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Ethical considerations for the inclusion of patient-reported outcomes in clinical research: The PRO ethics guidelines

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Key points

Question What ethical considerations should be considered by researchers, research ethics committees and funders when conducting or reviewing patient-reported outcome (PRO) clinical research?

Findings An international consensus Delphi process was developed according to the Enhancing Quality and Transparency of Health Research (EQUATOR) methodology; 14 items addressing ethical considerations were recommended for inclusion in the PRO ethics guidelines.

Meaning Addressing the items in the PRO ethics guidelines has the potential to improve the quality of PRO in clinical research while promoting and protecting participant autonomy and protecting participant and researcher welfare.

Abstract

Importance Patient-reported outcomes (PROs) can inform healthcare decisions, regulatory decisions, and healthcare policy, and also can be used for audit/benchmarking and to monitor symptoms and provide timely care tailored to individual needs. However, several ethical issues have been raised in relation to PRO use.

Objective To develop an international, consensus-based, PRO-specific ethical guidelines for clinical research.

Evidence Review The PRO ethics guidelines were developed following the Enhancing Quality and Transparency of Health Research (EQUATOR) Network's guideline development framework. This included a systematic review of the ethical

implications of PROs in clinical research. The databases MEDLINE (Ovid), EMBASE, AMED and CINAHL were searched from inception until May 2020. The keywords 'patient reported outcome*' and 'ethic*' were used to search the databases. Two reviewers independently conducted title and abstract screening before full-text screening to determine eligibility. The review was supplemented by the SPIRIT-PRO Extension recommendations for trial protocol. Subsequently, a two-round international Delphi process (n=96 participants; May and August 2021) and a consensus meeting (n=25 international participants; October 2021) were held. Prior to voting, consensus meeting participants were provided with a summary of the Delphi process results and information on whether the items aligned with existing ethical guidance.

Findings Twenty-three items were considered in the first round of the Delphi process: six relevant candidate items from the systematic review and seventeen additional items drawn from the SPIRIT-PRO Extension. Ninety-six international participants voted on the relevant importance of each item for inclusion in ethical guidelines and twelve additional items were recommended for inclusion in round 2 of the Delphi (35 items in total). Fourteen items were recommended for inclusion at the consensus meeting (n=25 participants). The final wording of the PRO ethical guidelines was agreed by consensus meeting participants with input from six additional individuals. Included items focused on PRO-specific ethical issues relating to research rationale, objectives, eligibility requirements, PRO concepts/domains, PRO assessment schedules, sample size, PRO data monitoring, barriers to PRO completion, participant acceptability and burden, administration of PRO questionnaires for participants who are unable to self-report PRO data, input on PRO

118 strategy by patient partners or members of the public, avoiding missing data and
119 dissemination plans.

120 **Conclusions and Relevance** The PRO ethics guidelines provide recommendations
121 for ethical issues that should be addressed in PRO clinical research. Addressing
122 ethical issues of PRO clinical research has the potential to ensure high-quality PRO
123 data while minimising participant risk, burden and harm and protecting participant
124 and researcher welfare.

Introduction

Patient-reported outcomes (PROs) are used in clinical research and routine care to provide information on the physical, functional, and psychological effects of disease and treatment from the patient perspective.¹ PRO data can inform healthcare decisions, regulatory decisions, healthcare policy and cost-effectiveness analyses. PROs can also be used for audit/benchmarking and monitoring of symptoms to provide timely care tailored to individual needs.^{1,2} Notwithstanding the potential benefits of incorporating PROs in research and routine practice, ethical considerations have been highlighted.³ For example, the PRO content of clinical trial protocols and reporting of PRO results is commonly inadequate. A 2019 evaluation of 160 cancer trials showed nearly 50,000 participants were included in studies that failed to publish their PRO data.⁴

The increasing use of PROs may lead to uncertainties for patients about why data are being collected and used. There is a lack of guidance on how research personnel should manage situations in which PRO data reveal concerning levels of psychological distress or physical symptoms.⁵ If concerning data are not managed appropriately, those data could lead to suboptimal participant care or biased trial results.⁶ In addition, PRO research may not reflect the perspectives of underserved groups such as older individuals, socioeconomically disadvantaged populations, and racial and ethnic minority groups, which could threaten the scientific validity of results.^{3,7}

