and quality, facilitate high quality analysis and reporting, and ultimately
410 improve the quality of the global PRO evidence base.

411

412 To maximize the benefit of PRO data in policy and practice, it is recommended that careful
413 consideration be given to the selection of outcomes and measures^{34,35}, analysis of PRO data,^{4,5,36} and
414 transparent reporting in accordance with CONSORT-PRO.²⁷ Patient and public involvement in all of
415 these aspects can help to ensure that PRO selection and application is transparent, relevant and
416 acceptable.³⁷⁻³⁸ Consistent with this philosophy, patient partners have been involved in all aspects of
417 the development of the SPIRIT-PRO extension.³⁷⁻³⁸ Ultimately, high quality PRO trial results will help
418 ensure that the patient's voice is central to informing shared-decision making, labelling claims, clinical
419 guidelines, and health policy, making patient-centered care a reality.

420

421 **Limitations**

422 Respondents to the stakeholder survey were self-selecting and Delphi and consensus meeting
423 participants were purposively sampled based on their roles and expertise relating to PROs.
424 Participants are therefore more likely to have more knowledge relating to PROs than broader
425 research personnel.

426

427 **Conclusions**

428 The SPIRIT-PRO guidelines provide recommendations for items that should be addressed and
429 included in clinical trial protocols in which PROs are a primary or key secondary outcome. Improved
430 design of clinical trials including PROs could help ensure high-quality data that may inform patient-
431 centered care.

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511

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Glossary Box

SPIRIT

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

SPIRIT-PRO Extension Item

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

SPIRIT Elaboration Item

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

Patient-Reported Outcome (PRO)

An outcome reported directly by patients themselves and not interpreted by an observer; PROs may include patient assessments of health status, quality of life, or symptoms.²⁷

Proxy-Reported Outcome

'A measurement based on a report by someone other than the patient reporting as if he or she is the patient.'¹⁴

Health-Related Quality of Life (HRQOL)

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

Primary Outcome/ Endpoint

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

Secondary Outcomes / Endpoint(s)

These are outcomes pre-specified in the protocol to assess additional effects of the intervention. Some PROs may be identified as important or key secondary outcomes.

'Important' or 'Key' Secondary Patient-Reported Outcomes / Endpoints

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

Concept

'The specific measurement goal (ie, the thing that is to be measured by a PRO instrument). In clinical trials, a PRO instrument can be used to measure the effect of a medical intervention on one or more concepts. PRO concepts represent aspects of how patients function or feel related to a health condition or its treatment.'⁴

Domain

'A subconcept represented by a score of an instrument that measures a larger concept comprised of multiple domains. For example, psychological function is the larger concept containing the domains subdivided into items describing emotional function and cognitive function.'¹⁴

Instrument

'A means to capture data (ie, a questionnaire) plus all the information and documentation that supports its use. Generally, that includes clearly defined methods and instructions for administration or responding, a standard format for data collection, and well-documented methods for scoring, analysis, and interpretation of results in the target patient population.'¹⁴

Item

'An individual question, statement, or task (and its standardized response options) that is evaluated by the patient to address a particular concept.'¹⁴

Time window

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

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

SPIRIT Section	SPIRIT Item No	SPIRIT Item Description	Addressed on page number#	SPIRIT-PRO Item No	SPIRIT PRO Extension Item Description	Addressed on page number#
Administrative information						
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym				
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry				
	2b	All items from the World Health Organization Trial Registration Data Set				
Protocol version	3	Date and version identifier				
Funding	4	Sources and types of financial, material, and other support				
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors		SPIRIT-5a-PRO Elaboration	Specify the individual(s) responsible for the PRO content of the trial protocol.	
	5b	Name and contact information for the trial sponsor				
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities				
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)				
Introduction						

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	SPIRIT-6a-PRO Extension	Describe the PRO specific research question and rationale for PRO assessment, and summarize PRO findings in relevant studies.
	6b	Explanation for choice of comparators		
Objectives	7	Specific objectives or hypotheses	SPIRIT-7-PRO Extension	State specific PRO objectives or hypotheses (including relevant PRO concepts/domains).
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)		
Methods: Participants, interventions, and outcomes				
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained		
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	SPIRIT-10-PRO Extension	Specify any PRO-specific eligibility criteria (eg, language/reading requirements or pre-randomization completion of PRO). If PROs will not be collected in the entire study sample, provide a rationale and describe the method for obtaining the PRO subsample.
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered		
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)		
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)		
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial		
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point	SPIRIT-12-PRO Extension	Specify the PRO concepts/domains used to evaluate the intervention (eg, overall HRQOL, specific domain, specific symptom) and, for each one, the analysis metric (eg, change from baseline, final value, time to event) and the principal time point or period of interest.

		for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended		
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	SPIRIT-13-PRO Extension	Include a schedule of PRO assessments, providing a rationale for the time points, and justifying if the initial assessment is not pre-randomization. Specify: time windows; whether PRO collection is prior to clinical assessments; and if using multiple questionnaires, whether order of administration will be standardized.
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	SPIRIT-14-PRO Elaboration	Where a PRO is the primary endpoint, state the required sample size (and how it was determined) and recruitment target (accounting for expected loss to follow-up). If sample size is not established based on PRO endpoint, then discuss the power of the principal PRO analyses.
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size		
Methods: Assignment of interventions (for controlled trials)				
Allocation:				
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions		
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned		
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions		
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how		
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial		
Methods: Data collection,				

management, and analysis				
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	SPIRIT-18a(i)-PRO Extension	Justify the PRO instrument to be used, and describe domains, number of items, recall period, instrument scaling/scoring (eg, range and direction of scores indicating a good/poor outcome). Evidence of PRO instrument measurement properties, interpretation guidelines, and patient acceptability/burden should be provided or cited if available, ideally in the population of interest. State whether the measure will be used in accordance with any user manual and specify and justify deviations if planned.
			SPIRIT-18a(ii)-PRO Extension	Include a data collection plan outlining the permitted mode(s) of administration (eg, paper, telephone, electronic, other) and setting (eg, clinic, home, other).
			SPIRIT-18a(iii)-PRO Extension	Specify whether more than one language version will be used, and state whether translated versions have been developed using currently recommended methods.
			SPIRIT-18a(iv)-PRO Extension	Where the trial context requires someone other than the trial participant to answer on their behalf (a proxy reported outcome), state and justify this. Provide/cite evidence of the validity of proxy assessment if available.
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	SPIRIT-18b(i)-PRO Extension	Specify PRO data collection and management strategies for minimising avoidable missing data.
			SPIRIT-18b(ii)-PRO Elaboration	Describe the process of PRO assessment for participants who discontinue or deviate from their assigned intervention protocol.
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol		

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	SPIRIT-20a-PRO Elaboration	State PRO analysis methods including any plans for addressing multiplicity/type 1 (α) error.
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)		
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	SPIRIT-20c-PRO Elaboration	State how missing data will be described and outline the methods for handling missing items or entire assessments (eg, approach to imputation and sensitivity analyses).
Methods: Monitoring				
	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed		
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial		
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	SPIRIT-22-PRO Extension	State whether or not PRO data will be monitored during the study to inform the clinical care of individual trial participants and, if so, how this will be managed in a standardized way. Describe how this process will be explained to participants, eg, in the participant information sheet and consent form.
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor		
Ethics and dissemination				
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval		
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)		

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

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