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The PROTEUS-Trials Consortium: Optimizing the use of patient-reported outcomes in clinical trials

Claire Snyder[1,2,3] Norah Crossnohere[4] Madeleine King[5] Bryce B Reeve[6] Andrew Bottomley[7] Melanie Calvert[8,9,10,11,12] Elissa Thorner[1,3] Albert W Wu[1,2] and Michael Brundage[13]; for the PROTEUS-Trials Consortium

Abstract

Background: The assessment of patient-reported outcomes in clinical trials has enormous potential to promote patient-centred care, but for this potential to be realized, the patient-reported outcomes must be captured effectively and communicated clearly. Over the past decade, methodologic tools have been developed to inform the design, analysis, reporting, and interpretation of patient-reported outcome data from clinical trials. We formed the PROTEUS-Trials Consortium (Patient-Reported Outcomes Tools: Engaging Users and Stakeholders) to disseminate and implement these methodologic tools.

Methods: PROTEUS-Trials are engaging with patient, clinician, research, and regulatory stakeholders from 27 organizations in the United States, Canada, Australia, the United Kingdom, and Europe to develop both organization-specific and cross-cutting strategies for implementing and disseminating the methodologic tools. Guided by the Knowledge-to-Action framework, we conducted consortium-wide webinars and meetings, as well as individual calls with participating organizations, to develop a workplan, which we are currently executing.

Results: Six methodologic tools serve as the foundation for PROTEUS-Trials dissemination and implementation efforts: the Standard Protocol Items: Recommendations for Interventional Trials-patient-reported outcome extension for writing protocols with patient-reported outcomes, the International Society for Quality of Life Research Minimum Standards for selecting a patient-reported outcome measure, Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints Data Consortium recommendations for patient-reported outcome data analysis, the Consolidated Standards for Reporting of Trials-patient-reported outcome extension for reporting clinical trials with patient-reported outcomes, recommendations for the graphic display of patient-reported outcome data, and a Clinician's Checklist for reading and using an article about patient-reported outcomes. The PROTEUS-Trials website (www.TheProteusConsortium.org) serves as a central repository for the methodologic tools and associated resources.

[1]Johns Hopkins School of Medicine, Baltimore, MD, USA
[2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
[3]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA
[4]College of Medicine, Ohio State University, Columbus, OH, USA
[5]School of Psychology, The University of Sydney, Sydney, NSW, Australia
[6]School of Medicine, Duke University, Durham, NC, USA
[7]European Organisation for the Research and Treatment of Cancer, Brussels, Belgium
[8]Birmingham Health Partners Centre for Regulatory Science and Innovation, University of Birmingham, Birmingham, UK
[9]Centre for Patient Reported Outcomes Research, Institute of Applied Health Research, University of Birmingham, Birmingham, UK
[10]National Institute for Health Research (NIHR) Birmingham Biomedical Research Centre, University of Birmingham, Birmingham, UK
[11]NIHR Applied Research Collaboration West Midlands, University of Birmingham, Birmingham, UK
[12]NIHR Surgical Reconstruction and Microbiology Research Centre University Hospitals Birmingham NHS Foundation Trust and University of Birmingham, Birmingham, UK
[13]Queen's Cancer Research Institute, Queen's University, Kingston, ON, Canada

Corresponding author:
Claire Snyder, Johns Hopkins School of Medicine, 624 N. Broadway, 6th Floor, Baltimore, MD 21205, USA.
Email: csnyder@jhu.edu

To date, we have developed (1) a roadmap to visually display where each of the six methodologic tools applies along the clinical trial trajectory, (2) web tutorials that provide guidance on the methodologic tools at different levels of detail, (3) checklists to provide brief summaries of each tool's recommendations, (4) a handbook to provide a self-guided approach to learning about the tools and recommendations, and (5) publications that address key topics related to patient-reported outcomes in clinical trials. We are also conducting organization-specific activities, including meetings, presentations, workshops, and webinars to publicize the existence of the methodologic tools and the PROTEUS-Trials resources. Work to develop communications strategies to ensure that PROTEUS-Trials reach key audiences with relevant information about patient-reported outcomes in clinical trials and PROTEUS-Trials is ongoing.

Discussion: The PROTEUS-Trials Consortium aims to help researchers generate patient-reported outcome data from clinical trials to (1) enable investigators, regulators, and policy-makers to take the patient perspective into account when conducting research and making decisions; (2) help patients understand treatment options and make treatment decisions; and (3) inform clinicians' discussions with patients regarding treatment options. In these ways, the PROTEUS Consortium promotes patient-centred research and care.

