The PROTEUS-Trials Consortium

Patient-**R**eported **O**utcomes **T**ools:
Engaging **U**sers & **S**takeholders

Handbook

TheProteusConsortium.org

How to Use This Handbook

This handbook accompanies a series of presentations about PROTEUS-Trials and the tools and resources available to optimize the use of patient-reported outcomes in clinical trials.

Chapter 1 introduces patient-reported outcomes and the PROTEUS-Trials Consortium. Chapters 2 to 7 present the six core PROTEUS-Trials tools and their role in guiding the design, conduct, analysis, reporting, and application of PRO clinical trial data. Additional information and resources are available on the PROTEUS website (TheProteusConsortium.org).

Use the headings in the Table of Contents on page 2 to go through the parts of the handbook suited to your current information needs. Important resources within this handbook can be jumped to via hyperlinks throughout the handbook for easier navigation.

Acknowledgements

This Handbook was developed by Dion Candelaria and The University of Sydney Quality of Life Office team (Claudia Rutherford, Rachel Campbell, and Margaret-Ann Tait) based on web tutorials presented by the PROTEUS-Trials Leadership Team and Steering Committee.

A Note on Referencing

This Handbook summarizes information described in detail in the primary research sources (listed under “References” for each chapter). To promote readability, we have limited in-text citations. However, when referencing the included information, we recommend citing the primary sources rather than the Handbook.

To reference the Handbook itself, please use:

> The PROTEUS-Trials Consortium (Patient-Reported Outcomes Tools: Engaging Users & Stakeholders). PROTEUS Handbook. Prepared by The University of Sydney Quality of Life Office for the PROTEUS-Trials Consortium. Available at: www.TheProteusConsortium.org.

Contents

PROTEUS-Trials Leadership Team

Principal Investigators

Claire Snyder, PhD

Dr. Claire Snyder is a PhD outcomes and health services researcher and a Professor of Medicine, Oncology, and Health Policy & Management at the Johns Hopkins School of Medicine and Bloomberg School of Public Health.

Michael Brundage, MD, MSc

Dr. Michael Brundage is a practicing radiation oncologist and Director of Cancer Care and Epidemiology at the Queen's Cancer Research Institute in Kingston, Ontario, Canada.

Project Manager

Norah Crossnohere, PhD

Dr. Norah Crossnohere is a PhD patient-centered outcomes researcher and a Research Scientist at the Ohio State University College of Medicine.

Steering Committee

Andrew Bottomley, PhD
European Organization for the
Research and Treatment of Cancer

Melanie Calvert, PhD
University of Birmingham

Madeleine King, PhD
University of Sydney

Bryce Reeve, PhD
Duke University
School of Medicine

Albert Wu, MD, MPH
Johns Hopkins
Bloomberg School of Public Health

Elissa Thorner, MHS
Patient Advocate

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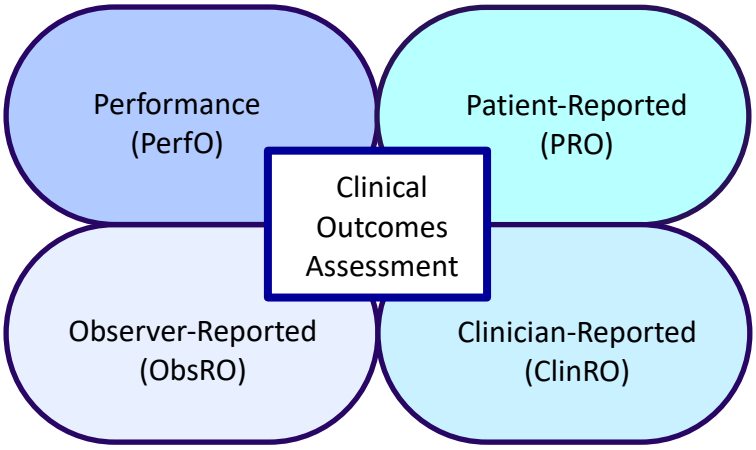
Chapter 1. Introduction to Patient-Reported Outcomes and PROTEUS-Trials

Types of Clinical Outcomes Assessment



There are four types of clinical outcomes assessments according to U.S. Food and Drug Administration (FDA) (2009):

1. Patient-reported outcomes (PROs) – reports about a health condition or its treatment that come directly from the patient, without interpretation by a clinician or anyone else

   Examples: global impression, functional status, well-being, symptoms, health-related quality of life

2. Clinician-reported outcomes (ClinROs) – a clinician rates outcomes such as toxicity or disease severity

   Examples: treatment toxicity, disease severity

3. Observer-reported outcomes (ObsROs) – someone such as a family member or informal caregiver may report on observable outcomes

   Examples: seizure frequency, surgical scar appearance

4. Performance-based outcomes (PerfOs) – involve performance of standardized tasks, such as a treadmill test

   Examples: treadmill exercise test, cognition, and attention

These different kinds of clinical outcomes complement other measures, such as laboratory assessments, for example prostate-specific antigen tests, and imaging studies, such as CT or PET scans.

Patient-Reported Outcomes (PROs)

PROTEUS-Trials is focused on patient-reported outcomes (PROs) specifically.

How are Patient Perceptions 'Measured'?

To measure PROs, and for all the clinical outcomes, standardization is critical. Great care must be taken in developing the questions, response options, and scoring algorithms during the development of PRO questionnaires (also called 'tools' and 'measures'). Here are some points to consider:

- Ask a standard set of questions
- Provide a standard set of response options
- Allocate numbers to those response options in a standard way
- Use a standard analysis and reporting algorithm

Example: Physical Function Measure

As an example, this is the physical function domain of a commonly used cancer questionnaire, the EORTC-QLQ-C30. This particular patient has quite a bit of difficulty doing strenuous activities, a little difficulty doing moderate activities, and no difficulty at all doing activities of daily living. When you go through the scoring algorithm, this patient's score is 60.

Example: Physical Function

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	(3)	4
2. Do you have any trouble taking a long walk?	1	2	(3)	4
3. Do you have any trouble taking a short walk outside of the house?	1	(2)	3	4
4. Do you need to stay in bed or chair during the day?	1	(2)	3	4
5. Do you need help with eating, dressing, washing yourself, or using the toilet?	(1)	2	3	4

The question is how we determine which questions to ask of patients, what the appropriate analytic approach is, and how best to report this information to patients, clinicians, and other decision-makers so that PRO data are most useful in research and practice.

