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"Give Us The Tools!" - Development of knowledge transfer tools to support the involvement of patient partners in the development of clinical trial protocols with patient-reported outcomes (PROs), in accordance with SPIRIT-PRO Extension.

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Abstract

Objectives a) To adapt the SPIRIT-PRO Extension guidance to a user-friendly format for patient partners; and b) to co-design a web-based tool to support the dissemination and uptake of the SPIRIT-PRO Extension by patient partners.

Design A one-day patient and public involvement session.

Participants Seven patient partners.

Methods A patient partner produced an initial lay summary of the SPIRIT-PRO guideline and a glossary. We held a one-day patient and public involvement session in November 2019 at the University of Birmingham. Five patient partners discussed the draft lay summary, agreed on the final wording. Co-designed and agreed the final content for both tools. Two additional patient partners were involved in writing the manuscript. The study compiled with INVOLVE guidelines and was reported according to the GRIPP 2 checklist.

Results Two user-friendly tools were developed to help patients and members of the public be involved in the co-design of clinical trials collecting PROs. The first tool presents a lay version of the SPIRIT-PRO Extension guidance. The second depicts the most relevant points, identified by the patient partners, of the guidance through an interactive flow diagram.

Conclusions These tools have the potential to support the involvement of patient partners in making informed contributions to the development of PRO aspects of clinical trial protocols, in accordance with the SPIRIT-PRO Extension guidelines. The involvement of patient partners ensured the tools focused on issues most relevant to them.

Strengths and limitations

- Two user-friendly tools were co-developed with PPI partners for the use of patient partners involved in the co-design of clinical trials collecting PROs.
- The research was reported according to GRIPP 2 checklist and adhered to INVOLVE recommendations.
- The user-friendly tools were not tested among a wider patient partner group.
- In addition, the PPI partners included in the co-development of the tools were mainly oncology patients.

Introduction

Patient-reported outcomes (PROs) provide information about the status of a patient's health, directly from the patient, without interpretation by a clinician.[1] PROs are collected in clinical trials to provide evidence of the impact of disease treatment on functional health, well-being, severity of symptoms or side effects, and psychological impact of the disease and/or the treatment.[2]

Clinical trials are medical research studies carried out to determine the activity, safety, efficacy, effectiveness and adverse effects of diagnostic and therapeutic interventions.[3] Clinical trial protocols describe the objective(s), design, procedures and statistical considerations needed to conduct a specific clinical trial. Recent research suggests important PRO protocol-items, such as hypotheses, data collection methods and statistical plans are often missing from trial protocols.[4-7] Furthermore, rates of avoidable missing PRO data are often high[4 5 8] and PRO data publications are reported long after other outcomes or not at all; [9 10] if reported, the PRO reporting is often inadequate.[7-9 11-14]

A recent review of 228 NIHR (National Institute of Health Research) Cancer portfolio studies identified that PRO data was left unreported for studies involving nearly 50,000 patients, which is unacceptable and unethical.[9] Moreover, such failures and omissions compromise the impact of PROs on future patient care and health policy, and also waste valuable resources in terms of patient and researcher time and funding.

In 2018, the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials)-PRO Extension was published with the aim to provide recommendations for researchers on which items should be addressed in clinical trial protocols with primary or key secondary PRO endpoints. However, there is a lack of training materials and tools to support the uptake of the SPIRIT-PRO guidance to promote quality and to simplify the approach for patient partners who are involved in the review and co-design of clinical trials with PRO objectives.[15] The aim of this research was to: a) adapt the SPIRIT-PRO Extension guidance to a user-friendly format for patient partners; and b) co-design a web-based tool to support the dissemination and uptake of the SPIRIT-PRO Extension by patient partners.

Methods

A patient partner (GP) produced an initial lay summary of the SPIRIT-PRO guideline and drafted a glossary with support from academic co-authors (MC and SCR). The patient partner selected to produce the initial lay summary and glossary was originally involved in the development of the SPIRIT-PRO Extension guideline. In addition, the patient partner has experienced completing PRO questionnaires and has been involved in different PRO-specific projects to provide his perspective from a patient's perspective.

A one-day PPI (Patient and Public Involvement) session was held with patient partners in November 2019 at the University of Birmingham, UK. The aim of the PPI session was to adapt the SPIRIT-PRO Extension guidance to a user-friendly format for patient partners, and co-design a tool to aid patient partners in the co-design of PRO clinical trials. The PPI session was conducted and reported according to the Guidance for Reporting Involvement of Patients and the Public (GRIPP) 2 reporting checklists. This international guidance on the key reporting items for reporting patient and public involvement in health and social care research.[16] In addition, the PPI session complied with the INVOLVE guideline, a government supported programme that supports active public involvement in NHS (National Health Service), public health and social care research.[17] Ethical approval for this study was gained from the University of Birmingham, UK, (ERN_19-0939).

Patient and Public Involvement

Seven PPI partners who were already known to the team who had relevant experience in clinical trials were recruited by the research team to assist at different stages in the development of the tools. The PPI partners were six patients and one carer with personal experience of different health conditions including oncology (four PPI partners), Parkinson's (one PPI partner) and chronic kidney disease (one PPI partner). Six PPI partners identified themselves as white and one as Sikh British. Only three of the PPI partners were previously involved as trial participants. One partner was involved in the development of the first version of the patient-friendly SPIRIT-PRO guidance. Five were involved in the co-design of the patient-friendly SPIRIT-PRO tools, and all seven contributed to writing this manuscript.

During the session, five PPI partners (GP/LR/LG/RV/PE) and two academics (MC and SCR) discussed the original SPIRIT-PRO Extension guideline and contrasted it with the initial lay summary drafted. PPI partners commented on the comprehension and refined and agreed the wording and clarity of the lay version of the SPIRIT-PRO guideline and glossary (Figure 1). Following the PPI session, attendees commented on the wording and agreed on the penultimate version of the user-friendly SPIRIT-PRO Extension content. Broader feedback on final guidance was sought from two additional patient partners (RW/RS).

Figure 1. User-friendly SPIRIT-PRO Extension and glossary methods

During the PPI session, patient partners discussed the design and content of a previously published diagram (PRO Learn resource for patient advocates involved in co-production of research or review, Appendix 1) on the PRO considerations for PPI partners in the design and review of trials collecting PROs.[18] PPI partners highlighted key SPIRIT-PRO items and additional information that should be incorporated in the published diagram. These changes led to the development of the web-tool.

Results

Seven PPI partners were involved in the co-design of two tools to promote the uptake and dissemination of the SPIRIT-PRO Extension guidance by patient partners involved in the co-development of clinical trials. PPI partners highlighted specific priorities and preferred formats. In addition, PPI partners contributed to the writing up of the discussion section and in particular around the benefits of the development of these tools.

a) User-friendly version of the SPIRIT-PRO Extension guidance

This tool was developed to adapt the SPIRIT-PRO Extension guidance to a user-friendly format for patient partners. The user-friendly tool (Table 1) presents five different key items for PPI partners to consider while involved in the co-design and/or review of trials collecting PROs: (1) SPIRIT-PRO item number and description; (2) questions for PPI partner(s) to consider; (3) key considerations for PPI partner(s); (4)

considerations for the lay summary; and (5) considerations for the participant information sheet and consent form. A glossary (Appendix 2) was also co-developed to aid PPI partners in the implementation of the user-friendly tool.

Table 1 - User-friendly version of the SPIRIT-PRO Extension guidance

SPIRIT-PRO item number and description	Questions for PPI partner(s) to consider	Key considerations for PPI partner(s)	Considerations for the lay summary	Considerations for participant information sheet and consent form
Administrative information				
SPIRIT-5a- PRO Elaboration: Specify the individual(s) responsible for the PRO content of the trial protocol	Are PPI partners being involved in the co-design of trials involving PROs? (Are they patients or carers; are there different considerations?)	• PPI partners who have made a significant contribution to the trial protocol should be acknowledged.[16] • Specify PPI partner role: co-applicant, trial management group or co-production.		
Introduction				
SPIRIT-6a-PRO Elaboration: Describe the PRO-specific research question and rationale for PRO assessment and summarize PRO findings in relevant studies	Is the research team collecting PROs? If not, why not? If yes, do the team have a clear reason for assessing PROs in the trial? Have the team specified their goals in assessing PROs?	• PPI partners can help to prioritise research questions. • What is the purpose of collecting the PRO data? • Has the research team explained to you (and in the protocol) about the likely effect of treatment on participants' symptoms, function and quality of life? If likely to be impacted by the intervention during the clinical trial. • Can the clinical team draw a graph showing quality of life progression for standard care vs. new treatment for the duration of the trial? Does this match your experience as patient (or carer)? • What evidence do they have to support this?	Has the research team looked at the literature around previous trials, qualitative work or COS (core outcome sets) on what matters to the patient (or carer)?	Describe the PRO specific research question and rationale for PRO assessment, and summarise PRO findings in relevant studies.