Keywords

Patient-reported outcomes, clinical trials, reporting methods, protocols, measure selection, data visualization

Background

Patients, clinicians, regulators, and policy-makers value data on patient-reported outcomes (PROs), such as symptoms, functioning, and health-related quality of life, from clinical trials to inform decision-making.[1–8] To be most informative, the PRO methods need to be specified appropriately, the PRO endpoints measured effectively, the PRO data analysed properly, and the PRO results reported clearly to multiple stakeholders. However, there is evidence that these goals are frequently not met at the protocol, analysis, reporting, or application levels.[6,9–13]

Methodologic tools have been developed to help clinical trialists optimize the capture and communication of PROs.[14–19] These tools, developed in partnership with patients and other stakeholders, provide guidance on designing the PRO aspects of clinical trials, collecting and analysing the PRO data, and interpreting and reporting the PRO findings. However, these tools require a coordinated, stakeholder-driven implementation and dissemination strategy to ensure their usefulness in practice.

In 2018, we formed the PROTEUS Consortium (Patient-Reported Outcomes Tools: Engaging Users & Stakeholders), first with a focus on advancing the use of PROs in clinical research (PROTEUS-Trials) and, subsequently, expanded to address the use of PROs in clinical practice (PROTEUS-Practice).[20] PROTEUS-Trials are partnering with stakeholders to promote the application of existing tools to optimize the capture and communication of PROs in clinical trials. The goal is to give researchers guidance to help them conduct their studies so that patients can make better-informed health decisions; regulators and policy-makers can take the patient perspective into account in their deliberations; and clinicians can have reliable, relevant, and interpretable PRO data to discuss treatment options with patients. Stated differently, the PROTEUS-Trials Consortium aims to promote patient-centred research and care at multiple levels.

Methods

The work of PROTEUS-Trials is guided by the Knowledge-to-Action framework, an implementation and dissemination, or knowledge translation, model with two parts.[21] First is knowledge development, which creates knowledge tools and products through inquiry and synthesis. Second is the action cycle, which encourages dissemination of the knowledge tools by identifying knowledge gaps, adapting the knowledge to the local context, assessing facilitators and barriers to knowledge use, and implementing tailored interventions. The cycle continues with monitoring and sustaining knowledge use while evaluating outcomes.

In the case of PROTEUS-Trials, the knowledge tools are the existing methodologic tools for integrating PROs in clinical trials, mentioned above and described in more detail below.[14–19] Therefore, PROTEUS-Trials focuses primarily on the action cycle. First, the Principal Investigators (C.S. and M.B.), Project Manager (N.C.), and other Steering Committee members (M.K., B.B.R., A.B., M.C., E.T., and A.W.W.) who played key roles in developing the PRO methodologic tools assembled the consortium, engaging relevant patient, clinician, research, and regulatory groups. Second, a consortium kick-off webinar reviewed PROTEUS' objectives and approach. Third, we held calls with representatives from each organization to obtain their input on knowledge translation strategies specific to their contexts and needs, and more generally. Fourth, we held an in-person meeting (June 2019)

Table 1. Organizations with PROTEUS-Trials participants.[a]

AcademyHealth
American Cancer Society
American Society of Clinical Oncology
American Society for Radiation Oncology
Australian Clinical Trials Alliance
Canadian Association of Radiation Oncology
Cancer Australia
Consolidated Standards for Reporting of Trials (CONSORT)
Critical Path Institute PRO Consortium
European Medicines Agency-Scientific Advice Working Party/ Dutch Medicines Evaluation Board
European Organisation for the Research and Treatment of Cancer
Food and Drug Administration
Health Canada
Industry (GlaxoSmithKline)
International Society for Quality of Life Research
ISPOR
Journal editor perspective
Medicines and Healthcare Products Regulatory Agency
National Cancer Institute
National Cancer Research Institute
National Clinical Trials Network PRO representatives
National Coalition for Cancer Survivorship
National Institute for Health and Care Excellence
Oncology Nursing Society
Patient-Centered Outcomes Research Institute
Society for Clinical Trials
Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)

[a]Participating in PROTEUS does not imply endorsement of any particular PRO tools or guidance documents.

to develop and prioritize cross-cutting knowledge translation strategies. Fifth and ongoing, we are executing the organization-specific and cross-cutting knowledge translation strategies. The consortium has a cancer focus because some of the methodologic tools were developed in oncology contexts; however, the expectation is that this work is largely applicable across health conditions.

