Ethical Considerations for the Inclusion of Patient-Reported Outcomes in Clinical Research
The PRO Ethics Guidelines

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

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

EVIDENCE REVIEW The PRO ethics guidelines were developed following the Enhancing the 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 March 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 2-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: 6 relevant candidate items from the systematic review and 17 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 12 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 on by consensus meeting participants with input from 6 additional individuals. Included items focused on PRO-specific ethical issues relating to research rationale, objectives, eligibility requirements, PRO concepts and 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 strategy by patient partners or members of the public, avoiding missing data, and dissemination plans.

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

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. PRO data can inform health care decisions, regulatory decisions, health care 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. Notwithstanding the potential benefits of incorporating PROs in research and routine practice, ethical considerations have been highlighted. 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.

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. If concerning data are not managed appropriately, those data could lead to suboptimal participant care or biased trial results. 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.

Ethical issues should be resolved with justifications that use established principles, theories, and values, as well as consider individual and societal welfare. In 2018, the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials)-PRO Extension was developed to provide PRO trial protocol guidance. These guidelines were not, however, developed specifically for the use of research ethics committees (RECs) and limited attention has been paid to providing PRO trial results. 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.

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 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 (MJ). Text excerpts on ethical considerations of PRO research from the included studies were independently extracted by the 2 investigators (SCR and OLA) into a qualitative data analysis software package (NVivo 12; QSR International). 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 Supplement 3 of that article.

### 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 (S.C.R., M.J.C., O.L.A., A.P.D.) and the Health Research Authority (HRA). A snowballing technique and social media (LinkedIn and Twitter) were used to identify further participants. Participants' characteristics are described in eTable 1 in the Supplement. DelphiManager software (version 5.0), developed and maintained by the COMET (Core Outcome Measures in Effectiveness Trials) Initiative, was used to undertake the 2 Delphi surveys.

### Methods

The PRO ethics guidelines were developed through an international Delphi process following the Enhancing the Quality and Transparency of Health Research (EQUATOR) Network's framework for guideline development (Figure). The PRO Ethics Steering Group, formed by 11 international experts with patient and public involvement (Acknowledgements in the 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 (ERN21-0075).

### Systematic Review and Generation of Candidate Items

Candidate items were identified by the steering group from the SPIRIT-PRO Extension guidelines and Supplement 3 of the accompanying SPIRIT-PRO Extension article. Explanation of the candidate items was derived from lay terminology of the SPIRIT-PRO Supplement. DelphiManager software (version 5.0), developed and maintained by the COMET (Core Outcome Measures in Effectiveness Trials) Initiative, was used to undertake the 2 Delphi surveys.
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 (89% 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 panelists 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 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 in the Supplement). The COMET Initiative guidance informed the inclusion criteria (eMethods in the Supplement).13

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 health care 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 the 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 (see the Participation in the Voting Process section, eMethods in the Supplement, for further details).

The aim of the meeting was to seek consensus on the content of the PRO ethics guidelines. Consensus panelists 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 70% or more was prespecified to demonstrate consensus when voting on the items (see the Consensus Meeting section, eMethods in the Supplement, for further details). The items were presented alongside the overall Delphi score and the number of participant groups whereby 70% or more 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 clarity and were approved by the steering group and patient partners. The eMethods section in the Supplement provides further information on methods.

Results
The PRO Ethics Guidelines
The final PRO ethics guidelines identified 14 key questions that capture core ethical issues (Table). The items incorporated content from...
Table. Implementation Tool for PRO Researchers and Research Ethics Committeesa