Ethical issues should be resolved with justifications that employ established principles, theories and values, and consider individual and societal welfare.³ In 2018, the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials)- PRO Extension was developed to provide PRO trial protocol guidance.⁸

These guidelines were not, however, developed specifically for the use of Research Ethics Committees (RECs) and limited attention has been given to the ethical dimensions of PROs in clinical research.⁷ Thus, there is a need to develop ethical guidelines to address this. The aim of this international effort was to develop consensus-based guidelines for the specific use of PROs in clinical research

Methods

The PRO ethics guidelines were developed through an international Delphi process following the Enhancing Quality and Transparency of Health Research (EQUATOR) Network's framework for guideline development (Figure 1).⁹

The PRO Ethics Steering Group, formed by 11 international experts with patient and public involvement (Appendix in Supplement), was established to oversee the design, and conduct of the study.

Ethical approval

Ethical approval was given by the University of Birmingham Ethical Review Board (ERN_21-0075).

Systematic review and generation of candidate items

Candidate items were identified by the Steering Group from the SPIRIT-PRO Extension⁸ guidelines and the accompanying SPIRIT-PRO Extension Supplementary Appendix 3 document.⁸ Explanation of the candidate items was derived from a lay terminology of the SPIRIT-PRO Extension.¹⁰ The candidate items were supplemented with items generated from a systematic review of articles describing the ethical implications of PROs in clinical research. The protocol for the systematic review was registered on PROSPERO (registration number CRD42020176177).

The databases MEDLINE (Ovid), EMBASE, Allied and Complimentary Medicine Database (AMED), and CINAHL Plus were searched from inception until March 2020 with the keywords ‘patient reported outcome*’ and ‘ethic*’.

Publications were deemed eligible if they discussed ethical implications and/or guidance in the context of PRO clinical trials research, routine clinical practice and broader PRO research. Two reviewers (SCR and OLA) independently conducted title and abstract screening before full-text screening to determine eligibility.

Discrepancies were resolved through the involvement of a third reviewer (MJC). Text excerpts on ethical considerations of PRO research from the included studies were independently extracted by the two investigators (SCR and OLA) into a qualitative data analysis software package (QRS NVivo 12). Both reviewers independently generated categories and themes under the thematic analysis approach. The review identified 14 relevant articles, including qualitative reports, opinion and debate articles, and special communications that discussed the ethical implications of PRO research.

Based on the review, 6 candidate items were identified, and 17 items were drawn from the SPIRIT-PRO Extension guidelines and Supplementary Appendix 3.

International Delphi process

In 2021, 201 international multidisciplinary individuals with interest in PRO research were invited to participate in the online Delphi process to vote on the candidate items and propose additional items. These participants comprised individuals responsible for developing PRO research submissions for ethical review, those undertaking ethical review, or using of data arising from PRO research. Potential participants were identified and contacted via the PRO Ethics Operations Group (SCR, MC, OLA,

AD) and the Health Research Authority (HRA). A snowballing technique and social media (LinkedIn and Twitter) were used to identify further participants. Participant characteristics are described in eTable 1 Supplement. DelphiManager software (version 5.0), developed and maintained by the COMET (Core Outcome Measures in Effectiveness Trials) initiative, was used to undertake the two Delphi surveys.¹¹

Participants were provided with written information about the study prior to consenting to participate. Participants voted anonymously on a 9-point scale (1- 3, not important; 4 – 6, important but not critical; and 7 – 9, important and critical) on the importance of the 23 items presented. Ninety-six responses were received for round 1 of the Delphi and 85 responses (88% of participants from round 1) were received for round 2. Participants were advised if they did not complete round 2, their round 1 responses would be retained. During round 1, participants had the option to suggest additional items. During round 2, 12 additional items were included. Anonymized item-level round 1 scores per participant group were presented to Delphi panellists for their consideration prior to round 2 voting.