SPIRIT-7-PRO Elaboration: State specific PRO objectives or hypotheses (including relevant PRO concepts/domains)	Has the research team clearly stated the purpose of the research?	• How do they plan to use the PRO data that they collect during and at the end of the trial? For instance, to inform clinical practice, inform future patient care, and inform NICE (National Institute for Health and Care Excellence) policy or health economics.	It is important that lay summary clearly describe the purpose of assessing PROs in the trial.	Include the purpose of assessing PROs in the trial.
Methods: participants, interventions and outcomes				
SPIRIT-10-PRO Elaboration: Specify any PRO-specific eligibility criteria (eg, language/reading requirements or prerandomization completion of PRO). If PROs will not be collected from the entire study sample, provide a rationale and describe the method for obtaining the PRO subsample.	Are there any specific reasons why a participant might not be able to complete the PRO questionnaire?	• PPI partners can provide advice to the research team on whether patients (or carers) are likely to be able to complete PROs in the trial. For example, some may be unable to complete them because of poor literacy, language, communication difficulties. Because their condition, or cultural or cognition considerations. • Consider whether these participants need to be excluded from the PRO study or trial. Try to be as inclusive as possible • It is important to consider that *proxy completion* (report of the patient health status by his/her carer or clinician or parents reporting on behalf of children) can be an option in some cases – please see SPIRIT-PRO 18a(iv) below		Has data protection been taken into consideration if *proxy completion* is a possibility?
SPIRIT-12-PRO Elaboration: Specify the PRO concepts/domains	Has the team specified exactly what is going to be measured?	• PPI partners can work with the broader research team to help determine which PROs (e.g. symptoms, side effects, aspects of functioning or mental health)		Include what questionnaire(s) are going to be completed during the trial.

used to evaluate the intervention (eg, overall health-related quality of life, 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	How and when do they plan to do this? For example, physical function, pain and/or HRQL, etc.	patients or carers should report on and how often these will be assessed.		
SPIRIT-13-PRO Elaboration: Include a schedule of PRO assessments, providing a rationale for the time points, and justifying if the initial assessment is not prerandomization. Specify time windows, whether PRO collection is prior to clinical assessments, and, if using multiple	How often will participants be asked to complete the questionnaire(s)?	• PPI partners can help determine whether the frequency of PRO assessments is likely to be feasible for patients or carers. If it is frequent is this likely to be a burden, and if so, will it cause drop out or failure to respond? • Is the time between assessment too long and likely to miss important events that matter to patients or carers? • PPI partners can provide feedback on the most important time-points to collect PROs based on their own experience of the condition or treatment. • How long will participants have to return the questionnaire? Is the timeframe too short – will participants have time to complete the PRO? Does it need to include a weekend?		How often are the participants going to be asked to complete the questionnaire(s), when and with what deadlines?

questionnaires, whether order of administration will be standardized		• Will it coincide with clinic visits or will it take place another time (e.g. diaries)? • If trial participants are having tests at clinic or may receive news, try to complete PRO questionnaire before.		

SPIRIT-14-PRO Elaboration: When a PRO is the primary end point, 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 the PRO end point, then discuss the power of the principal PRO analyses	Is the required number of participants feasible to recruit based on the population being assessed? Are the exclusion criteria too restrictive (i.e. they are excluding too many people)? Are there cultural/age related/geography/ frailty/language condition/working status reasons why people may not participate or may drop-out?	*PPI partners are not expected to assess whether the sample size is adequate, but you may have views on whether people are likely to be interested in participating in the PRO aspects of the trial.* *If you see something in the protocol that patients or carers might not like then please raise this with the trial team as it may affect whether they have big enough numbers for their study.*		

Methods: data collections, management and analysis				
SPIRIT-18a(i)-PRO Elaboration: Justify the PRO instrument to be used and describe domains, number of items, recall period, instrument scaling and scoring (eg, range and direction of scores indicating a good or poor outcome). Evidence of PRO instrument measurement properties, interpretation guidelines, and patient acceptability and 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	How did they select the questionnaire (e.g. literature, PPI session)? Which questionnaire(s) are they considering using? Does it cover patient priorities? Are the instructions for completion of the questionnaire clear? Can you understand the scoring categories? Are they properly explained and do they make sense?	• How appropriate and acceptable are the questionnaires? • How long will it take to complete the questionnaire? Trial team should ask PPI partners to complete it to give an estimate. • What burden/issues/symptoms/side-effects/ aspects of functioning or mental health are relevant in the context of the trial? Are these addressed in the questionnaire? • Is the recall/remember period (e.g. one month or 7 days) appropriate for the condition? For instance, are symptoms stable over time or fluctuating daily (which may require more frequent assessment)?		Include how long is going to take to complete the questionnaire. Are there any questions, such as sexual function, which patients may not wish to answer and may result in missing data? Specify the estimated time to complete each assessment, and discuss feasibility of assessment for the population.

justify deviations if planned				
SPIRIT-18a(ii)-PRO Elaboration: Include a data collection plan outlining the permitted mode(s) of administration (eg, paper, telephone, electronic, other) and setting (eg, clinic, home, other)	Where, when and how will the PRO questionnaire be completed?	• PPI partners can help determine the most convenient/practical method to collect PRO data. • Where is it going to be collected e.g. in clinic at home? • Can participants complete on paper/electronically or both? • Will all participants be able to do this? • Have the team got back up plans for those who cannot complete the PRO in a particular way?		Include a data collection plan outlining the permitted mode(s) of administration (e.g. paper, telephone, electronic, other) and setting (e.g. clinic, home, other).

SPIRIT-18a(iii)-PRO Elaboration: Specify whether more than 1 language version will be used and state whether translated versions have been developed using currently recommended methods	What languages are the chosen questionnaire(s) available? Have they got questionnaires available for trial population?	• Researchers to make PPI partners aware of the availability of PRO measures in other languages. • Are there groups of the population that require a translated version? • Have they costed for it? • Are they following translation guidelines? *These are the responsibilities of the trial team but PPI partners may be able to suggest ways of widening inclusivity.*		
SPIRIT-18a(iv)-PRO Elaboration: When the trial context requires someone other than a trial participant to answer on his or her behalf (a proxy-reported outcome), state and justify the use of a proxy respondent. Provide or cite evidence of the validity of proxy assessment if available	Has the research team made clear whether it is possible for someone other than the patient to complete the questionnaire from the patient's point of view?	• Generally in a trial we prefer to collect PROs directly from the patient as we want to know their views but sometimes a patient cannot complete the questionnaire (e.g. if they have memory problems or become too ill). If you think patients may not be able to complete PROs in the trial flag this to the broader research team. • Other things that should be considered: carer reported outcomes.		If it is permissible for another person to help the study participant complete the PROM, describe what type and level of assistance is acceptable.

SPIRIT-18b(i)-PRO Elaboration: Specify PRO data collection and management strategies for minimizing avoidable missing data	How will the team ensure that data collected is complete? So that it can be used to inform patient care. Ideally researchers should have plans in place to ensure that participants complete questionnaires as they are scheduled.	• PPI partners can help provide input on how to collect PRO data and strategies to ensure that participants complete questionnaires as they are scheduled (e.g. reminders for patients, training for staff/patients). • Can you think of any other ideas that may help promote completion?		Have participants been informed of why PROs are being collected? Important to provide guidance on PRO completion. State why we need as complete data as possible and how it will be used, and where it will be reported (e.g. publication).
SPIRIT-18b(ii)-PRO Elaboration: Describe the process of PRO assessment for participants who discontinue or deviate from the assigned intervention protocol	Is there a plan for collecting data provided by patients who stop receiving the treatment under study (discontinue), or receive the treatment in a way other than planned (deviation).	• PPI partners can provide input into developing a process for patients that stop receiving treatment or receive treatment in a way different to planned. This should be linked back to the trial research question. • Consider burden to patients and whether PRO completion is ethical.		

SPIRIT-20a-PRO Elaboration: State PRO analysis methods, including any plans for addressing multiplicity/type I (α) error	What method has the research team selected to analyse the PRO data?	*PPI partners are not expected to contribute in the selection of methods for addressing multiple testing. However, they could ask the team to explain what PRO analysis method has been chosen and why.*		
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)	How is the research team going to analyse the PRO data? How will the team deal with missing data?	*PPI partners are not expected to plan how data will be analysed, but* can question the trial team about the methods that will be used to handle missing data.		
Monitoring				
SPIRIT-22-PRO Elaboration: 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	Will questionnaire data be reviewed by the research or clinical team? If so, when? What happens if the PRO indicates patient deterioration or distress? Have the research team explained	• PPI partners can help develop the participant information sheet and consent form and any other process used to inform patients about how PRO data will be monitored during the study to inform the clinical care of individual trial participants. • PPI partners can question the team about their plan to manage concerning levels of psychological distress or		What measures are in place to ensure patient distress or deterioration is identified, communicated to patient and dealt with it? If data will not be clinically reviewed, how concerns are going to be dealt with by the clinical research team. For

in a standardized way. Describe how this process will be explained to participants; eg, in the participant information sheet and consent form	what sorts of scores would indicate distress or deterioration? How will participants be informed of this process? (i.e. in the participant information sheet and consent form).	physical symptoms that might require an immediate response.		instance, mobile phone to support (emergency number) and what resources are there to support participants. Include detailed plans for regular feedback to participants via letter/newsletter on PRO aspect of study.

b) Web-based tool

The web-based tool, presented in concertina style, illustrates the main key items PPI partners considered most relevant from the user-friendly SPIRIT-PRO Extension version. The web-tool,aimed at supporting the dissemination and uptake of the SPIRIT-PRO Extension by patient partners, provides PPI partners with six general PRO-specific questions to facilitate their role as co-designers and interaction with the trial team. PPI partners are not expected to answer these questions but to raise these questions with the research team while co-developing the clinical trial.