The PROTEUS-Trials Consortium

PROTEUS stands for Patient-Reported Outcomes Tools: Engaging Users and Stakeholders.

The PROTEUS-Trials Consortium aims to ensure that patients, clinicians, and other decision-makers have high quality PRO data from clinical trials so that they can make the best possible decisions about treatment options.

To achieve this objective, we are partnering with key stakeholder groups to disseminate and implement tools that have been developed to optimize the use of PROs in clinical trials.

*Organizations with PROTEUS-Trials Participants**

The PROTEUS-Trials Consortium includes research and methods groups, government and regulatory bodies, research funders, patient and clinician advocacy organizations, and the cooperative groups that conduct clinical trials. PROTEUS-Trials has a particular focus on cancer research, but many of the tools and resources also apply beyond cancer.

These are the 27 organizations with PROTEUS-Trials Consortium participants:

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

**Participation in PROTEUS-Trials does not imply endorsement of any PRO tools or guidance documents*

The PROTEUS-Trials Consortium's Objective

In order for patients, clinicians, and other decision-makers to have high-quality PRO data from clinical trials, research studies need to use a SMART approach:

- **Specify** the PRO methods appropriately
- **Measure** the PROs effectively
- **Analyze** the PRO data properly
- **Report** the PRO results clearly
- **Translate** the PRO findings in practice

PRO Tools for PROTEUS-Trials

A number of tools have been developed to provide guidance on how to meet the above objectives. Each of these tools guides different aspects of clinical trial design, execution, reporting, and implementation.

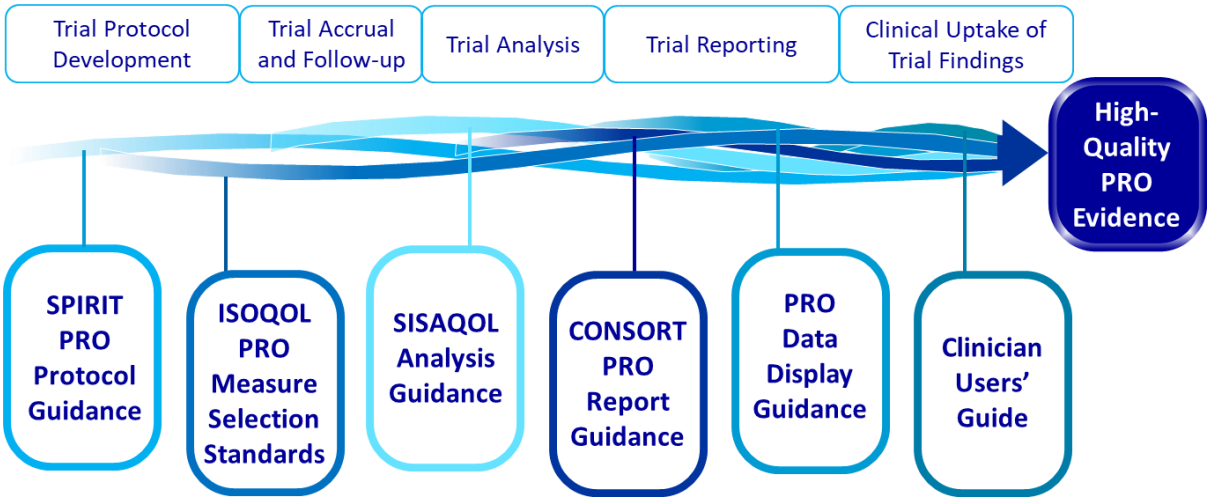
PURPOSE	TOOL
Writing PRO protocols	Standard Protocol Items: Recommendations for Interventional Trials-PRO Extension (SPIRIT-PRO)
Selecting PRO measures	ISOQOL Minimum Standards for PRO Measures in Patient-Centered and Comparative Effectiveness Research
Analyzing PRO data	Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data (SISAQOL) Consortium
Reporting PRO findings	Consolidated Standards of Reporting Trials-PRO Extension (CONSORT-PRO) Stakeholder-Driven, Evidence-Based Standards for Presenting PROs in Clinical Practice
Interpreting PRO papers	Clinicians Checklist for Reading and Using an Article about PROs

Each of these tools will be discussed in detail in succeeding chapters of this handbook.

The PROTEUS-Trials Roadmap

The PROTEUS-Trials Roadmap provides an overview of the six PROTEUS-Trials tools. Collectively, these tools aim to enable PRO aspects of protocol development, trial accrual and follow-up, analysis, reporting, and clinical uptake of the trial findings.

Implementing these tools will assist clinical trials in providing high quality PRO evidence to inform clinical decision-making and health services policy development.



References

U.S. Department of Health and Human Services Food and Drug Administration. (2009). Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Accessed at https://www.fda.gov/media/77832/download

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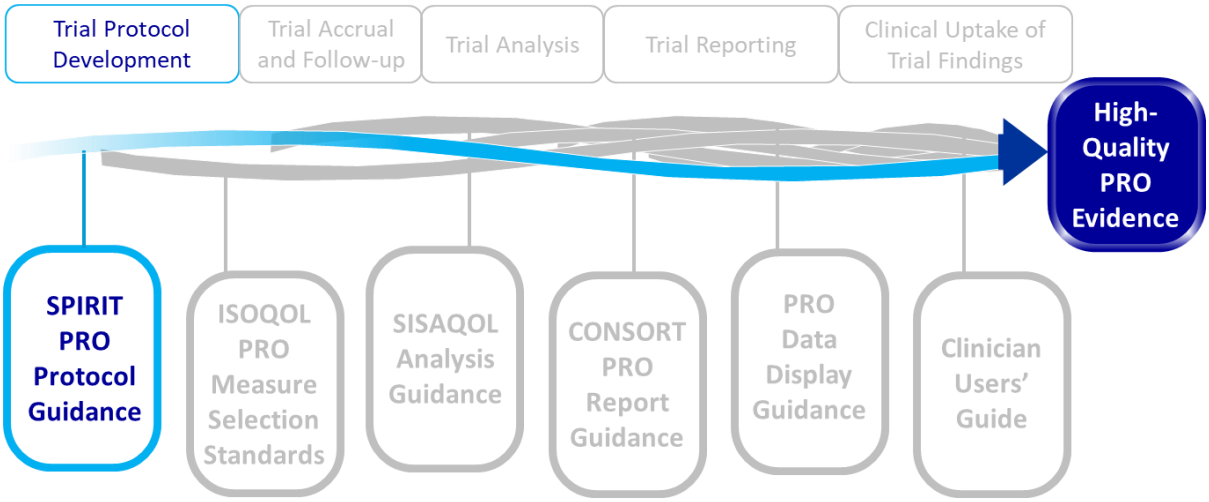
Please Note: When referencing information included in this Chapter, we recommend citing the primary sources rather than this Handbook.