International consensus meeting

The Operations Group mapped the 35 candidate PRO ethics items to existing HRA guidance from the UK, as an initial indicator of what may already be covered in existing ethics guidance,^{12,13} removing duplicates and revising wording to aid clarification. The Operations Group presented the consensus delegates with recommendations for the inclusion or exclusion of items based on the decision tree (eFigure 1 in Supplement). The COMET initiative guidance informed the inclusion criteria (Supplement).¹⁴.

An online consensus meeting took place in October 2021 hosted by the University of Birmingham, UK. Twenty-five international participants purposively selected from the Delphi survey attended the consensus meeting, comprising 7 clinical trialists/health academic researchers, 4 ethicists/members of an ethical review panel, 2 healthcare professionals, 3 PRO researchers from industry, 2 journal editors, 4 patients and members of the public, 1 policy maker, 1 regulator and 1 bioethicist (eTable 1 in Supplement). Delegates were presented with candidate items and anonymously voted using the Zoom poll tool. Participants had the following voting options: include, exclude, or further discussion required (Supplement, participation in the voting process for further details).

The aim of the meeting was to seek consensus on the content of the PRO ethics guidelines. Consensus panellists considered the focus of the guidelines and agreed that the guidelines covered ethical considerations when undertaking PRO clinical research. In addition, participants discussed the wording and explanatory text of each item. A threshold of $\geq 70\%$ was pre-specified to demonstrate consensus when voting on the items (Supplement, consensus meeting for further details). The items were presented alongside the overall Delphi score and the number of participant groups whereby $\geq 70\%$ of respondents scored an item as important and critical.

Final consultation

Following the consensus meeting, attendees commented on the wording and agreed on the final version of the PRO ethics guidelines. Final edits were made to improve the clarity and were approved by the Steering Group and patient partners. The Online Supplement provides further information on methods.

Results

The PRO Ethics Guidelines

The final PRO ethics guideline identified 14 key questions that capture core ethical issues (Table 1). The items incorporated content from 14 of the 35 original candidate items, comprising 6 items that were merged during the consensus meeting and 8 items that were not modified (see eTables 2, 3a and 3b in Supplement). Further details about the 21 excluded items are presented in eTables 4a and 4b in Supplement. An explanation describing each item with supporting evidence is presented below. The items are presented in accordance with SPIRIT-PRO Extension subheadings and findings from the systematic review.

Introduction: background and rationale

Item 1: How clear is the PRO-specific research question? What is the justification and rationale for PRO assessment?

Explanation: Evidence suggests that many trials include PROs without specifying the PRO-specific research question and without a rationale or reference to PROs in related studies.^{4,15,16} Researchers should carefully consider the PRO-specific research question to inform the selection of measures and methodological approach to help ensure results are meaningful.⁸ In addition, patients and research personnel should understand why PRO data are being collected and how their data will be used, and this should be communicated effectively.^{4,15,16} This can help build trust, particularly when participants may share potentially sensitive information. Why data are being collected and how these data will be used should be clearly explained in the information sheet, by research personnel, or both, during the consent process.

Item 2: How clearly are the PRO objectives or hypotheses defined?

267 *Explanation:* Clearly defined PRO objectives and hypotheses inform study design,
268 including the selection of key PRO concepts and measures, time points for
269 assessment and analyses.¹⁷ Poorly defined PRO objectives or hypotheses may
270 affect the quality of research design and reporting. Poor science undermines
271 participant consent (failing to respect autonomy) and exposes participants to
272 unnecessary risk/burdens as the results are ultimately not usable or not
273 generalisable.