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
<th>Notes/reflections on how and where each item has been addressed*</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>How clear is the PRO-specific research question? What is the justification and rationale for PRO assessment?</td>
<td>Essential for good-quality research, which is prerequisite for ethical research. Communicating this rationale to participants protects autonomy.</td>
<td></td>
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<tr>
<td>2</td>
<td>How clearly are the PRO objectives or hypotheses defined?</td>
<td>Essential for good-quality research, which is prerequisite for ethical research. Poor science undermines participant consent and autonomy.</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Are any PRO-specific eligibility requirements identified (eg, language, literacy requirements) and how clearly have these been justified?</td>
<td>Robust eligibility criteria promote good science. Fair and equitable eligibility criteria promote justice.</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Which PRO concepts/domains (eg, overall health-related quality of life, specific domain, specific symptom) and instruments have been specified? How has the PRO analysis metric (eg, change from baseline, final value, time to event) and the principal time point, or period of interest, been specified and justified?</td>
<td>Ensures that the PRO assessment(s) fulfill the research objective, which is prerequisite for ethical PRO research. Poor science undermines participant consent and autonomy.</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>What is the schedule of PRO assessments? How well does the participant information sheet provide information on the number and frequency of PRO assessments?</td>
<td>Clear processes promote good science. Communicating about this effectively to participants protects autonomy.</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>When the PRO is a primary end point, what justification is provided for the sample size?</td>
<td>Essential for good-quality research, which is prerequisite for ethical research.</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>What details about the data collection plan have been provided, including the permitted mode(s) of PRO administration (eg, paper, telephone, electronic, other) and setting (eg, clinic, home, other)?</td>
<td>Essential for good-quality research, which is prerequisite for ethical research. Providing options to participants protects autonomy and promotes inclusiveness.</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>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?</td>
<td>Mechanism for monitoring and responding to possible harm promotes nonmaleficence and can protect participants’ well-being. Clarity about what will be monitored and responded to promotes participant autonomy.</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>How have barriers to PRO completion (eg, mode of administration, language, cultural needs, accessibility) been minimized and addressed to promote participant inclusivity?</td>
<td>Promotes inclusivity and participant autonomy.</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>How has participant acceptability and burden been described and addressed?</td>
<td>Promotes autonomy and reduces risk of harm. Enhances quality of research, which is prerequisite for ethical research.</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>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 (eg, proxy reporting)?</td>
<td>Promotes beneficence and protects autonomy. This provides patient-centered information when it would otherwise not be available.</td>
<td></td>
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<tr>
<td>12</td>
<td>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?</td>
<td>Can enhance quality of research, which is prerequisite for ethical research. Involvement of patients representing the target population can promote inclusivity, diversity, and justice.</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>What mechanisms have been introduced to minimize missing PRO data? How have these been explained to participants (eg, reminders/notifications in an app or follow-up calls)?</td>
<td>Essential for good-quality research, which is prerequisite for ethical research. Poor science undermines participant consent and autonomy.</td>
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Dissemination

| 14   | What dissemination plans (eg, 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. |

Abbreviation: PRO, patient-reported outcome.

* To be completed by research teams preparing PRO research or by reviewers.

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 and 3a and 3b in the Supplement). Further details about the 21 excluded items are presented in eTables 4a and 4b in the 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?**

*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. Researchers should carefully consider the PRO-specific research question to inform the selection of measures and methodological approach to help ensure results are meaningful. 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. 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?**

*Explanation:* Clearly defined PRO objectives and hypotheses inform study design, including the selection of key PRO concepts and
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Methods: Participants, Interventions, and Outcomes

Item 3: Are Any PRO-Specific Eligibility Requirements Identified (eg, Language, Literacy Requirements) and How Clearly Have These Been Justified?

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

Item 4: Which PRO Concepts/Domains (eg, Overall Health-Related Quality of Life, Specific Domain, Specific Symptom) and Instruments Have Been Specified? How Has the PRO Analysis Metric (eg, Change From Baseline, Final Value, Time to Event) and the Principal Time Point, or Period of Interest, Been Specified and Justified?

Explanation: The PRO concept and analysis metric should be clearly outlined and aligned with the PRO objectives and hypothesis to ensure that they capture outcomes that matter to patients and other key interested groups, such as clinicians, regulators, and policy makers. Defining and justifying the selection of PRO instrument(s) are important aspects 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 standardized scoring. 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.