The main six SPIRIT-PRO items included were: 1) does the team have a clear reason for assessing PROs in the trial? And has the team clearly stated the purpose of the research? 2) which questionnaire(s) are they considering using?, 3) are there any reasons why a patient might not be able to complete the PRO questionnaire?, 4) how often, when and where will patients be asked to complete the questionaire(s)? 5) what languages are the chosen questionnaire(s) available in? and 6) how will the team ensure that they collect high quality data that can meaningfully inform future patient care? The diagram provides further detail to each question to help PPI partners ask more in depth questions and better understand the importance of capturing PROs in trials. In addition, the web-tool includes 'other considerations' and 'other resources' for PPI partners to faclitate their understanding and participation in the design of the trial. For intance, 'other considerations' includes key elements that should be covered in the participant information sheet for potential trial participants. 'Other resources' includeweb resources such as ePROVIDE and GRIPP 2 checklist.[19] The webtool is available from the CPROR (Centre for Patient Reported Outcomes Research) website.[20] Figure 2 presents an overview of the co-developed web-tool.

Figure 2. Web-tool for patient advocates involved in co-production of PRO research or review

Discussion

Two user-friendly tools were co-designed with the assistance of seven patient partners to assist PPI partners involved in the design or review of clinical trials and provide informed, patient-centred input into development of PRO aspects of clinical trial protocols. PPI in this research was essential to ensure that the tools were comprehensive and user friendly for PPI partners and enhance the dissemination and uptake of the SPIRIT-PRO Extension guidance.

The involvement of PPI partners helped ensure that the tools focused on issues that matter most to them. PPI should go beyond involvement; it should be a platform for patients to influence, design processes, identify relevant content and to make decisions significant for and acceptable to end users.[21 22] PPI partners raised important concerns related to the completion of PRO questionnaires such as: time needed to complete the PRO questionnaire(s) and frequency patients need to complete the questionnaire(s). Although these are covered by the SPIRIT-PRO Extension guidance, they were included in the patient information sheet section under the 'other resources' section.

Patients have recently advocated against regulatory agencies for approving oncology drugs based on surrogate endpoints rather than the value they add to patients' lives.[23 24] In addition, patients frequently do not completely understand their diagnostics and are not aware of the side effects of the interventions, as they are occasionally not effectively communicated by healthcare professionals.[24] Therefore, patient and public awareness and their involvement can help tackle these issues.[23 24] Currently, PRO stakeholders are making concerted efforts to incorporate the patients' experience into the drug development process, which has the potential to better inform shared decision-making. [25] For instance, the Food and Drug Administration (FDA) is patient-focused drug development (PFDD) guidance to address how stakeholders can collect and include PROs from patients and caregivers in the development and regulation of medical products.[26] In 2016, the European Medicine Agency (EMA) published Appendix 2 to the guideline on the evaluation of anticancer medicinal products in man. Appendix 2 describes the use of PRO endpoints in oncology studies and the value of PRO data from the regulatory perspective.[27]

PROs carry the 'voice' of the patients; hence, trials collecting PROs should include patients and carers as co-designers to inform PRO measure development, selection, and implementation and ensure that PRO data is analysed and published.[21 28] Thus maximising the impact on future patient benefit and reducing research waste. The design of trials collecting PROs without patient input can be considered unreasonable and unacceptable.[9 21] PPI partners should be empowered to be involved in the design of trials collecting PROs and their content, and make decisions by using the two different tools developed, while following the SPIRIT-PRO Extension guidance. The strengths of the research include the participation of seven PPI partners, who were selected with a range of levels of experience and exposure to trial development to ensure the outputs were well-informed, but also accessible for new patients and public. Adherence to GRIPP 2 guidance to report PPI involvement in research was a further strength of the study.[16] The tools presented in this manuscript were developed to aid patient partners in the co-development or review of clinical trials collecting PROs. Nonetheless, these tools have the potential to be used in other types of clinical studies in which the participation of patients and carers is essential.

However, the tools developed were not tested among patient partners with less trial experience or less experience with research, which could have helped in the refinement of the tools. A further limitation is that two PPI partners involved in the co-development of the user-friendly version of the SPIRIT-PRO Extension guidance were involved in the development of the original guidance. This previous knowledge and understanding of the SPIRIT-PRO items might have influenced the selection of lay vocabulary. However, to tackle this four additional PPI partners were included to agree on the best wording of the guidance. Patient partners were involved in the same way in both research projects. However, patient partners drove the agenda more during the co-development of the tools for patients as the aim of the research was to develop tools for them to use. An additional limitation is that PPI partners' perspectives may not be reflective of a larger patient population as the majority of the participants were oncology partners and only one carer was included.

In conclusion, the tools developed, if used appropriately, have the potential to facilitate the involvement of patient partners in providing informed input into the development of PRO aspects of clinical trial protocols, in accordance with the SPIRIT-PRO Extension guidelines.

Next steps

Feedback can be provided on the resource using an anonymised survey https://www.smartsurvey.co.uk/s/SPIRIT-PRO_Tools_for_patients/, which will help inform future developments. We encourage PPI partners and researchers involved in the design or review of trials collecting PROs to provide further feedback to the research team.

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Data sharing: All data relevant to the study are included in the article or uploaded as supplementary information

Figure 1. User-friendly SPIRIT-PRO Extension and glossary methods

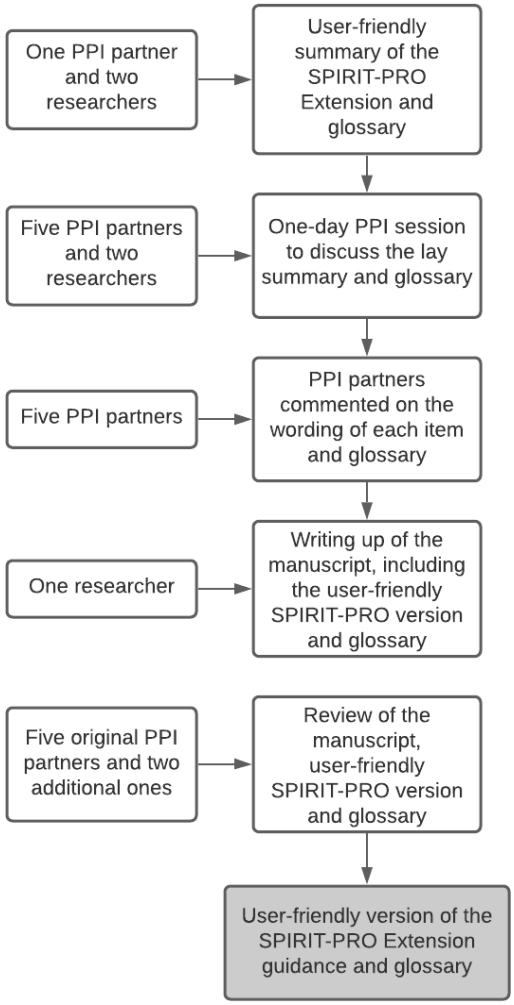
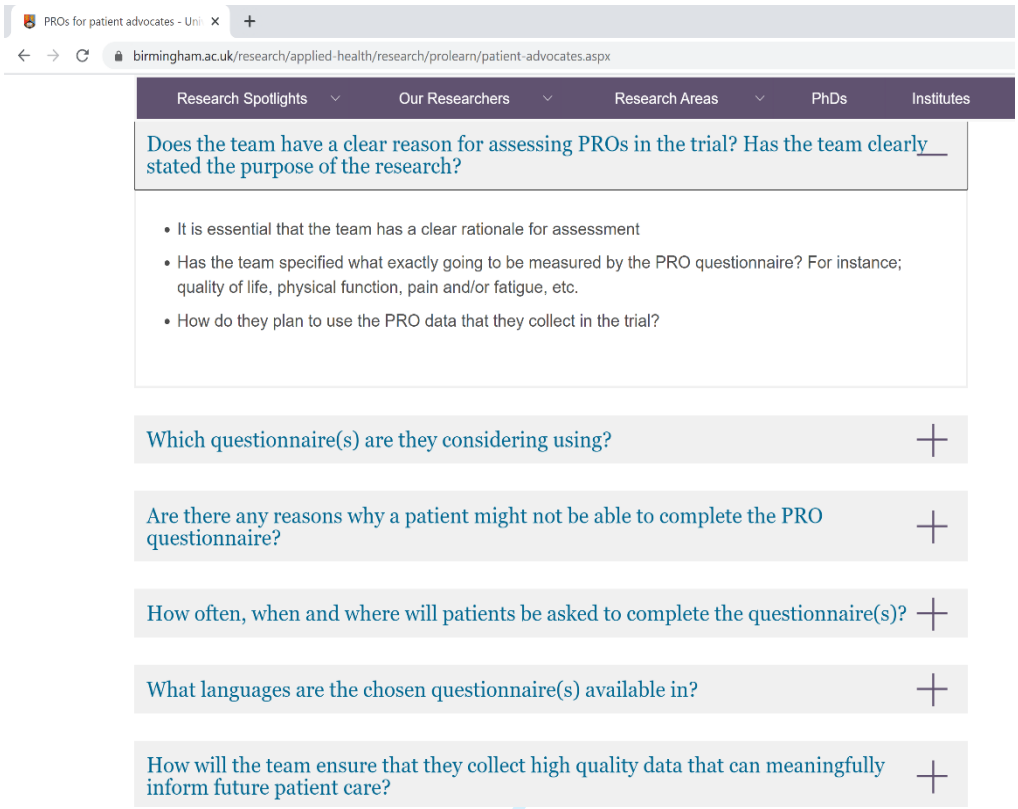