Results

Consortium formation

There are 27 organizations with participants in the PROTEUS-Trials Consortium (Table 1). Membership includes patient and clinician advocacy groups, government and regulatory agencies, clinical trial cooperative groups, organizations focused on research methods, and funding agencies.

Methodologic tools

The consortium's knowledge translation activities focus on these six methodologic tools, which are summarized in Figure 1.

Guidelines for inclusion of PROs in clinical trial protocols: the Standard Protocol Items: Recommendations for Interventional Trials-PRO extension. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)-PRO extension recommends best practices for writing the PRO aspects of randomized controlled trial protocols.[14] It extends the 2013 SPIRIT guidance that identifies the minimum elements generally required in clinical trial protocols.[22] The SPIRIT-PRO extension builds on the SPIRIT guidance by addressing the minimum elements related to PROs that should be included in clinical trial protocols. SPIRIT-PRO was developed through a Delphi process and consensus meeting, which was informed by a list of PRO-specific protocol items generated from a systematic review of existing guidance and a survey of international stakeholders. The resulting recommendations provide guidance on PRO issues relating to the trial rationale, objectives, eligibility criteria, concepts used to evaluate the intervention, timepoints for assessment, PRO instrument selection and measurement properties, data collection plan, translation to other languages, proxy completion, strategies to minimize missing data, and whether PRO data will be monitored during the study to inform clinical care.

International Society for Quality of Life Research minimum standards for PRO measures used in patient-centred outcomes and comparative effectiveness research. In 2013, the International Society for Quality of Life Research (ISOQOL) conducted a project to recommend minimum standards for PRO measures in patient-centred outcomes and comparative effectiveness research.[15] To develop these standards, the ISOQOL Task Force reviewed existing guidelines for the selection of PRO measures and surveyed ISOQOL members to obtain their input on potential PRO standards. The final recommendations, which helped to inform the Patient-Centered Outcomes Research Institute's methodology standards related to PROs,[23] address documentation of the conceptual and measurement model for the PRO measure; evidence for reliability and validity; interpretability of scores; translation quality; and patient and investigator burden.

Setting International Standards in Analysing PROs and Quality of Life Endpoints Data Consortium. The European Organisation for the Research and Treatment of Cancer (EORTC) formed the Setting International Standards in Analysing PROs and Quality of Life Endpoints Data (SISAQOL) Consortium to establish international standards in analysing PRO endpoint data.[16] The consortium includes researchers, statisticians, clinician researchers, regulators, patients, and stakeholders with multidisciplinary expertise and international perspectives. The goal is to set standards that

Tool	Clinical Trial Stage	Rationale	Objective	Approach
Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols: The SPIRIT-PRO Extension[14]	Design	To ensure that critical aspects of the PRO substudy are included in the trial protocol for successful conduct	• To provide international, consensus-based, PRO-specific protocol guidance • To address existing weaknesses related to PROs, including poor quality protocols, data, and reporting	Recommends items to address in clinical trial protocols where PROs are primary or key secondary outcomes
ISOQOL Minimum Standards for PRO Measures Used in Patient-Centered Outcomes and Comparative Effectiveness Research[15]	Design	PROs must be measured in a valid, standardized way using appropriate tools and methods to ensure valid conclusions	• To develop PRO measure minimum standards for the design and selection of a PRO measure for use in patient-centered outcomes research (PCOR) and comparative effectiveness research (CER) • The standards represent the minimum criteria required for a PRO measure to be judged suitable for a PCOR or CER study • These standards are intended to promote the appropriate use of PRO measures in PCOR and CER, which in turn can improve the effectiveness and efficiency of healthcare delivery	Provides guidance for selecting PRO measures for use in patient-centered and comparative effectiveness research
Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints Data (SISAQOL) Consortium[16]	Analysis	To ensure a consistent and methodologically appropriate PRO data analysis	• To recommend approaches to address issues related to multidimensional outcomes, longitudinal data analysis, and missing data • To promote clarity in specifying analytic objectives • To standardize terminology	Recommends statistical approaches for analyzing PRO data
Reporting of Patient-Reported	Reporting	To ensure that the PRO	• To provide international, consensus-based, PRO-specific reporting guidance	Identifies the relevant information to include
Recommendations for Graphically Displaying PRO Data[18]	Reporting	To promote consistent presentation of PRO data so that clinicians and patients can understand what the PRO scores mean	• To address the challenges patients and clinicians report when trying to interpret the meaning and implications of PRO data • To create standardized PRO graphic displays to minimize the confusion created by variation in how PRO measures are scored and scaled	Provides evidence-based recommendations for presenting PRO data clearly to patients and clinicians/researchers
Clinician's Checklist for Reading and Using an Article about Patient-Reported Outcomes[19]	Application	To help clinicians assess the quality of PRO research studies and determine whether findings are useful for clinical practice	• To address barriers to clinicians' application of PRO results, including a lack of training, variation in PRO measures, and inconsistency in how PRO results are reported • To help practicing clinicians apply results of clinical research studies that include PROs in their patient care	Provides a checklist to evaluate the quality of studies that use PROs