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.

Item 6: When Is the PRO Is a Primary End Point, 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. A priori sample size calculation should be provided for that specific end point. If PROs are a secondary outcome, the sample size should provide enough power to test the principal PRO hypothesis. This would not be required for exploratory PRO end points.

Methods: Data Collection, Management, and Analysis

Item 7: When Details About the Data Collection Plan Have Been Provided, Including the Permitted Mode(s) of PRO Administration (eg, Paper, Telephone, Electronic, Other) and Setting (eg, 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 (eg, telephone or electronic completion may be more feasible from home) and the needs of the target population. 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.

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) may protect the safety and welfare of participants, 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. 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 (eg, 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. Evidence suggests research personnel handle such data inconsistently, which may lead to inequitable patient care, cointervention bias, and confusion. In addition, personnel in charge of collecting PRO data may feel emotional and/or ethical burden while dealing with concerning PRO data (eg, reports from trial participants of low self-esteem, depression, or risk of self-harm or suicide).

Item 9: How Have Barriers to PRO Completion (eg, Mode of Administration, Language, Cultural Needs, Accessibility) Been Minimized 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 generalizable as possible.
a clinical trial of adults receiving chemotherapy at 50 community cancer centers promoted inclusivity by offering internet and no-internet (automated telephone call) options to complete PROs remotely. Thirty-five percent of the participants chose the automated call (no-internet) option vs 65% who chose internet-based completion. 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 (eg, turning pages, holding a pen, assistance with a telephone or computer keyboard). It is also important to consider the length, number of questionnaires, and end points, 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 (eg, 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. However, patient input during the selection of PRO measures is key because participants may be willing to complete lengthy questionnaires if they understand the value of data collection and how the data will be used. 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 (eg, Proxy Reporting)?

Explanation: It is well recognized in research governance that participants who lack capacity (eg, young children and adults who are cognitively impaired) are potentially vulnerable, and their interests in the context of research need to be protected. However, 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. This is different to assisting a participant to document their own answers (see item 9). 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.

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. The US Food and Drug Administration also discourages the use of proxy-reported outcomes to inform labeling claims, recommending observer reports for observable phenomenon only (eg, vomiting, but not nausea) instead. However, in palliative care, collecting both proxy and observer measures is acceptable.

It is important to recognize 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 codevelopment of research. 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. Incorporating these insights into research can make it prima facie more ethical in 2 ways: by democratizing the research agenda and/or helping to improve participant-facing documents and processes.

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 maximizing 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 maximizing the response rate (see item 13). For example, recent patient involvement in the Therapies...
Item 13: What Mechanisms Have Been Introduced to Minimize Missing PRO Data? How Have These Been Explained to Participants (eg, Reminders/Notifications in an App or Follow-up Calls)?

**Explanation:** Missing PRO data are a major problem in clinical research. Missing data are normally caused by a combination of factors relating to methodology, logistic, administrative, and patient-related issues. Protocols should describe how missing data will be minimized. Missing PRO data can complicate interpretation, lead to invalid conclusions, or may mean that the PRO data are not published. 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. Specific recommendations related to data collection and management include using the minimum number of questionnaires appropriate to address the PRO research question, establishing standardized and documented PRO administration procedures, engaging and educating participants in the study by providing updates or incentives, using 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 center, training staff, and offering alternative modes of administration. Reminders, notifications, or follow-up calls may be used to minimize missing data. Although different strategies exist to minimize 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 (eg, Publications and Plain-Language Summaries for the Research Participants and the Public) Are Proposed for 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. 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. 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.

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. 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 randomized clinical trials with either a primary or secondary PRO end point.

<table>
<thead>
<tr>
<th>Box. Aims of the PRO Ethics Guidelines</th>
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<tbody>
<tr>
<td>• Maximize beneficial effect from research resources</td>
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<tr>
<td>• Promote and protect participant autonomy</td>
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<tr>
<td>• Protect participant research welfare</td>
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<td>• Promote accessible research</td>
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<td>• Minimize participant burden and harm</td>
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<td>• Minimize participant risk</td>
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<tr>
<td>• Promote high-quality research</td>
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<td>• Disseminate PRO research</td>
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PRO indicates patient-reported outcome.