Chapter 2. Writing PRO Protocols



Standard Protocol Items: Recommendations for Interventional Trials-PRO Extension (SPIRIT-PRO)

The SPIRIT-PRO Extension recommends best practices for writing the PRO aspects of randomized controlled trial protocols. It is an extension of the general 2013 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidance that identified the minimum elements required in clinical trial protocols, generally (Chan et al., 2013). The SPIRIT-PRO Extension builds on the general SPIRIT guidance by addressing the minimum elements related to PROs that should be included in clinical trial protocols.

View SPIRIT-PRO Extension article

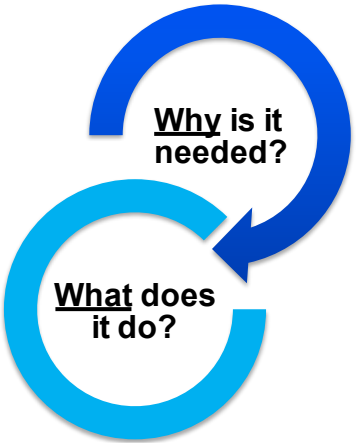
View SPIRIT-PRO Explanation and Elaboration article

View the Checklist for the SPIRIT-PRO Protocol Guidance

References

Acknowledgements

Why is This Resource Needed?



To ensure that critical aspects of the PRO study are included in the protocol for successful conduct

Recommends items to address in clinical trial protocols where PROs are primary or key secondary outcomes

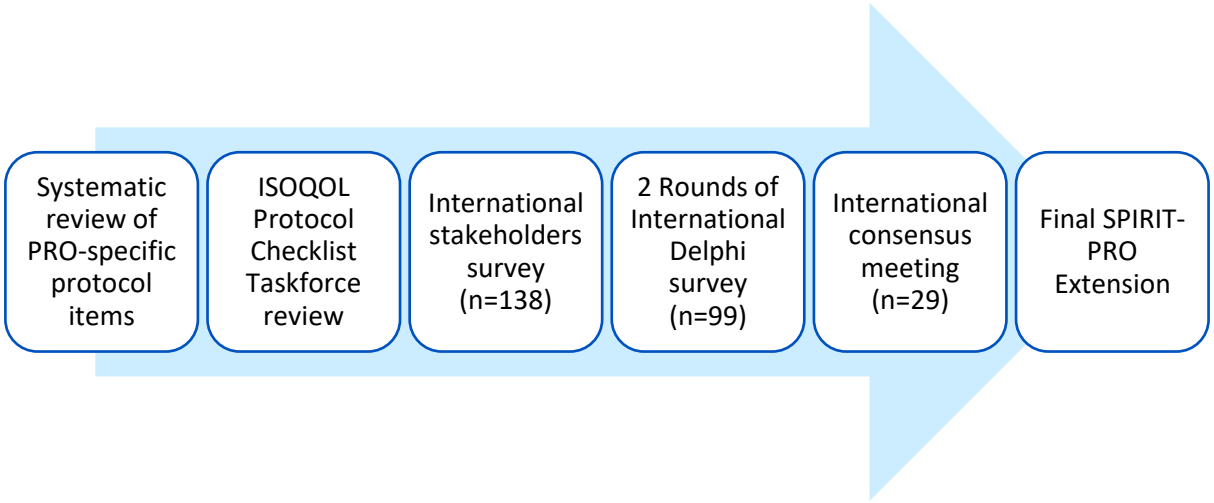
Patient-reported outcome (PRO) data from clinical trials can provide valuable evidence to inform shared decision making, labeling claims, clinical guidelines, and health policy; however, the PRO content of clinical trial protocols is often suboptimal. Although the SPIRIT (Standard Protocol Items: Recommendations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

Objective of the Resource

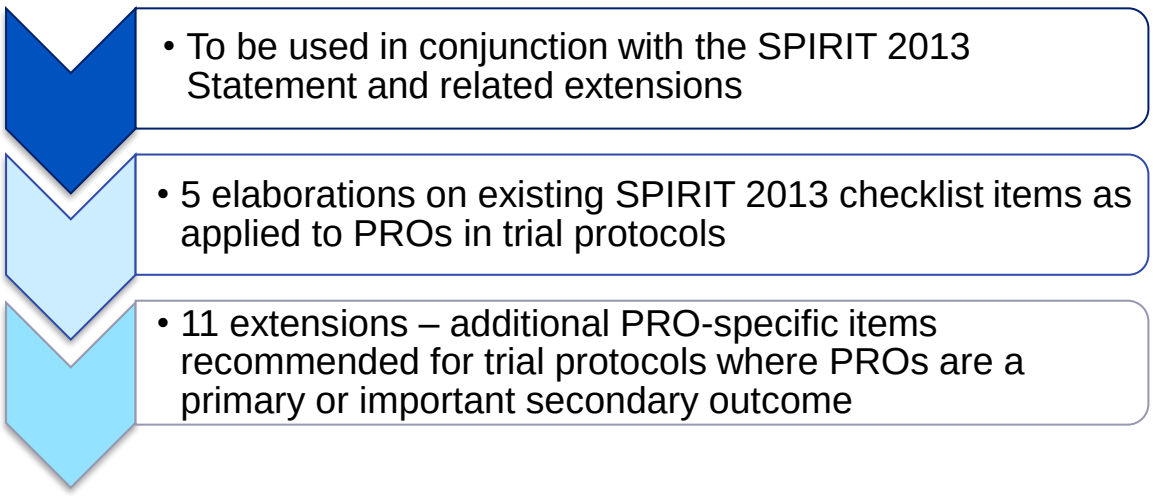
To provide international, consensus-based, PRO-specific protocol guidance: an official SPIRIT-PRO extension.