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

275 **Item 3: Are any PRO-specific eligibility requirements identified (e.g., language,**
276 **literacy requirements) and how clearly have these been justified?**

277 *Explanation:* Researchers should consider PRO-specific eligibility requirements at
278 the design stage of the study and robustly justify excluding a subpopulation. It would
279 undermine the principle of justice to exclude eligible people either directly or
280 indirectly (e.g., as a result of a failure to consider PRO accessibility or other equity,
281 diversity and inclusion issues).¹⁸

282 **Item 4: Which PRO concepts/domains (e.g., overall health-related quality of**
283 **life, specific domain, specific symptom) and instruments have been specified?**
284 **How has the PRO analysis metric (e.g., change from baseline, final value, time**
285 **to event) and the principal time point, or period of interest, been specified and**
286 **justified?**

287 *Explanation:* The PRO concept and analysis metric should be clearly outlined and
288 aligned with the PRO objectives and hypothesis to ensure that they capture
289 outcomes that matter to patients and other key interested groups, such as clinicians,

regulators and policy-makers. Defining and justifying the selection of PRO instruments(s) is an important aspect of ethical research. If possible, the PRO measure should be validated in the target population. The number of questionnaires used, acceptability of the questions and participant burden should be considered carefully. PRO measures ideally should be used in accordance with existing user manuals to promote data quality and ensure standardised scoring.⁸ When a PRO is being considered for a new population, representative patient input should be obtained about the suitability and appropriateness of the questions to determine whether the questions are relevant to the target population.¹⁹

Item 5: What is the schedule of PRO assessments? How well does the participant information sheet provide information on the number and frequency of PRO assessments?

Explanation: Providing the schedule of PRO assessments in the study protocol and participant information sheet is the first step to ensuring potential participants understand the commitment and effort involved in taking part in the PRO study. A robust consent process includes information provision and checks on understanding. A poor process compromises respect for participant autonomy.^{20,21}

Item 6: When the PRO is a primary endpoint, what justification is provided for the sample size?

Explanation: Exposing participants to the risks and burdens of PRO research is only justifiable if these are outweighed by the potential value of the PRO data. A sample size that is too small may produce inconclusive and therefore not valuable results. A sample size that is too large will expose more participants than necessary to risks

and burdens and incur unnecessary costs.²² The SPIRIT-PRO Extension, item 14, indicates that if PROs are the primary outcome of a study, *a priori* sample size calculation should be provided for that specific endpoint. If PROs are a secondary outcome, the sample size should provide enough power to test the principal PRO hypothesis.⁸ This would not be required for exploratory PRO endpoints.

Methods: Data Collection, Management, and Analysis

Item 7: What details about the data collection plan have been provided, including the permitted mode(s) of PRO administration (e.g., paper, telephone, electronic, other) and setting (e.g., clinic, home, other)?

Explanation: Research personnel should understand how and where PRO data will be collected, and clear communication of this to potential participants is an essential component of a robust informed consent process. The mode(s) of administration should be influenced by the setting in which PRO data will be collected (e.g., telephone or electronic completion may be more feasible from home) and the needs of the target population.²³ Ideally, participants from the target population would provide input on modes. Offering alternative modes of completion may help improve response rates and promote inclusivity and equity; all of which improve the quality of the results.²⁴ The SPIRIT-PRO Extension, item 18a(ii), provides further information regarding the modes of PRO administration and setting for PRO randomised clinical trials.⁸

Item 8: What, if any, PRO data monitoring for concerning responses will occur during the study and how will this inform the clinical care of individual study participants?

Explanation: Responding to PRO alerts (concerning levels of psychological distress or physical symptoms that require timely response)⁶ may protect the safety and welfare of participants,¹⁸ which is an important ethical consideration. The research protocol should state whether, why and by whom PRO data will be monitored during the study and this information should be shared with participants.^{5,6} In low-risk studies in which alerts for concerning symptoms are not anticipated, PRO monitoring may not be necessary. Similarly, protocols should state whether research data will be shared with the patient's care team or entered in the electronic medical record. Alternative support mechanisms (e.g., 24-hour helpline) for participants should be outlined. All research personnel involved in the management of PRO alerts should receive appropriate training and have clear pathways for support.^{25,26} Evidence suggests research personnel handle such data inconsistently, which may lead to inequitable patient care, co-intervention bias and confusion.⁶ In addition, personnel in charge of collecting PRO data may feel emotional and/or ethical burden while dealing with concerning PRO data (e.g., reports from trial participants of low self-esteem, depression or risk of self-harm or suicide).²⁶

Item 9: How have barriers to PRO completion (e.g., mode of administration, language, cultural needs, accessibility) been minimised and addressed to promote participant inclusivity?