The Table shows an implementation tool for PRO researchers and RECs to be completed by research teams preparing PRO research or by reviewers.

### Discussion

The PRO ethics guidelines provide international consensus-based recommendations on questions that should be asked of a study’s design to facilitate the evaluation of its ethical acceptability. The guidelines highlight the ethical imperative to conduct robust science and the ethical issues to consider in the design and review of PRO clinical research. While a number of ethical issues identified are not unique to PROs and apply to research more widely, they raise particular challenges in the context of PROs, which is the focus of the work developed. The PRO ethics guidelines comprise 14 items to consider for use alongside the existing SPIRIT-PRO and CONSORT-PRO Extension guidelines and other ethical recommendations relevant to the jurisdiction of interest.

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

The recommendations within the PRO ethics guidelines reflect widely accepted ethical norms encapsulated in instruments such as the Declaration of Helsinki, the Belmont Report, and the Council for International Organizations of Medical Sciences guidelines. The recommendations are in line with the 3 principles of respect of persons, concern for welfare, and justice outlined in the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans and the widely used 4 principles of biomedical ethics: autonomy, justice, beneficence, and nonmaleficence. As such, the guiding ethical questions 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 minimization of research waste (Box).
The Table 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. Collaborations 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; an additional 569 articles were screened and no further relevant literature was identified. Third, because participants ranked items according to their general importance, it is possible that some items might be less relevant for certain types of trials.

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

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Accepted for Publication: April 5, 2022.
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Other - helped with formulation of interpretation and analysis regarding ethical values/principles: Draper.

Other - Delphi panel member, reviewed and commented on the study documents and publications: Scott.