Figure 1. Methodologic tools for implementing patient-reported outcomes (PROs) in clinical trials.

are methodologically rigorous, comprehensive, and practical. Initial SISAQOL recommendations focus on establishing the research objectives a priori, distinguishing between domains with confirmatory analyses (superiority, non-inferiority, and equivalence) versus those that are exploratory/descriptive. The recommendations also address specifying the assumptions, endpoints of interest, recommended statistical models, and handling missing data. The initial SISAQOL work is continuing through the SISAQOL-IMI (Innovative Medicines Initiative) Consortium.[24]

Reporting of PROs in randomized trials: the Consolidated Standards of Reporting Trials-PRO extension. The CONSORT (Consolidated Standards of Reporting Trials) guidance provides recommendations for publications reporting clinical trial results.[25] In 2013, a PRO-specific extension was published, which includes recommendations for identifying the PRO as an outcome in the abstract, providing the background and rationale for PRO assessment, describing the PRO hypothesis, providing evidence of the PRO measure's reliability and validity, detailing the mode of PRO

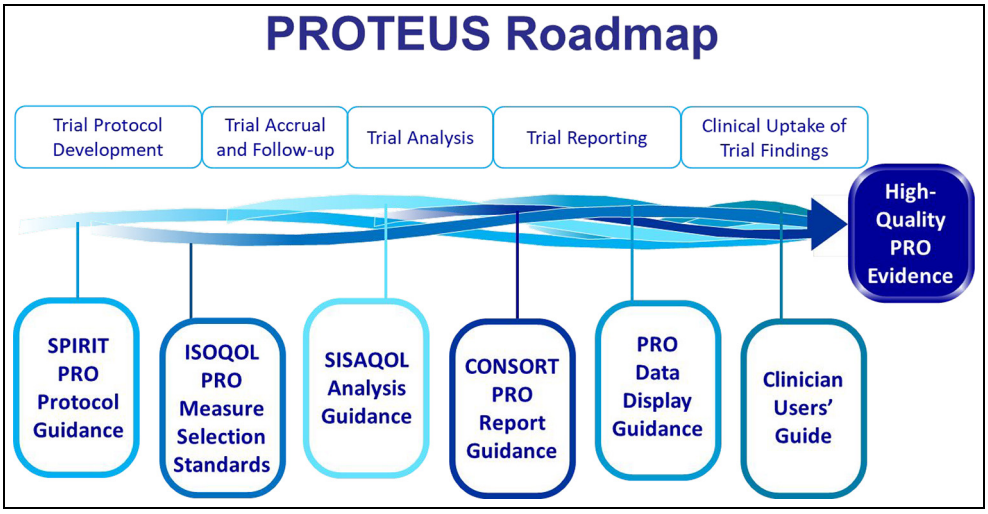

Figure 2. PROTEUS-Trials roadmap.

completion, describing missing PRO data rates and statistical methods, reporting baseline PRO data and results for each domain and timepoint pre-specified for analysis, and discussing the PRO-specific limitations and generalizability.[17]

Recommendations for graphically displaying PRO data. A specific issue related to reporting PRO results is the best way to graphically report the data so that patients and clinicians can easily and accurately interpret the PRO findings.[18] Patients and clinicians value the information provided by PRO results from clinical trials, but due to variations in how PRO measures are scored and scaled, and the different approaches to analysing them (e.g. modelling scores over time and proportions meeting a responder definition (i.e. improved/stable/worsened)), they have also reported challenges interpreting PRO results.[6] To address these issues, a multi-phase research study explored approaches for displaying clinical trial PRO results graphically to identify formats that are interpreted most accurately and rated clearest.[26–30] These results informed the development of stakeholder-engaged, evidence-driven recommendations for how to display PRO data to promote understanding and use.[18]