Explanation: PRO protocols should promote participant inclusivity while recruiting a diverse population that is representative of patients with the condition of interest. Barriers to participation, such as access to technology in rural areas, areas of socioeconomic disadvantage, or both, as well as disability, language, and cultural requirements, should be addressed to promote fairness and ensure results are as

accurate and generalisable as possible.²⁷ For example, a clinical trial of adults receiving chemotherapy at 50 community cancer centres promoted inclusivity by offering internet and no-internet (automated phone call) options to complete PROs remotely. 35% of the participants chose the automated call (no-internet) option versus 65% who chose internet-based completion.²⁸ Without an alternative PRO mode, more than one-third of the vulnerable population may have been excluded.

Researchers may consider different modes of completion (Item 7) to promote inclusivity and should be explicit about how the PRO strategy promotes or hinders the goal of recruiting a diverse sample representative of the target population. For instance, trials involving participants with different languages require the availability of validated language and culturally adapted PRO questionnaires, while some participants may need physical help or other types of assistance in responding (e.g., turning pages, holding a pen, assistance with a telephone or computer keyboard).^{8,17,25}

Item 10: How has participant acceptability and burden been described and addressed?

Explanation: PROs should be acceptable to the population in which they will be administered, both in terms of the questions they ask and the overall burden to the patient (e.g., is the completion time for the PRO measure acceptable).²⁹ The degree of participant burden depends on the frequency and timing of PRO assessments and on issues such as participant cognition, illness severity, treatment toxicity and literacy.¹⁷ Researchers should consider issues such as whether the questionnaire(s) capture important and relevant concepts to interested groups (such as overall health-related quality of life, specific domain or symptoms as described in Item 4) and

whether PROs include overlapping content and/or particularly sensitive questions. It is also important to consider the length, number of questionnaires and endpoints, with respect to burden for subgroups of participants and if the mode of delivery (Item 7) and schedule of assessments (Item 5) are appropriate. If researchers demonstrate acceptable participant burden via robust involvement from representatives of the target patient population in the PRO selection process, RECs should not override the PRO strategy without strong ethical justification (e.g., RECs should avoid automatically rejecting a proposal with a large number of PROs if justification is provided).

Short questionnaires minimize participant burden and assure greater completeness of PRO data while minimizing missing data.³⁰ However, patient input during the selection of PRO measures is key as participants may be willing to complete lengthy questionnaires if they understand the value of data collection and how the data will be used.³¹ Thus, the views of the affected population are authoritative in this regard. Failure to seek participant input to core design issues such as concepts to measure that matter most to patients, selection of questionnaires, time points and mode of assessment may lead to poor concordance, and therefore flawed results that cannot inform clinical practice. Poorly designed studies mislead participants who participate to help others, and misuse research resources.

Item 11: In contexts where participants are not able to report for themselves or may become unable to self-report PRO data, how will PRO questionnaire(s) be completed or managed (e.g., proxy reporting)?

Explanation: It is well recognised in research governance that participants who lack capacity (e.g., young children and adults who are cognitively impaired) are

potentially vulnerable and their interests in the context of research need to be protected; but it is also important that such people are not unjustifiably excluded from relevant research. PRO research needs to meet the same well-defined standards.

These individuals may require a proxy; someone else to report the participant's outcomes on their behalf.⁸ This is different to assisting a participant to document their own answers (see Item 9).^{32,33} The correct administration of PRO tools when proxies need to be used, contributes to the collection of robust and reliable data. The justification for including vulnerable participants in research is that it will either benefit them directly or it will benefit the population to which they belong.³⁴

In many research contexts, it is reasonable to anticipate the need for proxy response throughout all or some of the research (although the possibility can never be excluded) and this should be clearly documented in the research protocol.