Methods for Resource Development

The SPIRIT-PRO Extension was developed through a systematic review of existing PRO-specific protocol guidance, a stakeholder survey of a group of international experts, and a Delphi exercise and consensus meeting, followed by consultation on the final SPIRIT-PRO Extension.



Overview of the SPIRIT-PRO Guidance



The SPIRIT-PRO guidance constitutes an extension to the SPIRIT 2013 statement that guides the reporting of various parts of the trial protocol sections. The key items relevant to the reporting of PROs include the following:

Introduction

- Describe PRO-specific research question, rationale, and relevant previous findings
- State PRO-specific objectives or hypotheses (including relevant PRO concepts/domains)

Methods – Participants, Interventions, Outcomes

- Specify any PRO-specific eligibility criteria
- Specify the PRO concepts/domains used to evaluate the intervention and related analysis metric

Methods – Data Collection, Management and Analysis

- Describe the PRO measure and its psychometric characteristics
- Include a data collection plan (e.g., time points, mode, setting)
- Specify language versions available
- State and justify use of proxy reporting, if relevant
- Specify strategies to minimize missing data and address missing data in analysis

Harms

- State whether PRO data will be monitored to inform clinical care

The specific elaborations and extensions are detailed below.

SPIRIT-PRO items by Protocol Sections

Administrative Information & Introduction

SPIRIT-PRO Elaboration Item 5a – Roles & Responsibilities

SPIRIT 2013:	**PRO Elaboration 2018:**
Names, affiliations, and roles of protocol contributors.	Specify the individual(s) responsible for the PRO content of the trial protocol.

Explanation:

Providing information (e.g., name, affiliation, contact details) on expert on PRO-specific aspects of the trial protocol promotes transparency and accountability and identifies the appropriate point of contact for resolution of any PRO-specific queries.

When patients have actively contributed to this process, this should be documented as per recent guidance for the reporting of patient and public involvement.

SPIRIT-PRO Extension Item 6a – Background and Rationale

SPIRIT 2013:	PRO Extension 2018:
Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention.	Describe the PRO specific research question and rationale for PRO assessment, and summarize PRO findings in relevant studies.

Explanation:

A clearly defined question helps with selection of measures and specification of hypotheses and analyses. Many trials include PROs without specifying the PRO-specific research question and a rationale or any reference to PROs in related studies. Staff and patients may not understand why PROs are being assessed, and missing data may result. When the PRO is a secondary outcome, a brief rationale may be adequate.

SPIRIT-PRO Extension Item 7 – Objectives

SPIRIT 2013:	PRO Extension 2018:
Specific objectives or hypotheses.	State specific PRO objectives or hypotheses (including relevant PRO concepts/domains).

Explanation:

PRO measures may be multidimensional (e.g., health-related quality of life) or unidimensional (e.g., specific symptoms such as pain). Pre-specification of objectives and hypotheses encourages identification of key PRO domains and time points, reducing the risk of multiple statistical testing and selective reporting of PROs based on statistically significant results.

Methods: Participants, Interventions, and Outcomes

SPIRIT-PRO Extension Item 10 – Eligibility Criteria

SPIRIT 2013:	**PRO Extension 2018:**
Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centers and individuals who will perform the interventions (e.g., surgeons, psychotherapists).	Specify any PRO-specific eligibility criteria (e.g., language/reading requirements or pre-randomization completion of PRO). If PROs will not be collected in the entire study sample, provide a rationale and describe the method for obtaining the PRO subsample.

Explanation:

Any PRO-specific eligibility criteria should be considered at the design stage of the trial and clearly specified in the protocol. In large trials, sufficient power may be achieved by collecting PROs from a representative subset of participants, while in some trials it may not be possible to collect PROs in the entire population (e.g., because validated questionnaires may not be available in all languages); in such instances, the rationale for the sampling method should be described.

SPIRIT-PRO Extension Item 12 – Outcomes

SPIRIT 2013:	**PRO Extension 2018:**
Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended.	Specify the PRO concepts/domains used to evaluate the intervention (e.g., overall health-related quality of life, specific domain, specific symptom) and, for each one, the analysis metric (e.g., change from baseline, final value, time to event) and the principal time point or period of interest.

Explanation:

The PRO concepts/domains and time points for assessment should closely align with the trial objectives and hypotheses. Because of the risk of multiple statistical testing, the domain(s) and principal time point(s) for analyses should be specified *a priori*.

SPIRIT-PRO Extension Item 13 – Participant Timeline

SPIRIT 2013:	PRO Extension 2018:
Time schedule of enrollment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended.	Include a schedule of PRO assessments, and rationale for the time points. Justify if the initial assessment is not pre-randomization. Specify time windows and whether PROs collected prior to clinical assessments. If using multiple questionnaires, whether order of administration standardized.

Explanation:

Provision of an easy-to-follow schedule will assist staff and may help reduce missing data. Collecting PRO data prior to randomization helps ensure an unbiased baseline assessment, and if specified as an eligibility criterion, ensures data completeness.

This is important because baseline PRO data are often used as a covariate in analyses and are essential to calculating change from baseline. Completion of PROs prior to clinical assessments (as these may influence patient responses) and standardization of the order of questionnaire administration are advised to help reduce measurement error. Allowable time windows for each scheduled PRO assessment should be specified to ensure that PRO data collection captures the effect of the clinical event(s) of interest.

SPIRIT-PRO Extension Item 14 – Sample Size

SPIRIT 2013:	PRO Elaboration 2018:
Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations.	Where a PRO is the primary endpoint, state the required sample size (and how it was determined) and recruitment target (accounting for expected loss to follow-up). If sample size is not established based on PRO endpoint, then discuss the power of the principal PRO analyses.