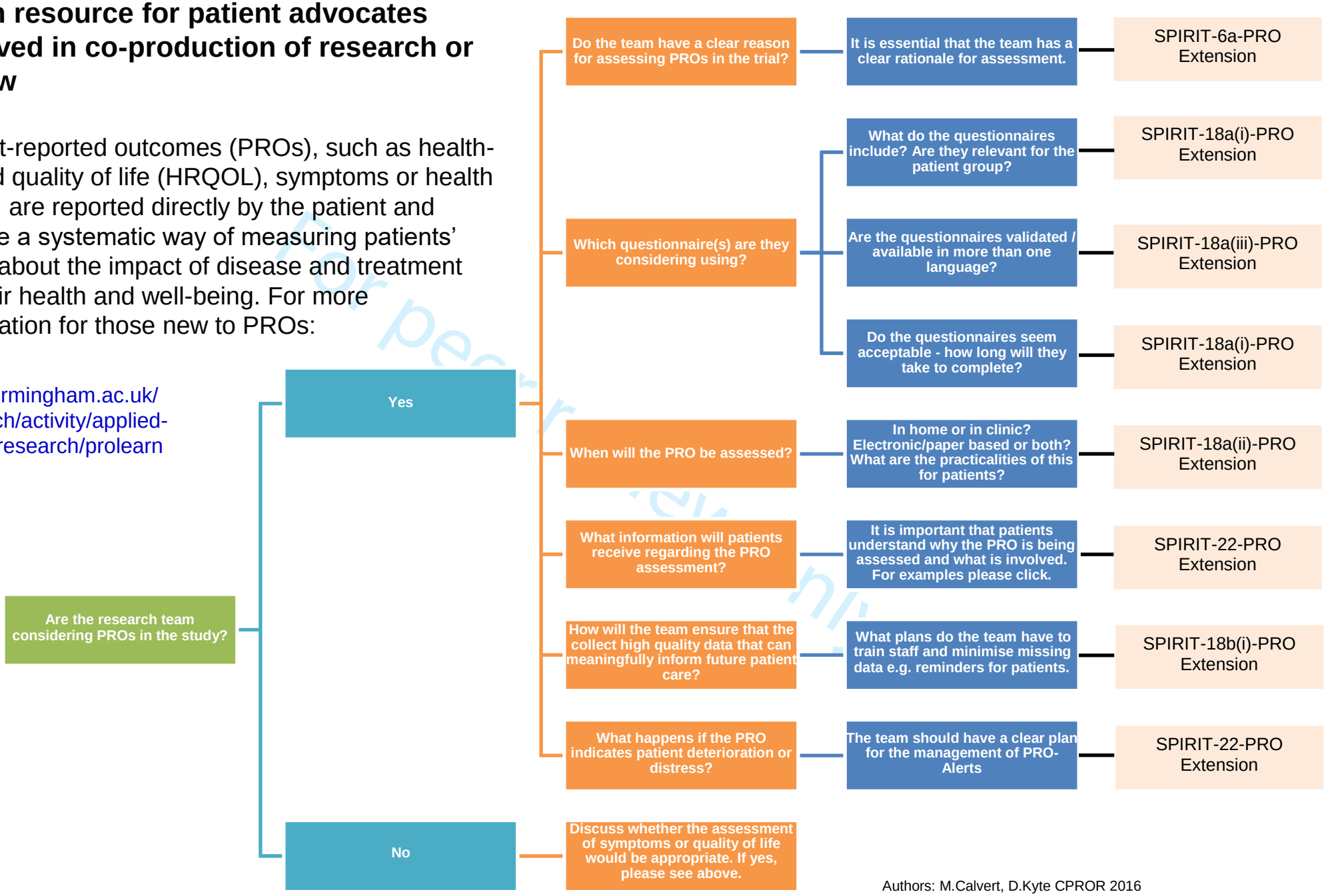
Figure 2. Web-tool for patient advocates involved in co-production of PRO research or review



University of Birmingham CPROR PRO Learn resource for patient advocates involved in co-production of research or review

Patient-reported outcomes (PROs), such as health-related quality of life (HRQOL), symptoms or health status, are reported directly by the patient and provide a systematic way of measuring patients' views about the impact of disease and treatment on their health and well-being. For more information for those new to PROs:

www.birmingham.ac.uk/research/activity/applied-health/research/prolearn



Authors: M.Calvert, D.Kyte CPROR 2016

Appendix 1 - Glossary

Administration of PRO questionnaire	Refers to providing a questionnaire. The PRO questionnaire(s) may be provided to the participant/patient by a nurse or research team member known as 'trial coordinator', 'research nurse' or 'site coordinator'. Alternatively, the questionnaire may be sent by post or electronically.
Analysis metric	How the PRO concepts/domains used to evaluate the intervention is going to be analysed (e.g. change from baseline, final value, time to event)
Consent form	A form signed by the participant/patient prior receiving a treatment to confirm he/she agrees to the procedure and is aware of the potential benefits and risks of taking part.
Core Outcome Set (COS)	Refers to the minimum recommendations of what should be measured and reported in clinical trials of a specific healthcare area.
Discontinuation/deviation	Refers to the situation in which a patient departs from the approved protocol's procedure (see protocol).
Health-related quality of life	Multidimensional concept that describes or characterises the effect of a disease or treatment on a number of domains that capture a patients' physical functioning, psychological impact and social functioning.
Hypothesis	An idea or explanation for something that is based on known facts but has not yet been proved.
Imputation analysis	Mathematical approach used to 'fill in' missing data with plausible values to analyse incomplete data. This method has the potential to solve missing data.
Instrument scaling	Refers to the scale used to measure patients' responses. For example strongly disagree, disagree, neither agree nor disagree, agree and strongly agree.
Instrument scoring	A number derived from a patient's response to items in a questionnaire.
Interpretation guidelines	Statement in which it is indicates how to decide on the meaning of the PRO data collected during the clinical trial.
Intervention	Refers to the drugs, medical devices, procedures, vaccines, and other products that can be the focus of the study of the clinical trial.

Lost to follow-up	Refers to the participants who at one point in time were actively participating in a clinical research trial, but have become lost (either by error in a computer tracking system or by being unreachable) at the point of follow-up in the trial. They may drop out of a study because they have moved away, become ill, are unable to communicate or have died.[1]
Measurement properties	Criteria by which you can assess how good the questionnaire is. Some properties include 'reliability, validity and responsiveness' (see below).
Missing data	Situation in which participants fail to complete one or more components of an evaluation, fail to attend an evaluation, or are unavailable for the evaluation because of illness, death or other events such as moving house or holidays. Missing data is a problem for the trial as you have less information to analyse than planned.[1]
Mode(s) of PRO administration	Refers to the different ways a PRO questionnaire can be answered by a patient such as on paper or electronic.
Monitor of PRO data	Refers to the checking of questionnaire responses either to check for missing data and in some instances to inform the clinical care of trial participants.
Multiplicity or multiple testing	The more comparisons or multiple tests (e.g. analysis of multiple outcomes and comparisons across multiple treatment arms) are made, there is more chance of thinking that some real effects is present in the data when, in fact, none exists.
PRO objective	Provides the justification and purpose of assessing PROs in a clinical trial.
Participant information sheet	Document that provides potential participants information on the reason for the trial, any procedures that they might have to do (such as blood tests, PROs) and detailed information of the study to allow them to decide whether to take part and give informed consent.
Power of the principal PRO analyses	The number of patients required in order to detect a difference between PRO analyses.
PPI	PPI (patient and public involvement) refers to the research carried out 'with' or 'by' members of the public.[2]
Primary endpoint	The main result to see if a given treatment in a trial worked.[3]

PRO concepts	The PRO concept is a specific measurement goal (i.e., the thing that is to be measured by a PRO instrument).[4]
PRO domains	A PRO domain is a meaningful sub-set of a PRO measure such as emotional well-being or physical function.[4]
PRO-alerts	PRO data “concerning levels of psychological distress or physical symptoms that may require an immediate response".[5]
Protocol	Document that describes the objective(s), design, methodology and statistical considerations to conduct a specific clinical trial.
Proxy-reported outcome	Refers to those individuals (carer or family member) who answer a PRO questionnaire on behalf of the patient or trial participant.
Randomisation	An experimental study design in which participants are allocated by a random process to two or more study groups.
Recruitment target	The number of patients or trial participants that need to be enrolled in the clinical trial to meet protocol requirements.
Sensitivity analysis	Allows researchers and policy makers to assess how uncertainty in the results of the mathematical calculation is affected by different source of uncertainty. For example, if there is missing PRO data how much does this influence the results on whether a treatment worked.
Time windows	Specific period of time in which PRO data will be collected.
Type I error	The incorrect conclusion that two treatments differ, when in reality they do not.[1]
Validity	It is the degree to which an assessment measures what it is supposed to measure.[6]

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"Give Us The Tools!" - Development of knowledge transfer tools to support the involvement of patient partners in the development of clinical trial protocols with patient-reported outcomes (PROs), in accordance with SPIRIT-PRO Extension.