Researchers should be aware that proxy reporting is acceptable in some contexts and not in others. For example, the European Medicines Agency discourages proxy reporting because their data are often subject to biases and should only be used if it is the only effective means of obtaining vital information that might otherwise be lost.²⁹ The US Food and Drug Administration also discourages the use of proxy-reported outcomes to inform labelling claims, recommending observer reports for observable phenomenon only (e.g., vomiting, but not nausea) instead.¹⁷ However, in palliative care, collecting both proxy and observer measures is acceptable.³⁵

It is important to recognise that lack or loss of capacity to consent to research participation will not always be accompanied by an inability to self-complete PROs (with or without assistance), and appropriate support for such participants should be specified.

Item 12: How has input from patient partners and/or members of the public been incorporated in the PRO study design? If input has not been sought or incorporated, how has this been justified?

Explanation: Patient and public involvement refers to the partnership between patients, members of the public and researchers in the co-development of research.³⁶ Patients and members of the public have unique insight derived from their lived experiences making research more relevant and enhancing the design, conduct and quality of the research.³⁷⁻³⁹ Incorporating these insights into research can make it *prima facie* more ethical in two ways: by democratising the research agenda and/or helping to improve participant facing documents and processes.⁴⁰

The inclusion of patient and/or public involvement should be considered best practice during the study design stage. Involvement of individuals with the disease can provide valuable insights into their lived experience and help ensure the research is relevant to their needs and acceptable, while public involvement may generate broader insights from a societal perspective. In addition, their inclusion should be integral to all the stages of research. The inclusion of patient involvement, public involvement, or both, in the development of the PRO strategy may help to ensure that research measures what matters to patients, thereby maximising its beneficial effect. It is also the best means of ensuring that PRO tools, and how they are administered, are acceptable (see item 10), and thereby may be influential in maximising the response rate (see item 13). For example, recent patient involvement in the Therapies for Long COVID study has led to the development of a new Symptom Burden Questionnaire™ as existing measures were felt to omit key symptoms experienced by those with the condition.⁴¹

Item 13: What mechanisms have been introduced to minimise missing PRO data? How have these been explained to participants (e.g., reminders/notifications in an app or follow up calls)?

Explanation: Missing PRO data is a major problem in clinical research.^{24,42} Missing data are normally caused by a combination of factors relating to methodology, logistic, administrative and patient-related issues⁴². Protocols should describe how missing data will be minimised. Missing PRO data can complicate interpretation, lead to invalid conclusions or may mean that the PRO data are not published.^{4,43,44} When this occurs, it undermines the consent of participants who took part in the study and wastes research resources.

Although not all missing PRO data can be avoided, different strategies exist to mitigate this problem.²⁴ Specific recommendations related to data collection and management include: using the minimum number of questionnaires appropriate to address the PRO research question, standardized and documented PRO administration procedures, engaging and educating participants in the study by providing updates or incentives, employing active quality assurance measures (such as monitoring of completion rates, reminders for upcoming or missed assessments), appointing a dedicated staff member responsible for PRO assessment at each centre, staff training, and offering alternative modes of administration.^{24,32}

Reminders, notifications or follow up calls may be used to minimize missing data.

Although different strategies exist to minimise avoidable PRO missing data, participants should be notified and provide consent, prior to accepting being part of the study, about the mechanisms the study will follow.

Dissemination

Item 14: What dissemination plans (e.g., publications and plain language summaries for the research participants and the public) are proposed for sharing the PRO findings?

Explanation: The dissemination of PRO findings is essential to achieve beneficial outcomes. PRO data are, however, commonly omitted from primary and secondary publications.⁴ Failing to report PRO data could limit the interpretation of the results and may hinder the translation of PRO findings into clinical practice, resulting in lost opportunities to benefit patients and the perpetuation of harmful practices. Failure to disseminate PRO findings is disrespectful of participants' time, effort, and contribution to research. It may also undermine participants' consent if they were misinformed about dissemination plans.⁴⁴ Sharing a summary of the PRO research results in accessible plain language for use by patients, participants, and members of the public promotes autonomy by empowering patients in shared decision-making around their care.⁴⁵

It is recommended that PRO findings should be incorporated into the main research publication or reported in a secondary publication providing a detailed explanation of the PRO data.⁴⁶ The CONSORT-PRO Extension guideline was developed to address the reporting of PRO trial data. The CONSORT-PRO provides evidence-based recommendations to improve completeness of reporting randomised clinical trials with either a primary or secondary PRO endpoint.⁴⁷ Table 1 shows an implementation tool for PRO researchers and RECs to be completed by research teams preparing PRO research, or by reviewers.