Clinician's Checklist for reading and using an article about PROs. As noted above, clinicians value the PRO information from clinical trials, but they also report challenges interpreting the findings so that they can use them in practice.[6] Another tool developed to address this issue is the Clinician's Checklist for reading and using an article about PROs.[19] The checklist includes five questions: (1) Was the PRO assessment strategy appropriate? (2) Did they measure PRO effectively? (3) Should I believe the results? (4) Were the results placed in clinical context? (5) Do the results apply to my patients? For each question, the checklist provides a description of what to look for in the article, guiding clinicians who are not expert in PRO research on how to use PRO findings in their practice.

Workplan

Based on our consultations with the PROTEUS-Trials participating organizations individually, and then jointly at the in-person meeting, we developed a prioritized knowledge translation workplan, including the below activities.

Website. www.TheProteusConsortium.org includes background on PROTEUS-Trials, links to the six methodologic tools, and the resources developed to-date, including those listed below.

Roadmap. We created a visual display of the clinical trial continuum and where each of the six methodologic tools apply (Figure 2).

Web tutorials. The PROTEUS-Trials Steering Committee members who developed the tools recorded a series of presentations on PROs, PROTEUS-Trials, and the PROTEUS-Trials tools. High-level presentations are directed at, for example, principal investigators who want to ensure that the researchers responsible for the PRO aspects follow best practices. Intermediate-level presentations provide sufficient detail for someone who is reviewing the PRO aspects of a trial (e.g. a manuscript peer-reviewer), but not someone implementing the recommendations directly. Advanced-level presentations are directed to the researchers responsible for implementing the recommendations themselves.

Checklists. A checklist, with citations, for each of the six tools helps users follow the guidance document recommendations without having to refer to lengthy, academic publications.

Handbook. To complement the web tutorials, a handbook provides a self-guided approach to learning about the tools and recommendations.

Publications. Several papers were prioritized to advance the PROTEUS-Trials objectives. For example, we conducted a project comparing different guidance documents' recommendations for PRO measure selection.[31] We also developed recommendations for grant applicants and reviewers regarding the key information to include/review in grant proposals.[32] A paper that highlights some of the 'greatest hits' (focused on value-added) of PROs in clinical trials is forthcoming.

Meetings/presentations/workshops/webinars. Most of our organization-specific strategies involve meetings, presentations, workshops, and webinars to key groups. We have presented on PROTEUS on over 35 occasions to a variety of audiences, in-person and virtually. These presentations are a critical aspect of engaging with different stakeholders and reaching relevant audiences to disseminate information about the tools.

Communication strategy. We are developing communications strategies to further publicize our work, ensure we reach key audiences, and promote the consortium's objectives.

Discussion

The assessment of PROs in clinical trials has enormous potential to promote patient-centred care, but for this potential to be realized, PRO data must be captured effectively and communicated clearly to diverse audiences. The PROTEUS-Trials Consortium aims to engage with stakeholders to develop organization-specific and cross-cutting strategies for implementing and disseminating methodologic tools for optimizing the use of PROs in clinical trials. It is always advisable to include a researcher with PRO expertise on the clinical trial team. This article summarizes the tools and resources available to these PRO experts, as well as others who engage with PROs at a higher level (e.g. peer-reviewers and principal investigators). Future work will evaluate the impact of PROTEUS-Trials on the capture and communication of PROs from clinical trials.

While the PROTEUS-Trials Consortium has focused on six core tools, users are encouraged to consider other guidance as applicable to their purpose and jurisdiction. For example, if planning a regulatory submission to the Food and Drug Administration, its PRO guidance would be most applicable.[1] Reassuringly, the PROTEUS paper comparing various guidance documents regarding PRO measure selection found general consistency in their recommendations.[31]

In summary, through the PROTEUS-Trials Consortium, we hope that researchers will be better able to generate PRO data from clinical trials to (1) enable investigators, regulators, and policy-makers to take the patient perspective into account when conducting research and making decisions; (2) help patients understand treatment options and make treatment decisions; and (3) inform clinicians' discussions with patients regarding treatment options. In these ways, the PROTEUS Consortium aims to promote patient-centred research and care.

Declaration of conflicting interests

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ORCID iD

Claire Snyder https://orcid.org/0000-0001-8952-4561

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