Explanation:

The target sample size will generally be based on an *a priori* sample size calculation for the PRO end point. Ideally, the criteria for clinical significance (e.g., minimal important difference) should be specified if known. If PROs are a secondary end point, researchers should specify whether the sample size provides sufficient power to test the principal PRO hypotheses.

Methods: Data Collection, Management, and Analysis

SPIRIT 2013 Item 18a - Data Collection Methods

SPIRIT 2013:

Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol.

Four PRO Extensions 2018

(each explained below)

SPIRIT-PRO Extension Item 18a (i) – Data Collection Methods

PRO Extension (i) 2018:

Justify the PRO instrument, describe domains, number of items, recall period, instrument scaling/scoring (e.g., range and direction of scores indicating a good/poor outcome).

Evidence of PRO instrument measurement properties, interpretation guidelines, and patient acceptability/burden should be cited if available, ideally in the population of interest. State whether the measure will be used in accordance with any user manual and specify and justify deviations if planned.

Explanation:

The selection of PRO questionnaires requires careful consideration, particularly patient burden and acceptability. Questionnaires should be used in accordance with any existing user manuals to promote data quality and ensure standardized scoring, and any deviations should be described.

SPIRIT-PRO Extension Item 18a (ii) – Data Collection Methods

PRO Extension (ii) 2018:

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).

Explanation:

It is important that both research personnel and trial participants understand how, when, and where PRO data will be collected in the study. If electronic PRO measures contain only minor modifications with respect to the paper-based versions, usability testing and cognitive debriefing may provide sufficient evidence of equivalence. The setting for PRO data collection should be described and standardized across trial intervention groups and sites.

SPIRIT-PRO Extension Item 18a (iii) – Data Collection Methods

PRO Extension (iii) 2018:

Specify whether more than one language version will be used.

State whether translated versions have been developed using currently recommended methods.

Explanation:

Multinational trials, or national trials involving participants with different languages, require measures that have been translated and culturally adapted where needed using appropriate methodology. This may influence the selection of measure to be used because inclusion of a wide range of participants can help ensure the generalizability of trial results. Plans to use translated versions should be specified in the protocol, citing references when available.

SPIRIT-PRO Extension Item 18a (iv) – Data Collection Methods

PRO Extension (iv) 2018:

When the trial context requires someone other than the trial participant to answer on their behalf (a proxy reported outcome), state and justify this.

Provide/cite evidence of the validity of proxy assessment if available.

Explanation:

In some contexts, such as trials involving young children or cognitively impaired participants, it may be necessary for someone other than a trial participant to respond on that participant's behalf. Clear justification and specification of proxy reporting in the protocol allows external reviewers to assess potential bias and facilitates trial reporting in accordance with CONSORT-PRO. Evidence of the size and direction of proxy bias is a key aspect of the validity of proxy versions of PRO measures, informing valid interpretation, and comparison of results. The European Medicines Agency states that "in general proxy reporting should be avoided, unless the use of such proxy raters may be the only effective means of obtaining

information that might otherwise be lost." The US Food and Drug Administration also discourages the use of proxy reported outcomes to inform labeling claims, recommending observer reports instead.

SPIRIT 2013 Item 18b - Data Collection Methods

SPIRIT 2013:	**One PRO Extension & One PRO Elaboration 2018**
Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	**(see below)**

PRO Extension Item 18b (i) - Data Collection Methods

PRO Extension (i) 2018:

Specify PRO data collection and management strategies for minimizing *avoidable* missing data.

Explanation:

Missing data are a particular problem for PROs for 3 reasons: 1) unlike some other trial outcomes, data cannot be obtained retrospectively beyond the time frame of interest or from medical records; 2) missing data reduce the effective sample size hence power for PRO analyses; 3) importantly – they are a potentially significant source of bias. Why? Because participants with the poorest outcomes in a trial often are those who do not complete planned PRO assessments.

It is important to note that not all missing PRO data are avoidable: patients have the right to decide not to complete questionnaires, which may happen if they feel too unwell. Common reasons for *avoidable* missing PRO data are administrative errors, lack of explanation of the importance of PRO data, and overly burdensome questionnaires. Addressing these in the protocol should help minimize avoidable missing data.

A key part of a management strategy for minimizing avoidable missing data is a plan to collect reasons for missed assessments and to review these reasons during trial conduct. Information about the rates of and reasons for missing data are also valuable during analysis and write-up, as explained in chapters 4 and 5.

A recent systematic review provides a range of design, implementation, and reporting strategies to help minimize and address missing PRO data. Examples of protocol content include ensuring that PRO end points and hypotheses are clearly defined and scientifically compelling, providing a rationale for PRO assessment,

clearly specifying the PRO assessment time points, defining acceptable PRO assessment time windows, aligning PRO assessment time points to clinic visits (if clinically informative), minimizing patient burden, and specifying the importance of complete PRO data.

SPIRIT-PRO Elaboration Item 18b (ii) – Data Collection Methods

PRO Elaboration (ii) 2018:

Describe the process of PRO assessment for participants who discontinue or deviate from their assigned intervention protocol.

Explanation:

A clear plan for collection of PROs for trial participants who withdraw early from a study or who discontinue the intervention helps minimize bias, ensures that staff collect all required PRO data in a standardized and timely way, and may assist ethical appraisal of the study.

SPIRIT-PRO Elaboration Item 20a – Statistical Methods

SPIRIT 2013:

Statistical methods for analyzing primary and secondary outcomes.

Reference to where other details of the statistical analysis plan (SAP) can be found, if not in the protocol.

PRO Elaboration 2018:

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

Explanation:

Statistical analysis of all domains and time points implies multiple hypothesis testing, which inflates the probability of false-positive results (type I error). This can be contained by prespecifying the key PRO domain(s) or overall score of interest and the principal time point(s). Any plans to address multiplicity, such as stepwise or sequential analyses or conventional non-hierarchical methods (e.g., Bonferroni correction), should be specified *a priori*. The protocol should either fully address these issues or provide a summary with reference to where full details can be found (e.g., in the statistical analysis plan).