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Abstract

Objectives a) To adapt the SPIRIT-PRO Extension guidance to a user-friendly format for patient partners; and b) to co-design a web-based tool to support the dissemination and uptake of the SPIRIT-PRO Extension by patient partners.

Design A one-day patient and public involvement session.

Participants Seven patient partners.

Methods A patient partner produced an initial lay summary of the SPIRIT-PRO guideline and a glossary. We held a one-day patient and public involvement session in November 2019 at the University of Birmingham. Five patient partners discussed the draft lay summary, agreed on the final wording. Co-designed and agreed the final content for both tools. Two additional patient partners were involved in writing the manuscript. The study compiled with INVOLVE guidelines and was reported according to the GRIPP 2 checklist.

Results Two user-friendly tools were developed to help patients and members of the public be involved in the co-design of clinical trials collecting PROs. The first tool presents a lay version of the SPIRIT-PRO Extension guidance. The second depicts the most relevant points, identified by the patient partners, of the guidance through an interactive flow diagram.

Conclusions These tools have the potential to support the involvement of patient partners in making informed contributions to the development of PRO aspects of clinical trial protocols, in accordance with the SPIRIT-PRO Extension guidelines. The involvement of patient partners ensured the tools focused on issues most relevant to them.

Strengths and limitations

- Two user-friendly tools were co-developed with PPI partners for the use of patient partners involved in the co-design of clinical trials collecting PROs.
- The research was reported according to GRIPP 2 checklist and adhered to INVOLVE recommendations.
- The user-friendly tools were not tested among a wider patient partner group.
- In addition, the PPI partners included in the co-development of the tools were mainly oncology patients.

Introduction

Patient-reported outcomes (PROs) provide information about the status of a patient's health, directly from the patient, without interpretation by a clinician.[1] PROs are collected in clinical trials to provide evidence of the impact of disease treatment on functional health, well-being, severity of symptoms or side effects, and psychological impact of the disease and/or the treatment.[2]

Clinical trials are medical research studies carried out to determine the activity, safety, efficacy, effectiveness and adverse effects of diagnostic and therapeutic interventions.[3] Clinical trial protocols describe the objective(s), design, procedures and statistical considerations needed to conduct a specific clinical trial. Recent research suggests important PRO protocol-items, such as hypotheses, data collection methods and statistical plans are often missing from trial protocols.[4-7] Furthermore, rates of avoidable missing PRO data are often high[4 5 8] and PRO data publications are reported long after other outcomes or not at all; [9 10] if reported, the PRO reporting is often inadequate.[7-9 11-14]

A recent review of 228 NIHR (National Institute of Health Research) Cancer portfolio studies identified that PRO data was left unreported for studies involving nearly 50,000 patients, which is unacceptable and unethical.[9] Moreover, such failures and omissions compromise the impact of PROs on future patient care and health policy, and also waste valuable resources in terms of patient and researcher time and funding.

In 2018, the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials)-PRO Extension was published with the aim to provide recommendations for researchers on which items should be addressed in clinical trial protocols with primary or key secondary PRO endpoints. However, there is a lack of training materials and tools to support the uptake of the SPIRIT-PRO guidance to promote quality and to simplify the approach for patient partners who are involved in the review and co-design of clinical trials with PRO objectives.[15] The aim of this research was to: a) adapt the SPIRIT-PRO Extension guidance to a user-friendly format for patient partners; and b) co-design a web-based tool to support the dissemination and uptake of the SPIRIT-PRO Extension by patient partners.

Methods

A patient partner (GP) produced an initial lay summary of the SPIRIT-PRO guideline and drafted a glossary with support from academic co-authors (MC and SCR). The patient partner selected to produce the initial lay summary and glossary was originally involved in the development of the SPIRIT-PRO Extension guideline. In addition, the patient partner has experienced completing PRO questionnaires and has been involved in different PRO-specific projects to provide his perspective from a patient's perspective.

A one-day PPI (Patient and Public Involvement) session was held with patient partners in November 2019 at the University of Birmingham, UK. The aim of the PPI session was to adapt the SPIRIT-PRO Extension guidance to a user-friendly format for patient partners, and co-design a tool to aid patient partners in the co-design of PRO clinical trials. The PPI session was conducted and reported according to the Guidance for Reporting Involvement of Patients and the Public (GRIPP) 2 reporting checklists. This international guidance on the key reporting items for reporting patient and public involvement in health and social care research.[16] In addition, the PPI session complied with the INVOLVE guideline, a government supported programme that supports active public involvement in NHS (National Health Service), public health and social care research.[17] Ethical approval for this study was gained from the University of Birmingham, UK, (ERN_19-0939).

Patient and Public Involvement

Seven PPI partners who were already known to the team who had relevant experience in clinical trials were recruited by the research team to assist at different stages in the development of the tools. The PPI partners were six patients and one carer with personal experience of different health conditions including oncology (four PPI partners), Parkinson's (one PPI partner) and chronic kidney disease (one PPI partner). Six PPI partners identified themselves as white and one as Sikh British. Only three of the PPI partners were previously involved as trial participants. One partner was involved in the development of the first version of the patient-friendly SPIRIT-PRO guidance. Five were involved in the co-design of the patient-friendly SPIRIT-PRO tools, and all seven contributed to writing this manuscript.

During the session, five PPI partners (GP/LR/LG/RV/PE) and two academics (MC and SCR) discussed the original SPIRIT-PRO Extension guideline and contrasted it with the initial lay summary drafted. PPI partners commented on the comprehension and refined and agreed the wording and clarity of the lay version of the SPIRIT-PRO guideline and glossary (Figure 1). Following the PPI session, attendees commented on the wording and agreed on the penultimate version of the user-friendly SPIRIT-PRO Extension content. Broader feedback on final guidance was sought from two additional patient partners (RW/RS).

Figure 1. User-friendly SPIRIT-PRO Extension and glossary methods

During the PPI session, patient partners discussed the design and content of a previously published diagram (PRO Learn resource for patient advocates involved in co-production of research or review, Appendix 1) on the PRO considerations for PPI partners in the design and review of trials collecting PROs.[18] PPI partners highlighted key SPIRIT-PRO items and additional information that should be incorporated in the published diagram. These changes led to the development of the web-tool.

Results

Seven PPI partners were involved in the co-design of two tools to promote the uptake and dissemination of the SPIRIT-PRO Extension guidance by patient partners involved in the co-development of clinical trials. PPI partners highlighted specific priorities and preferred formats. In addition, PPI partners contributed to the writing up of the discussion section and in particular around the benefits of the development of these tools.

a) User-friendly version of the SPIRIT-PRO Extension guidance

This tool was developed to adapt the SPIRIT-PRO Extension guidance to a user-friendly format for patient partners. The user-friendly tool (Table 1) presents five different key items for PPI partners to consider while involved in the co-design and/or review of trials collecting PROs: (1) SPIRIT-PRO item number and description; (2) questions for PPI partner(s) to consider; (3) key considerations for PPI partner(s); (4)

considerations for the lay summary; and (5) considerations for the participant information sheet and consent form. A glossary (Appendix 2) was also co-developed to aid PPI partners in the implementation of the user-friendly tool.

Table 1 - User-friendly version of the SPIRIT-PRO Extension guidance

SPIRIT-PRO item number and description	Questions for PPI partner(s) to consider	Key considerations for PPI partner(s)	Considerations for the lay summary	Considerations for participant information sheet and consent form
Administrative information				
SPIRIT-5a- PRO Elaboration: Specify the individual(s) responsible for the PRO content of the trial protocol	Are PPI partners being involved in the co-design of trials involving PROs? (Are they patients or carers; are there different considerations?)	• PPI partners who have made a significant contribution to the trial protocol should be acknowledged.[16] • Specify PPI partner role: co-applicant, trial management group or co-production.		
Introduction				
SPIRIT-6a-PRO Elaboration: Describe the PRO-specific research question and rationale for PRO assessment and summarize PRO findings in relevant studies	Is the research team collecting PROs? If not, why not? If yes, do the team have a clear reason for assessing PROs in the trial? Have the team specified their goals in assessing PROs?	• PPI partners can help to prioritise research questions. • What is the purpose of collecting the PRO data? • Has the research team explained to you (and in the protocol) about the likely effect of treatment on participants' symptoms, function and quality of life? If likely to be impacted by the intervention during the clinical trial. • Can the clinical team draw a graph showing quality of life progression for standard care vs. new treatment for the duration of the trial? Does this match your experience as patient (or carer)? • What evidence do they have to support this?	Has the research team looked at the literature around previous trials, qualitative work or COS (core outcome sets) on what matters to the patient (or carer)?	Describe the PRO specific research question and rationale for PRO assessment, and summarise PRO findings in relevant studies.