Discussion

503 The PRO ethics guidelines provide international consensus-based recommendations
504 on questions that should be asked of a study's design to facilitate the evaluation of
505 its ethical acceptability. The guidelines highlight the ethical imperative to conduct
506 robust science and the ethical issues to consider in the design and review of PRO
507 clinical research. While a number of ethical issues identified are not unique to PROs
508 and apply to research more widely, they raise particular challenges in the context of
509 PROs, which is the focus of the work developed. The PRO ethics guidelines
510 comprise 14 items to consider for use alongside the existing SPIRIT-PRO and
511 CONSORT-PRO Extension guidelines^{8,47} and other ethical recommendations
512 relevant to the jurisdiction of interest.^{12,13,48,49}

513 The guidelines do not aim to mandate how ethical research should look, nor to
514 mandate the correct response to the questions it asks. Instead, the guidelines aim to
515 highlight issues that should be considered by research groups and ethics
516 committees, including patients, research participants and the public.

517 The recommendations within the PRO ethics guidelines reflect widely accepted
518 ethical norms encapsulated in instruments such as the Declaration of Helsinki,⁵⁰ the
519 Belmont report,⁵¹ and the Council for International Organisations of Medical
520 Sciences (CIOMS) guidelines.⁵² The recommendations are in line with the three
521 principles of respect of persons, concern for welfare, and justice outlined in the Tri-
522 Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS
523 2)⁴⁹ and the widely used four principles of biomedical ethics: autonomy, justice,
524 beneficence and non-maleficence.²⁰ As such, the guiding ethical questions
525 presented here do not set out any new ethical ideas, but rather specify widely

accepted norms in the context of PROs and frame them in a way that is accessible to PRO researchers and useful for reviewers of PRO research.

The use of the PRO ethics guidelines has the potential to reduce participant risk and burden. In addition, addressing the items of the PRO ethics guidelines may help promote and protect participant autonomy, and the welfare of participants and researchers. Furthermore, it may promote inclusive, equitable PRO research, the sharing of PRO research findings with participants and patients and minimize research waste (Box 1).

Box 1: The PRO ethics guidelines aims

- Maximize beneficial outcomes from research resources
- Promote and protect participant autonomy
- Protect participant research welfare
- Promote accessible research
- Minimize participant burden and harm
- Minimize participant risk
- Promote high quality research
- Disseminate PRO research

Table 1 provides an implementation tool for PRO researchers to reflect how each item has been addressed prior to ethical submission and for RECs to make notes on the research submitted and discuss in detail any relevant points at the ethics meeting. This tool is a starting point and can be tailored according to the users' needs. Collaboration with national and international networks are being planned to promote the implementation of the PRO ethics guidelines.

Limitations

This study has several limitations. First, the review identified only limited literature on which to base items for inclusion in the Delphi. Therefore, some relevant candidate items may not have been included; however, additional items were proposed by the Steering Group, and further items were informed by the SPIRIT-PRO Extension work, based on an extensive review of PRO protocol guidance. Furthermore, participants had the opportunity to propose additional items during round 1 of the Delphi process. Second, only literature available until March 2020 was considered in development of the guidelines. However, an updated search was performed on March 23 2022, and an additional 569 articles were screened, and no further relevant literature was identified. Third, as participants ranked items according to their general importance, it is possible that some items might be less relevant for certain types of trials.

Conclusion

The PRO ethics guidelines provide recommendations for ethical issues that should be addressed in PRO clinical research. Addressing these ethical issues could ensure the collection of high-quality PRO data while minimizing participant risk, burden and harm and protecting participant and researcher welfare.