SPIRIT-PRO Elaboration Item 20c – Statistical Methods

SPIRIT 2013:	PRO Elaboration 2018:
Definition of analysis population relating to protocol non-adherence (e.g., as randomized analysis), and any statistical methods to handle missing data (e.g., multiple imputation).	State how missing data will be described and outline the methods for handling missing items or entire assessments (e.g., approach to imputation and sensitivity analyses).

Explanation:

There are 2 levels of missing PRO data: (1) patient completion of some but not all items within an instrument and (2) absence of the entire PRO assessment. Whether and how missing items should be imputed is usually specified in an instrument's scoring algorithm. When entire PRO assessments are missed, analysis requires assumptions about why those data were missing (i.e., the missing data mechanism). There are a range of statistical approaches, each with specific assumptions. Common methods include complete case analysis, imputation (various approaches), a range of maximum likelihood modeling approaches, and sensitivity analysis. Inappropriate method selection may lead to potentially biased and misleading results. The protocol should acknowledge and summarize these issues, with full details provided in the statistical analysis plan.

Methods: Monitoring

SPIRIT-PRO Extension Item 22 – Harms

SPIRIT 2013:	PRO Extension 2018:
Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct.	State whether or not PRO data will be monitored during the study to inform the clinical care of trial participants. If so, how this will be managed in a standardized way. Describe how this process will be explained to participants, e.g., in the participant information sheet and consent form.

Explanation:

Evidence suggests that monitoring and management of PRO alerts (psychological distress or physical symptoms evident from PRO responses that may require an immediate response) vary across and within trials. To protect the interests of trial

participants and minimize potential bias, it is important to specify plans for monitoring. If monitoring is not planned (for example, in a low-risk study in which alerts are not anticipated), this should also be briefly stated in the protocol, the participant information sheet, and the consent form. Alternative support mechanisms for patients should be outlined.

Implications of Using SPIRIT-PRO Guidance

Inclusion of PRO-specific protocol content will have multiple benefits:

- Protocol writers: Encourage and facilitate careful planning of PRO components of trials, hence improve PRO trial design
- Protocol reviewers: Help research ethics committees and patient partners assess the PRO elements
- Trial staff and participants: Help staff and patients understand the rationale for PRO assessment, improve PRO data completeness and quality
- ➢ This in turn will facilitate high-quality analysis and reporting, and ultimately improve the quality of the global PRO evidence base

Checklist for the SPIRIT-PRO Protocol Guidance

Protocol Section	SPIRIT-PRO Item	Recommended Content	Page Addressed
Administrative Information			
Roles and responsibilities	SPIRIT-5a-PRO Elaboration	Specify the individual(s) responsible for the PRO content of the trial protocol.	
Introduction			
Background and rationale	SPIRIT-6a-PRO Extension	Describe the PRO-specific research question and rationale for PRO assessment and summarize PRO findings in relevant studies.	
Objectives	SPIRIT-7-PRO Extension	State specific PRO objectives or hypotheses (including relevant PRO concepts/domains).	
Methods: Participants, Interventions, and Outcomes			
Eligibility criteria	SPIRIT-10-PRO Extension	Specify any PRO-specific eligibility criteria (e.g., 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.	
Outcomes	SPIRIT-12-PRO Extension	Specify the PRO concepts/domains used to evaluate the intervention (e.g., overall health-related quality of life, specific domain, specific symptom) and, for each one, the analysis metric (e.g., change from baseline, final value, time to event) and the principal time point or period of interest.	
Participant timeline	SPIRIT-13-PRO Extension	Include a schedule of PRO assessments, providing a rationale for the time points, and justifying if the initial assessment is not prerandomization. Specify time windows, whether PRO collection is prior to clinical assessments, and, if using multiple questionnaires, whether order of administration will be standardized.	
Sample size	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.	

Protocol Section	SPIRIT-PRO Item	Recommended Content	Page Addressed
Methods: Data Collection, Management, and Analysis			
Data collection methods	SPIRIT-18a(i)-PRO Extension	Justify the PRO instrument to be used and describe domains, number of items, recall period, and instrument scaling and scoring (e.g., 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 justify deviations if planned.	
	SPIRIT-18a(ii)-PRO Extension	Include a data collection plan outlining permitted mode(s) of administration (e.g., paper, telephone, electronic, other) and setting (e.g., clinic, home, other).	
	SPIRIT-18a(iii)-PRO Extension	Specify whether more than 1 language version will be used and state whether translated versions have been developed using currently recommended methods.	
	SPIRIT-18a(iv)-PRO Extension	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.	
	SPIRIT-18b(i)-PRO Extension	Specify PRO data collection and management strategies for minimizing avoidable missing data.	
	SPIRIT-18b(ii)-PRO Elaboration	Describe the process of PRO assessment for participants who discontinue or deviate from the assigned intervention protocol.	
Statistical methods	SPIRIT-20a-PRO Elaboration	State PRO analysis methods, including any plans for addressing multiplicity/ type I (α) error.	
	SPIRIT-20c-PRO Elaboration	State how missing data will be described and outline the methods for handling missing items or entire assessments (e.g., approach to imputation and sensitivity analyses).	
Methods: Monitoring			
Harms	SPIRIT-22-PRO Extension	State whether or not PRO data will be monitored during the study to inform the clinical care of individual trial participants and, if so, how this will be managed in a standardized way. Describe how this process will be explained to participants; e.g., in the participant information sheet and consent form.	

References

Calvert M, Kyte D, Mercieca-Bebber R, Slade A, Chan A-W, King MT; the SPIRIT-PRO Group. Guidelines for inclusion of patient-reported outcomes in clinical trial protocols: The SPIRIT-PRO Extension. *JAMA*. 2018;319:483-494.

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Kyte D, Draper H, Calvert M. Patient-reported outcome alerts: ethical and logistical considerations in clinical trials. *JAMA*. 2013;310(12):1229-1230.