Conflict of Interest Disclosures: Dr Cruz Rivera reported receiving funding from UK SPINE and European Regional Development Fund-Demand Hub and personal fees from Merck. Dr Aiyegbusi reported receiving grants from the National Institute for Health and Care Research (NIHR) Birmingham Biomedical Research Centre, NIHR Applied Research Collaboration West Midlands, UK Research and Innovation (UKRI), Health Foundation, Janssen, Gilead, and GlaxoSmithKline and personal fees from Gilead Sciences Ltd, Merck, and GlaxoSmithKline outside the submitted work. Dr Draper reported receiving unrelated research funding from UK SPINE (UKRI), AHRC, and the University of Warwick and being a member of the Defence Medical Services ethics committee. Birmingham Women’s and Children’s NHS Foundation Trust clinical ethics committee, and NHS Blood and Transplant Deceased Donor Family Tissue Advisory Group. Dr Scott reported receiving a pension from Janssen and holding stock in Johnson & Johnson. Drs Ells and Fernandez are...
members of the Canadian Interagency Panel on Research Ethics, which is responsible for the interpretation and evolution of the Canadian Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. Ms Anderson reported receiving funding from the Health Education England/NIHR Integrated Clinical Academic Program Clinical Doctoral Research Fellowship. Dr Hof Davies reported owning an ePRO software platform called Atoms Through Aparato. Dr Lord reported being a member of the Nuffield Bioethics Working Group on the Future of Ageing. Dr Mahendratarum reported owning stock options at Aetion Inc. Mr Miyaji reported grants (paid to the Department of Clinical Trial Data Management, Graduate School of Medicine, The University of Tokyo) from AC Medical, A2 Healthcare, New Age Trading, Japan Tobacco Inc, Japan Media Corp, Medidata Solutions, Ono Pharmaceutical, FMD K&L, Japan, 3M Health Solution, NOBORI, Medrio Inc, Welby Inc, Nipro Corp, and Intellim and personal fees from Pfizer Japan Inc, Takeda Pharmaceutical Co, Merck, Ayumi Pharmaceutical, and Welby Inc. Dr Morel reported owning shares of UCB Pharma. Dr Zwiler reported being chair of the national clinical coordinating group on PRO in cardiac diseases. Dr Peipert reported receiving unrelated research funding from the National Cancer Institute, the National Institutes of Health, the Food and Drug Administration, the ECOG-ACRIN Medical Research Foundation, the Peter G. Peterson Foundation, Veloxis Pharmaceuticals, Pfizer, and the Northwestern University George M. O’Brien Kidney Core Center. He has received unrelated personal fees from AstraZeneca, IMPAQ International, and FACIT.org. In addition, he is the International Society for Quality of Life Research’s psychometric special interest group chair. Through his institution, he is supported by unrelated grants and contracts from Bristol Myers Squibb, Clovis Oncology, Pfizer, and Veloxis Pharmaceuticals. Dr Roydhouse reported receiving unrelated personal fees in the last 24 months from Amgen. Through her institution, she is supported by an unrelated Select Foundation and has received unrelated research funding from the Royal Horticultural Society Fund and the Food and Drug Administration. Dr Stover reported receiving unrelated consulting fees or speaking honoraria in the last 24 months from Navigating Cancer, Association of Community Cancer Centers, Genentech, Purchaser Business Group on Health, and Kaiser Permanente Cancer Center and unrelated research funding from Sivan Innovation and UroGen Pharma Ltd. Dr Yap reported receiving unrelated consulting fees and speaking honoraria from Faron Pharmaceuticals and Celgene, respectively, and being an expert advisor for the Merck Japan Healthcare products Regulatory Agency’s Clinical Trials, Biologicals and Vaccines Expert Advisory Group and a funding panel member for the Medical Research Council Experimental Medicine and Cancer Research UK Clinical Research Committee. Dr Calvert reported serving as director of the Birmingham Health Partners Centre for Regulatory Science and Innovation, director of the Centre for Patient Reported Outcome Research, and an NIHR senior investigator and receiving funding from the NIHR, UK Research and Innovation (UKRI), NIHR Birmingham Biomedical Research Centre, the NIHR Surgical Reconstruction and Microbiology Research Centre, NIHR ARC West Midlands, UK SPINE, European Regional Development Fund-Demand Hub and Health Data Research UK at the University of Birmingham and University Hospitals Birmingham NHS Foundation Trust, Innovate UK (part of UKRI), Macmillan Cancer Support, UCB Pharma, Janssen, GlaxoSmithKline, and Gilead. Dr Calvert has received personal fees from Astellas, Aparato Ltd, C1S Oncology, Takeda, Merck, Daichi Sankyo, Glaxo, GlaxoSmithKline, and the Patient-Centered Outcomes Research Institute outside the submitted work. In addition, a family member owns shares in GlaxoSmithKline. No other disclosures were reported.

**Funding/Support:** This work was sponsored by the University of Birmingham, the NIHR Birmingham Biomedical Research Centre, UK Research and Innovation, UK SPINE, and the European Regional Development Fund.

**Role of the Funder/Sponsor:** The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Several authors are employees of the University of Birmingham; however, beyond the declared author contributions, the sponsor had no additional role.

**Disclaimer:** The views expressed in this article are those of the author(s) and not necessarily those of national agencies (eg, the NIHR, Food and Drug Administration, Medicines and Healthcare products Regulatory Agency, Health Research Authority, Canadian Institutes of Healthcare Research, the Department of Health and Social Care, Canadian Interagency Panel on Research Ethics, or the Canadian Tri-Council Policy Statement 2. Dr Golub is Executive Deputy Editor of JAMA but was not involved in any of the decisions regarding review of the manuscript or its acceptance.

**Additional Information:** Dr Scott retired from Janssen Global Services in March 2021, however, she was still involved in the development of the guideline until its final stage. Coauthor Amanda Hunn, MA, died February 8, 2022.

**REFERENCES**


Ethical Considerations for the Inclusion of Patient-Reported Outcomes in Clinical Research