SPIRIT-7-PRO Elaboration: State specific PRO objectives or hypotheses (including relevant PRO concepts/domains)	Has the research team clearly stated the purpose of the research?	• How do they plan to use the PRO data that they collect during and at the end of the trial? For instance, to inform clinical practice, inform future patient care, and inform NICE (National Institute for Health and Care Excellence) policy or health economics.	It is important that lay summary clearly describe the purpose of assessing PROs in the trial.	Include the purpose of assessing PROs in the trial.
Methods: participants, interventions and outcomes				
SPIRIT-10-PRO Elaboration: Specify any PRO-specific eligibility criteria (eg, language/reading requirements or prerandomization completion of PRO). If PROs will not be collected from the entire study sample, provide a rationale and describe the method for obtaining the PRO subsample.	Are there any specific reasons why a participant might not be able to complete the PRO questionnaire?	• PPI partners can provide advice to the research team on whether patients (or carers) are likely to be able to complete PROs in the trial. For example, some may be unable to complete them because of poor literacy, language, communication difficulties. Because their condition, or cultural or cognition considerations. • Consider whether these participants need to be excluded from the PRO study or trial. Try to be as inclusive as possible • It is important to consider that *proxy completion* (report of the patient health status by his/her carer or clinician or parents reporting on behalf of children) can be an option in some cases – please see SPIRIT-PRO 18a(iv) below		Has data protection been taken into consideration if *proxy completion* is a possibility?
SPIRIT-12-PRO Elaboration: Specify the PRO concepts/domains	Has the team specified exactly what is going to be measured?	• PPI partners can work with the broader research team to help determine which PROs (e.g. symptoms, side effects, aspects of functioning or mental health)		Include what questionnaire(s) are going to be completed during the trial.

used to evaluate the intervention (eg, overall health-related quality of life, 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	How and when do they plan to do this? For example, physical function, pain and/or HRQL, etc.	patients or carers should report on and how often these will be assessed.		
SPIRIT-13-PRO Elaboration: Include a schedule of PRO assessments, providing a rationale for the time points, and justifying if the initial assessment is not prerandomization. Specify time windows, whether PRO collection is prior to clinical assessments, and, if using multiple	How often will participants be asked to complete the questionnaire(s)?	• PPI partners can help determine whether the frequency of PRO assessments is likely to be feasible for patients or carers. If it is frequent is this likely to be a burden, and if so, will it cause drop out or failure to respond? • Is the time between assessment too long and likely to miss important events that matter to patients or carers? • PPI partners can provide feedback on the most important time-points to collect PROs based on their own experience of the condition or treatment. • How long will participants have to return the questionnaire? Is the timeframe too short – will participants have time to complete the PRO? Does it need to include a weekend?		How often are the participants going to be asked to complete the questionnaire(s), when and with what deadlines?

questionnaires, whether order of administration will be standardized		• Will it coincide with clinic visits or will it take place another time (e.g. diaries)? • If trial participants are having tests at clinic or may receive news, try to complete PRO questionnaire before.		

SPIRIT-14-PRO Elaboration: When a PRO is the primary end point, 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 the PRO end point, then discuss the power of the principal PRO analyses	Is the required number of participants feasible to recruit based on the population being assessed? Are the exclusion criteria too restrictive (i.e. they are excluding too many people)? Are there cultural/age related/geography/ frailty/language condition/working status reasons why people may not participate or may drop-out?	*PPI partners are not expected to assess whether the sample size is adequate, but you may have views on whether people are likely to be interested in participating in the PRO aspects of the trial.* *If you see something in the protocol that patients or carers might not like then please raise this with the trial team as it may affect whether they have big enough numbers for their study.*		

Methods: data collections, management and analysis				
SPIRIT-18a(i)-PRO Elaboration: Justify the PRO instrument to be used and describe domains, number of items, recall period, instrument scaling and scoring (eg, range and direction of scores indicating a good or poor outcome). Evidence of PRO instrument measurement properties, interpretation guidelines, and patient acceptability and 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	How did they select the questionnaire (e.g. literature, PPI session)? Which questionnaire(s) are they considering using? Does it cover patient priorities? Are the instructions for completion of the questionnaire clear? Can you understand the scoring categories? Are they properly explained and do they make sense?	• How appropriate and acceptable are the questionnaires? • How long will it take to complete the questionnaire? Trial team should ask PPI partners to complete it to give an estimate. • What burden/issues/symptoms/side-effects/ aspects of functioning or mental health are relevant in the context of the trial? Are these addressed in the questionnaire? • Is the recall/remember period (e.g. one month or 7 days) appropriate for the condition? For instance, are symptoms stable over time or fluctuating daily (which may require more frequent assessment)?		Include how long is going to take to complete the questionnaire. Are there any questions, such as sexual function, which patients may not wish to answer and may result in missing data? Specify the estimated time to complete each assessment, and discuss feasibility of assessment for the population.

justify deviations if planned				
SPIRIT-18a(ii)-PRO Elaboration: Include a data collection plan outlining the permitted mode(s) of administration (eg, paper, telephone, electronic, other) and setting (eg, clinic, home, other)	Where, when and how will the PRO questionnaire be completed?	• PPI partners can help determine the most convenient/practical method to collect PRO data. • Where is it going to be collected e.g. in clinic at home? • Can participants complete on paper/electronically or both? • Will all participants be able to do this? • Have the team got back up plans for those who cannot complete the PRO in a particular way?		Include a data collection plan outlining the permitted mode(s) of administration (e.g. paper, telephone, electronic, other) and setting (e.g. clinic, home, other).

SPIRIT-18a(iii)-PRO Elaboration: Specify whether more than 1 language version will be used and state whether translated versions have been developed using currently recommended methods	What languages are the chosen questionnaire(s) available? Have they got questionnaires available for trial population?	• Researchers to make PPI partners aware of the availability of PRO measures in other languages. • Are there groups of the population that require a translated version? • Have they costed for it? • Are they following translation guidelines? *These are the responsibilities of the trial team but PPI partners may be able to suggest ways of widening inclusivity.*		
SPIRIT-18a(iv)-PRO Elaboration: When the trial context requires someone other than a trial participant to answer on his or her behalf (a proxy-reported outcome), state and justify the use of a proxy respondent. Provide or cite evidence of the validity of proxy assessment if available	Has the research team made clear whether it is possible for someone other than the patient to complete the questionnaire from the patient's point of view?	• Generally in a trial we prefer to collect PROs directly from the patient as we want to know their views but sometimes a patient cannot complete the questionnaire (e.g. if they have memory problems or become too ill). If you think patients may not be able to complete PROs in the trial flag this to the broader research team. • Other things that should be considered: carer reported outcomes.		If it is permissible for another person to help the study participant complete the PROM, describe what type and level of assistance is acceptable.

SPIRIT-18b(i)-PRO Elaboration: Specify PRO data collection and management strategies for minimizing avoidable missing data	How will the team ensure that data collected is complete? So that it can be used to inform patient care. Ideally researchers should have plans in place to ensure that participants complete questionnaires as they are scheduled.	• PPI partners can help provide input on how to collect PRO data and strategies to ensure that participants complete questionnaires as they are scheduled (e.g. reminders for patients, training for staff/patients). • Can you think of any other ideas that may help promote completion?		Have participants been informed of why PROs are being collected? Important to provide guidance on PRO completion. State why we need as complete data as possible and how it will be used, and where it will be reported (e.g. publication).
SPIRIT-18b(ii)-PRO Elaboration: Describe the process of PRO assessment for participants who discontinue or deviate from the assigned intervention protocol	Is there a plan for collecting data provided by patients who stop receiving the treatment under study (discontinue), or receive the treatment in a way other than planned (deviation).	• PPI partners can provide input into developing a process for patients that stop receiving treatment or receive treatment in a way different to planned. This should be linked back to the trial research question. • Consider burden to patients and whether PRO completion is ethical.		

SPIRIT-20a-PRO Elaboration: State PRO analysis methods, including any plans for addressing multiplicity/type I (α) error	What method has the research team selected to analyse the PRO data?	*PPI partners are not expected to contribute in the selection of methods for addressing multiple testing. However, they could ask the team to explain what PRO analysis method has been chosen and why.*		
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)	How is the research team going to analyse the PRO data? How will the team deal with missing data?	*PPI partners are not expected to plan how data will be analysed, but* can question the trial team about the methods that will be used to handle missing data.		
Monitoring				
SPIRIT-22-PRO Elaboration: 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	Will questionnaire data be reviewed by the research or clinical team? If so, when? What happens if the PRO indicates patient deterioration or distress? Have the research team explained	• PPI partners can help develop the participant information sheet and consent form and any other process used to inform patients about how PRO data will be monitored during the study to inform the clinical care of individual trial participants. • PPI partners can question the team about their plan to manage concerning levels of psychological distress or		What measures are in place to ensure patient distress or deterioration is identified, communicated to patient and dealt with it? If data will not be clinically reviewed, how concerns are going to be dealt with by the clinical research team. For

in a standardized way. Describe how this process will be explained to participants; eg, in the participant information sheet and consent form	what sorts of scores would indicate distress or deterioration? How will participants be informed of this process? (i.e. in the participant information sheet and consent form).	physical symptoms that might require an immediate response.		instance, mobile phone to support (emergency number) and what resources are there to support participants. Include detailed plans for regular feedback to participants via letter/newsletter on PRO aspect of study.

b) Web-based tool

The web-based tool, presented in concertina style, illustrates the main key items PPI partners considered most relevant from the user-friendly SPIRIT-PRO Extension version. The web-tool,aimed at supporting the dissemination and uptake of the SPIRIT-PRO Extension by patient partners, provides PPI partners with six general PRO-specific questions to facilitate their role as co-designers and interaction with the trial team. PPI partners are not expected to answer these questions but to raise these questions with the research team while co-developing the clinical trial.