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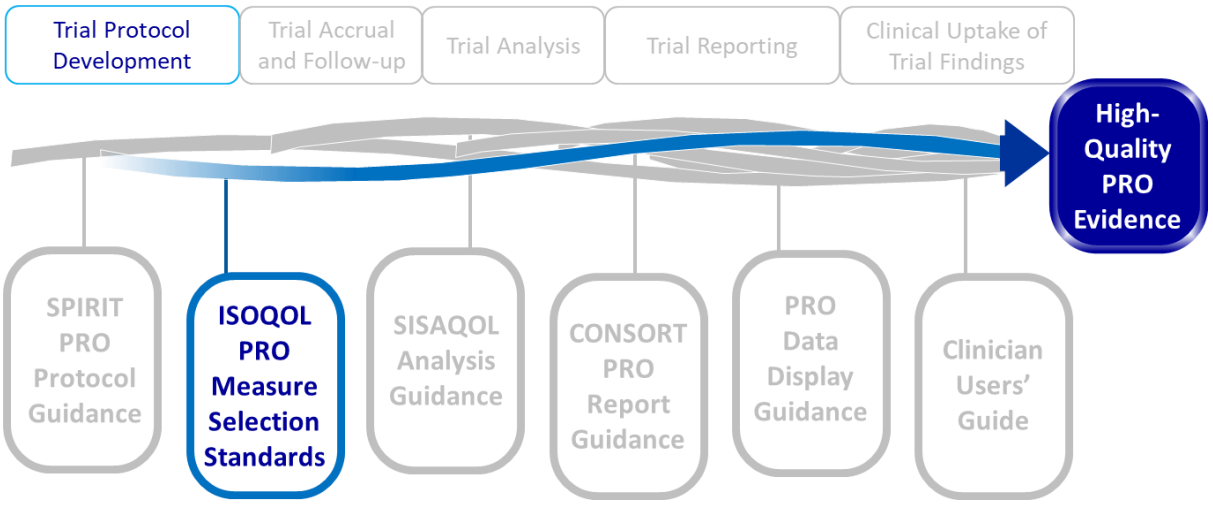
Please Note: When referencing information included in this Chapter, we recommend citing the primary sources rather than this Handbook.

Chapter 3. Selecting PRO Measures



ISOQOL Minimum Standards for PRO Measures in Patient-Centered and Comparative Effectiveness Research

In 2013, the International Society for Quality of Life Research (ISOQOL) led an initiative to inform the selection of PRO measures for use in patient-centered outcomes and comparative effectiveness research by identifying minimum standards. These standards define the critical attributes of a PRO measure for these research studies.

This chapter summarizes the recommendations for selecting PRO measures for research studies.

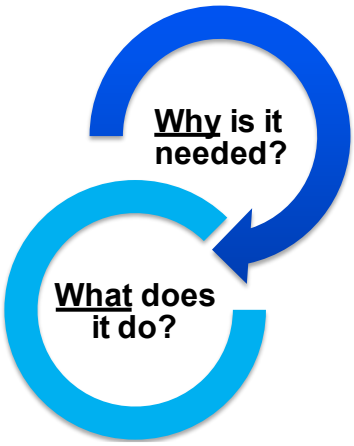
View ISOQOL Minimum Standards article

View the Checklist for the ISOQOL Measure Selection Standards

References

Acknowledgements

Why is This Resource Needed?



PROs must be measured in a valid, standardized way using appropriate methods to ensure valid conclusions

Provides guidance for selecting PRO measures for use in patient-centered and comparative effectiveness research

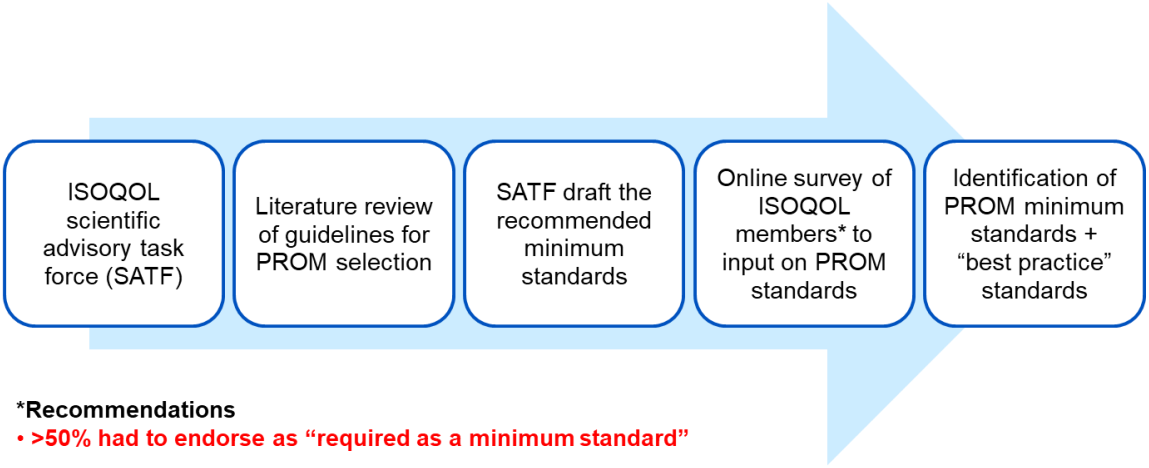
- An essential aspect of patient-centered outcomes research (PCOR) and comparative effectiveness research (CER) is integration of patient perspectives and experiences about their health with clinical and biological data to evaluate the safety and effectiveness of interventions
- Clinical trials are one kind of PCOR/CER; the ISOQOL minimum standards address PCOR/CER more broadly, but we will refer to clinical trials in this handbook
- It is widely accepted that patients' reports are the best source of information about what they are experiencing
- A challenge for PCOR and CER is how to best capture patient-reported data to inform decision making in healthcare delivery, research, and policy settings
- To draw valid research conclusions regarding patient-centered outcomes, PROs should be measured in a standardized way using appropriate methods
- A PRO is the measurement of any aspect of a patient's health that comes directly from them without interpretation by another
- PROs can be symptoms (e.g., pain, anxiety, nausea, fatigue), aspects of functioning (e.g., role, physical, emotional, social) and multidimensional constructs (e.g., health-related quality of life)
- A PRO measure is the questionnaire, index, checklist, instrument, or tool, along with the algorithm used to score patient responses into summary scores for analysis and reporting

Objective of Resource

The objective of the ISOQOL PRO measure selection guidance was to develop minimum standards for the design and selection of a PRO measure for use in PCOR and CER. These standards represent the minimum criteria required for a PRO measure to be judged suitable for inclusion in a PCOR or CER study. These minimum 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.