Author's contributions

Drs Cruz Rivera and Calvert had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Cruz Rivera, Calvert, Mercieca-Bebber, Aiyegbusi, Scott, Hunn, Fernandez, Ives, Ells, Price and Draper. Acquisition and analysis: Cruz Rivera and Calvert, Interpretation of data: All authors. Drafting of the manuscript: Cruz Rivera and Calvert. Critical revision of the manuscript for important intellectual content: All

570 authors. Supervision: Cruz Rivera, Calvert, Mercieca-Bebber, Aiyegbusi, Scott,
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Table 1. Implementation tool for PRO researchers and research ethics committees (RECs)^a

Item	Description	Notes/reflections on how and where each item has been addressed*	Rationale
Introduction: background and rationale			
1	How clear is the PRO-specific research question? What is the justification and rationale for PRO assessment?		Essential for good quality research, which is pre-requisite for ethical research. Communicating this rationale to participants protects autonomy.
2	How clearly are the PRO objectives or hypotheses defined?		Essential for good quality research, which is pre-requisite for ethical research. Poor science undermines participant consent and autonomy.
Methods: Participants, Interventions, and Outcomes			
3	Are any PRO-specific eligibility requirements identified (e.g., language, literacy requirements) and how clearly have these been justified?		Robust eligibility criteria promote good science. Fair and equitable eligibility criteria promote justice.
4	Which PRO concepts/domains (e.g., overall health-related quality of life, specific domain, specific symptom) and instruments have been specified? How has the PRO analysis metric (e.g., change from baseline, final value, time to event) and the principal time point, or period of interest, been specified and justified?		Ensures that the PRO assessment(s) fulfil the research objective, which is pre-requisite for ethical PRO research. Poor science undermines participant consent and autonomy.

5	What is the schedule of PRO assessments? How well does the participant information sheet provide information on the number and frequency of PRO assessments?		Clear processes promote good science. Communicating about this effectively to participants protects autonomy.
6	When the PRO is a primary endpoint, what justification is provided for the sample size?		Essential for good quality research, which is pre-requisite for ethical research.
Methods: Data Collection, Management, and Analysis			
7	What details about the data collection plan have been provided, including the permitted mode(s) of PRO administration (e.g., paper, telephone, electronic, other) and setting (e.g., clinical, home, other)?		Essential for good quality research, which is pre-requisite for ethical research. Providing options to participants protects autonomy and promotes inclusiveness.
8	What, if any, PRO data monitoring for concerning responses will occur during the study and how will this inform the clinical care of individual study participants?		Mechanism for monitoring and responding to possible harm promotes non-maleficence and can protect participants wellbeing. Clarity about what will be monitored and responded to promotes participant autonomy.
9	How have barriers to PRO completion (e.g., mode of administration, language, cultural		Promotes inclusivity and participant autonomy.

	needs, accessibility) been minimised and addressed to promote participant inclusivity?		
10	How has participant acceptability and burden been described and addressed?		Promotes autonomy and reduces risk of harm. Enhances quality of research, which is pre-requisite for ethical research.
11	In contexts where participants are not able to report for themselves or may become unable to self-report PRO data, how will PRO questionnaire(s) be completed or managed (e.g., proxy reporting)?		Promotes beneficence and protects autonomy. This provides patient-centred information when it would otherwise not be available.
12	How has input from patient partners and/or members of the public been incorporated in the PRO study design? If input has not been sought or incorporated, how has this been justified?		Can enhance quality of research, which is pre-requisite for ethical research. Involvement of patients representing the target population can promote inclusivity diversity and justice.
13	What mechanisms have been introduced to minimise missing PRO data? How have these been explained to participants (e.g., reminders/notifications in an app or follow up calls)?		Essential for good quality research, which is pre-requisite for ethical research. Poor science undermines participant consent and autonomy.
Dissemination			

14	What dissemination plans (e.g., publications and plain language summaries for the research participants and the public) are proposed for sharing the PRO findings?		Dissemination promotes beneficence and protects autonomy.
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^aTo be completed by research teams preparing PRO research or by reviewers