The main six SPIRIT-PRO items included were: 1) does the team have a clear reason for assessing PROs in the trial? And has the team clearly stated the purpose of the research? 2) which questionnaire(s) are they considering using?, 3) are there any reasons why a patient might not be able to complete the PRO questionnaire?, 4) how often, when and where will patients be asked to complete the questionaire(s)? 5) what languages are the chosen questionnaire(s) available in? and 6) how will the team ensure that they collect high quality data that can meaningfully inform future patient care? The diagram provides further detail to each question to help PPI partners ask more in depth questions and better understand the importance of capturing PROs in trials. In addition, the web-tool includes 'other considerations' and 'other resources' for PPI partners to faclitate their understanding and participation in the design of the trial. For intance, 'other considerations' includes key elements that should be covered in the participant information sheet for potential trial participants. 'Other resources' includeweb resources such as ePROVIDE and GRIPP 2 checklist.[19] The webtool is available from the CPROR (Centre for Patient Reported Outcomes Research) website.[20] Figure 2 presents an overview of the co-developed web-tool.

Figure 2. Web-tool for patient advocates involved in co-production of PRO research or review

Discussion

Two user-friendly tools were co-designed with the assistance of seven patient partners to assist PPI partners involved in the design or review of clinical trials and provide informed, patient-centred input into development of PRO aspects of clinical trial protocols. PPI in this research was essential to ensure that the tools were comprehensive and user friendly for PPI partners and enhance the dissemination and uptake of the SPIRIT-PRO Extension guidance.

The involvement of PPI partners helped ensure that the tools focused on issues that matter most to them. PPI should go beyond involvement; it should be a platform for patients to influence, design processes, identify relevant content and to make decisions significant for and acceptable to end users.[21 22] PPI partners raised important concerns related to the completion of PRO questionnaires such as: time needed to complete the PRO questionnaire(s) and frequency patients need to complete the questionnaire(s). Although these are covered by the SPIRIT-PRO Extension guidance, they were included in the patient information sheet section under the 'other resources' section.

Patients have recently advocated against regulatory agencies for approving oncology drugs based on surrogate endpoints rather than the value they add to patients' lives.[23 24] In addition, patients frequently do not completely understand their diagnostics and are not aware of the side effects of the interventions, as they are occasionally not effectively communicated by healthcare professionals.[24] Therefore, patient and public awareness and their involvement can help tackle these issues.[23 24] Currently, PRO stakeholders are making concerted efforts to incorporate the patients' experience into the drug development process, which has the potential to better inform shared decision-making. [25] For instance, the Food and Drug Administration (FDA) is patient-focused drug development (PFDD) guidance to address how stakeholders can collect and include PROs from patients and caregivers in the development and regulation of medical products.[26] In 2016, the European Medicine Agency (EMA) published Appendix 2 to the guideline on the evaluation of anticancer medicinal products in man. Appendix 2 describes the use of PRO endpoints in oncology studies and the value of PRO data from the regulatory perspective.[27]

PROs carry the 'voice' of the patients; hence, trials collecting PROs should include patients and carers as co-designers to inform PRO measure development, selection, and implementation and ensure that PRO data is analysed and published.[21 28] Thus maximising the impact on future patient benefit and reducing research waste. The design of trials collecting PROs without patient input can be considered unreasonable and unacceptable.[9 21] PPI partners should be empowered to be involved in the design of trials collecting PROs and their content, and make decisions by using the two different tools developed, while following the SPIRIT-PRO Extension guidance. The strengths of the research include the participation of seven PPI partners, who were selected with a range of levels of experience and exposure to trial development to ensure the outputs were well-informed, but also accessible for new patients and public. Adherence to GRIPP 2 guidance to report PPI involvement in research was a further strength of the study.[16] The tools presented in this manuscript were developed to aid patient partners in the co-development or review of clinical trials collecting PROs. Nonetheless, these tools have the potential to be used in other types of clinical studies in which the participation of patients and carers is essential.

However, the tools developed were not tested among patient partners with less trial experience or less experience with research, which could have helped in the refinement of the tools. A further limitation is that two PPI partners involved in the co-development of the user-friendly version of the SPIRIT-PRO Extension guidance were involved in the development of the original guidance. This previous knowledge and understanding of the SPIRIT-PRO items might have influenced the selection of lay vocabulary. However, to tackle this four additional PPI partners were included to agree on the best wording of the guidance. Patient partners were involved in the same way in both research projects. However, patient partners drove the agenda more during the co-development of the tools for patients as the aim of the research was to develop tools for them to use. An additional limitation is that PPI partners' perspectives may not be reflective of a larger patient population as the majority of the participants were oncology partners and only one carer was included.

In conclusion, the tools developed, if used appropriately, have the potential to facilitate the involvement of patient partners in providing informed input into the development of PRO aspects of clinical trial protocols, in accordance with the SPIRIT-PRO Extension guidelines.

Next steps

Feedback can be provided on the resource using an anonymised survey https://www.smartsurvey.co.uk/s/SPIRIT-PRO_Tools_for_patients/, which will help inform future developments. We encourage PPI partners and researchers involved in the design or review of trials collecting PROs to provide further feedback to the research team.

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Competing interests: MC and AS receive funding from the National Institute for Health Research (NIHR) Birmingham Biomedical Research Centre, the NIHR Surgical Reconstruction and Microbiology Research Centre and NIHR ARC West Midlands at the University of Birmingham and University Hospitals Birmingham NHS Foundation Trust, Health Data Research UK, Innovate UK (part of UK Research and Innovation), Macmillan Cancer Support, UCB Pharma. The views expressed in this article are those of the author(s) and not necessarily those of the NIHR, or the Department of Health and Social Care. RMB is supported by the Australian Government by a National Health and Medical Research.

Role of the Funder/Sponsor: The funder 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 manuscripts; or decision to submit the manuscript for publication.

Patient and Public Involvement statement: The study was supported by a patient and public advisory group which helped in the co-design of the tools for patients and writing up of the manuscript. In addition, a one-day meeting was held for the patient and public advisory group to comment on the tools developed. At the end of the study, the patient and public advisory group commented on the findings and contributed to the dissemination plan.

Ethics approval: This study did not require ethica approval.

Data sharing: All data relevant to the study are included in the article or uploaded as supplementary information

Figure 1. User-friendly SPIRIT-PRO Extension and glossary methods

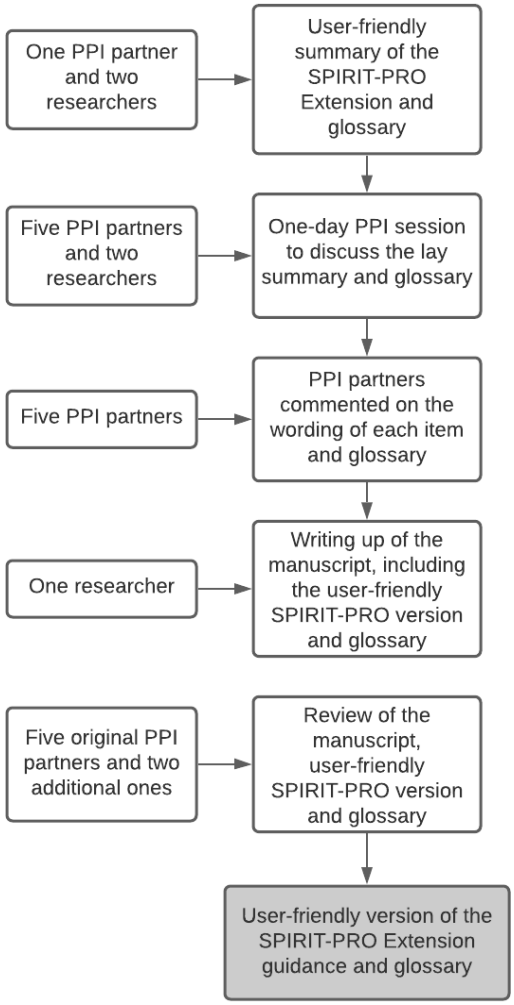
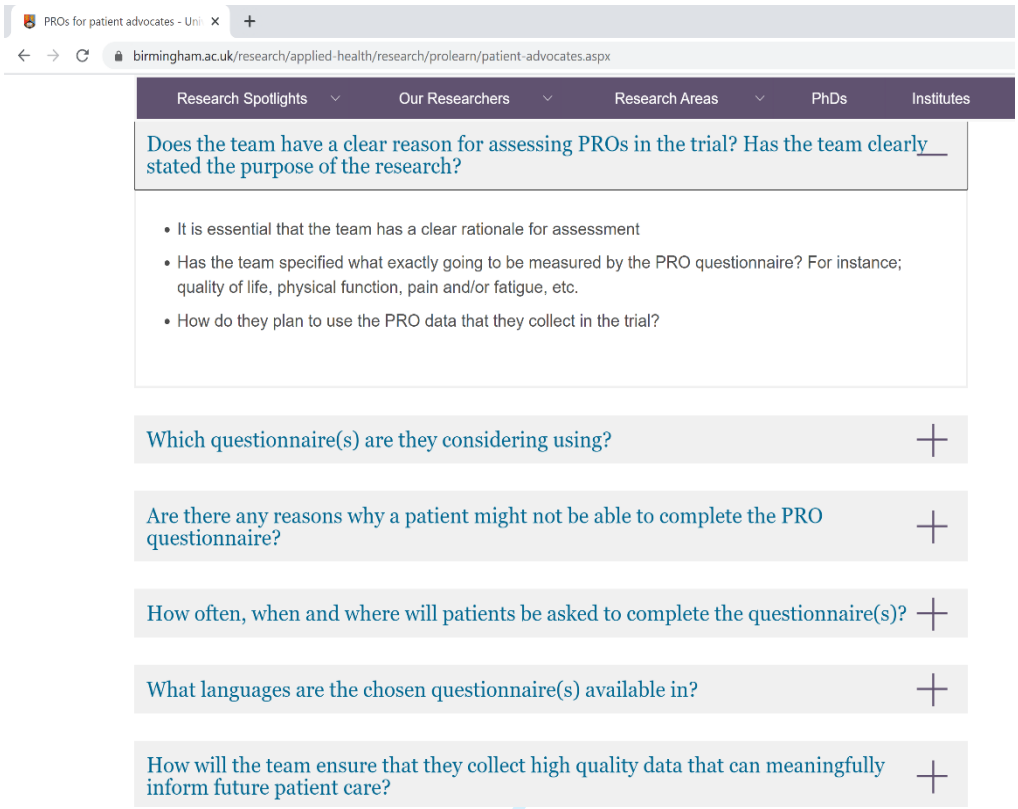


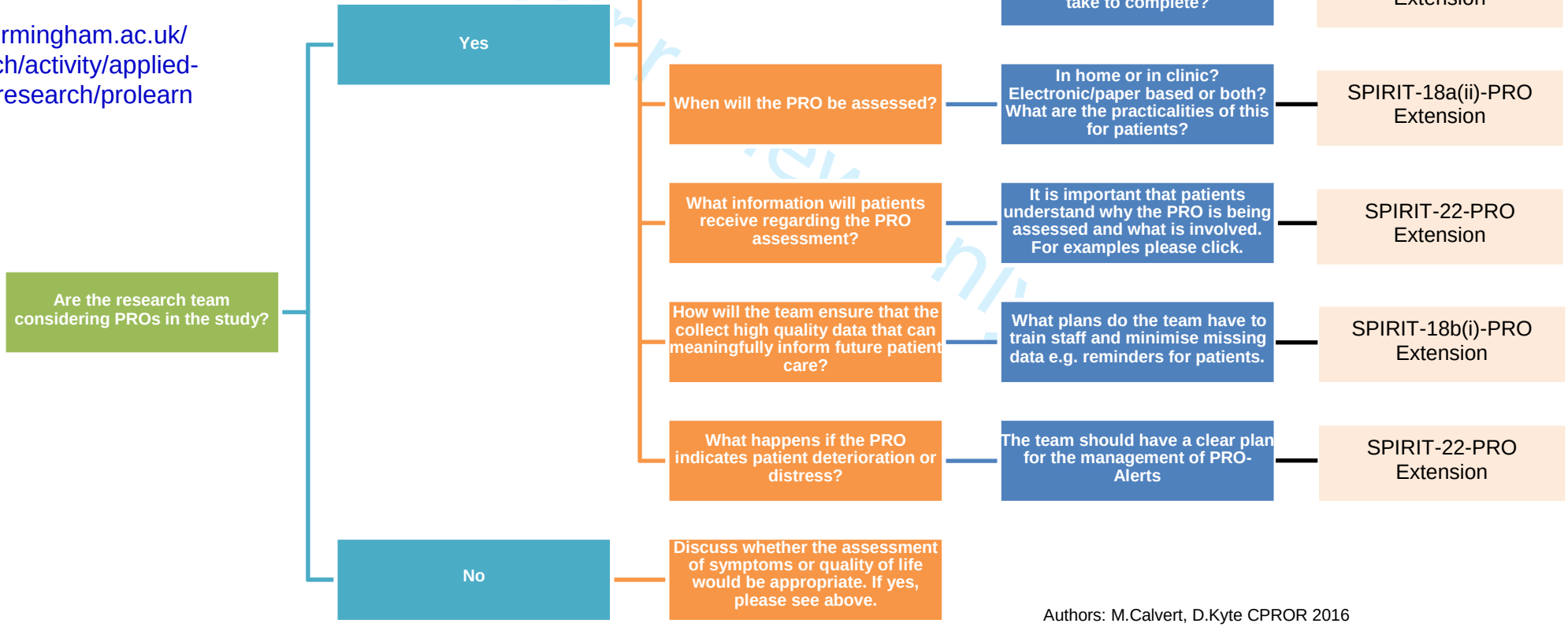
Figure 2. Web-tool for patient advocates involved in co-production of PRO research or review



University of Birmingham CPROR PRO Learn resource for patient advocates involved in co-production of research or review

Patient-reported outcomes (PROs), such as health-related quality of life (HRQOL), symptoms or health status, are reported directly by the patient and provide a systematic way of measuring patients' views about the impact of disease and treatment on their health and well-being. For more information for those new to PROs:

www.birmingham.ac.uk/research/activity/applied-health/research/prolearn



Authors: M.Calvert, D.Kyte CPROR 2016

Appendix 2 - Glossary

Administration of PRO questionnaire	Refers to providing a questionnaire. The PRO questionnaire(s) may be provided to the participant/patient by a nurse or research team member known as 'trial coordinator', 'research nurse' or 'site coordinator'. Alternatively, the questionnaire may be sent by post or electronically.
Analysis metric	How the PRO concepts/domains used to evaluate the intervention is going to be analysed (e.g. change from baseline, final value, time to event)
Consent form	A form signed by the participant/patient prior receiving a treatment to confirm he/she agrees to the procedure and is aware of the potential benefits and risks of taking part.
Core Outcome Set (COS)	Refers to the minimum recommendations of what should be measured and reported in clinical trials of a specific healthcare area.
Discontinuation/deviation	Refers to the situation in which a patient departs from the approved protocol's procedure (see protocol).
Health-related quality of life	Multidimensional concept that describes or characterises the effect of a disease or treatment on a number of domains that capture a patients' physical functioning, psychological impact and social functioning.
Hypothesis	An idea or explanation for something that is based on known facts but has not yet been proved.
Imputation analysis	Mathematical approach used to 'fill in' missing data with plausible values to analyse incomplete data. This method has the potential to solve missing data.
Instrument scaling	Refers to the scale used to measure patients' responses. For example strongly disagree, disagree, neither agree nor disagree, agree and strongly agree.
Instrument scoring	A number derived from a patient's response to items in a questionnaire.
Interpretation guidelines	Statement in which it is indicates how to decide on the meaning of the PRO data collected during the clinical trial.
Intervention	Refers to the drugs, medical devices, procedures, vaccines, and other products that can be the focus of the study of the clinical trial.

Lost to follow-up	Refers to the participants who at one point in time were actively participating in a clinical research trial, but have become lost (either by error in a computer tracking system or by being unreachable) at the point of follow-up in the trial. They may drop out of a study because they have moved away, become ill, are unable to communicate or have died.[1]
Measurement properties	Criteria by which you can assess how good the questionnaire is. Some properties include 'reliability, validity and responsiveness' (see below).
Missing data	Situation in which participants fail to complete one or more components of an evaluation, fail to attend an evaluation, or are unavailable for the evaluation because of illness, death or other events such as moving house or holidays. Missing data is a problem for the trial as you have less information to analyse than planned.[1]
Mode(s) of PRO administration	Refers to the different ways a PRO questionnaire can be answered by a patient such as on paper or electronic.
Monitor of PRO data	Refers to the checking of questionnaire responses either to check for missing data and in some instances to inform the clinical care of trial participants.
Multiplicity or multiple testing	The more comparisons or multiple tests (e.g. analysis of multiple outcomes and comparisons across multiple treatment arms) are made, there is more chance of thinking that some real effects is present in the data when, in fact, none exists.
PRO objective	Provides the justification and purpose of assessing PROs in a clinical trial.
Participant information sheet	Document that provides potential participants information on the reason for the trial, any procedures that they might have to do (such as blood tests, PROs) and detailed information of the study to allow them to decide whether to take part and give informed consent.
Power of the principal PRO analyses	The number of patients required in order to detect a difference between PRO analyses.
PPI	PPI (patient and public involvement) refers to the research carried out 'with' or 'by' members of the public.[2]
Primary endpoint	The main result to see if a given treatment in a trial worked.[3]

PRO concepts	The PRO concept is a specific measurement goal (i.e., the thing that is to be measured by a PRO instrument).[4]
PRO domains	A PRO domain is a meaningful sub-set of a PRO measure such as emotional well-being or physical function.[4]
PRO-alerts	PRO data “concerning levels of psychological distress or physical symptoms that may require an immediate response".[5]
Protocol	Document that describes the objective(s), design, methodology and statistical considerations to conduct a specific clinical trial.
Proxy-reported outcome	Refers to those individuals (carer or family member) who answer a PRO questionnaire on behalf of the patient or trial participant.
Randomisation	An experimental study design in which participants are allocated by a random process to two or more study groups.
Recruitment target	The number of patients or trial participants that need to be enrolled in the clinical trial to meet protocol requirements.
Sensitivity analysis	Allows researchers and policy makers to assess how uncertainty in the results of the mathematical calculation is affected by different source of uncertainty. For example, if there is missing PRO data how much does this influence the results on whether a treatment worked.
Time windows	Specific period of time in which PRO data will be collected.
Type I error	The incorrect conclusion that two treatments differ, when in reality they do not.[1]
Validity	It is the degree to which an assessment measures what it is supposed to measure.[6]

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