Methods for Resource Development

An ISOQOL Scientific Advisory Task Force (SATF) was established to guide the drafting and final determination of recommended minimum standards. Based on a literature review, the SATF developed draft recommendations, which were subsequently reviewed by ISOQOL members through a formal survey. The literature review and feedback from ISOQOL members informed the final recommendations.



Summary of Recommendations

The ISOQOL PRO measure minimum standards recommends that a PRO measure should include the following attributes:

- Conceptual and measurement model
- Evidence that supports the measure's ability to assess the concepts covered in the measurement model, such as:
    - Reliability
    - Validity
        - Content
        - Construct
        - Responsiveness
- Interpretability of scores
- Translation
- Patient and investigator burden

Conceptual and Measurement Model

The conceptual model provides a description of and framework for the targeted concept(s) to be included in a PRO measure. The measurement model maps the individual items in the PRO measure to the concept(s).

- A PRO measure should have documentation defining and describing the concept(s) included and the intended population(s) for use
- There should be documentation of how the concept(s) are organized into a measurement model, including evidence for the dimensionality of the measure, how items relate to each measured concept, and the relationship among concepts included in the PRO measure

Reliability

Reliability is the degree to which a PRO measure is free from measurement error.

There are two types of reliability relevant for PRO measures:

1. **Internal consistency (for multi-item scales)**

   Internal consistency reliability is the degree of the interrelatedness among the items in a multi-item PRO measure. The internal consistency reliability of a PRO measure should preferably be at or above **0.70** for group-level comparisons, but may be lower if appropriately justified.

2. **Test-retest**

   Test-retest reliability is a measure of the reproducibility of the scale, that is, the ability to provide consistent scores over time in a stable population. However, some populations studied in PCOR are not stable and their health-related quality of life can fluctuate. This phenomenon would reduce estimates of test–retest reliability, making the PRO measure look unreliable when it may be accurately detecting changes over time.

Validity

Validity is the extent to which a PRO scale measures what it purports to measure.

There are multiple types of validity; the more frequently assessed types for PRO measures are:

1. **Content Validity**

   Content validity is the extent to which the PRO measure includes the most relevant and important aspects of a concept in the context of a given measurement application.

   A PRO measure should have evidence supporting its content validity, including evidence that patients and experts considered the content of the PRO measure relevant and comprehensive for the concept, population, and aim of the measurement application.

   This includes documentation of:

   a. qualitative and/or quantitative methods used to solicit and confirm the attributes (i.e., concepts measured by the items) of the PRO measure relevant to the measurement application
   b. the characteristics of the participants included in the evaluation (e.g., race/ethnicity, culture, age, gender, socio-economic status, literacy level) with an emphasis on similarities or differences with respect to the target population
   c. justification for the recall period for the measurement application

2. Construct Validity

Construct validity is the degree to which scores on the PRO measure relate to other measures (e.g., patient-reported or clinical indicators) in a manner that is consistent with theoretically derived *a priori* hypotheses concerning the concepts that are being measured.

A PRO measure should have evidence supporting its construct validity, including documentation of empirical findings that support predefined hypotheses on the expected associations among measures similar or dissimilar to the concepts measured by the PRO measure.

Types of construct validity:

a. Structural Validity
   - extent to which the empirical data support the conceptual model
b. Convergent Validity
   - extent to which the PRO measure is similar to other established measures assessing the same concept
c. Discriminant Validity
   - extent to which the PRO measure is dissimilar to other established measures measuring different concepts
d. Known Groups Validity
   - extent to which the PRO measure can differentiate between groups known to differ on the measured concept

3. Responsiveness

Responsiveness is the extent to which a PRO measure can detect changes in the construct being measured over time. A PRO measure for use in longitudinal research studies should have evidence of responsiveness, including empirical evidence of changes in scores consistent with predefined hypotheses regarding changes in the measured PRO in the target population for the research application.

Interpretability of Scores

A PRO measure should have documentation to support interpretation of scores, including what low and high scores represent for the measured concept(s). Knowing what comprises a meaningful difference or change in the score from one group to another (or one time to another) improves understanding of the outcome being measured. Another way to enhance the interpretability of PRO measure scores involves comparing scores from a study to known scores in a population (e.g., the general US population or a specific disease population). The availability of such benchmarks improves understanding of how the study group scored as compared to some reference or normative group.

Translation of the PRO Measure

PCOR and CER are often carried out in multi-national or multi-cultural settings that require the PRO measure to be translated into different languages. To be able to compare or combine PRO results across those groups, it is critical that the measured concepts and PRO measure wording is interpreted in the same way across translations.

A PRO measure translated to one or more languages should have documentation of the methods used to translate and evaluate the PRO measure in each language. Established international guidance for the linguistic and cross-cultural adaptation of PRO measures should be followed. It is important that not only the words, but also the concepts, are applicable and interpretable across cultural settings. Studies should at least include evidence from forward and backward translations and qualitative methods (e.g., cognitive testing) with the target population to evaluate the translations.

Patient and Investigator Burden

A PRO measure must not be overly burdensome for patients or investigators. The length of the PRO measure should be considered in the context of other PRO measures included in the assessment. How often the PRO measure is administered in the clinical research study should also be considered. Lastly, the literacy demand of the items in the PRO measure should be at a 6th grade education level or lower (i.e., 12 year old or lower) to be acceptable; however, it should be appropriately justified for the context of the proposed application.

Checklist for the ISOQOL Measure Selection Standards

Minimum Standard	Explanation	Notes/comments
1. Conceptual and measurement model	A PRO measure should have documentation defining and describing the concept(s) included and the intended population(s) for use. In addition, there should be documentation of how the concept(s) are organized into a measurement model, including evidence for the dimensionality of the measure, how items relate to each measured concept, and the relationship among concepts included in the PRO measure.	
2. Reliability	The reliability of a PRO measure should preferably be at or above 0.70 for group-level comparisons, but may be lower if appropriately justified. Reliability can be estimated using a variety of methods including internal consistency reliability, test–retest reliability, or item response theory. Each method should be justified.	
3. Validity <u>3a Content validity</u>	A PRO measure should have evidence supporting its content validity, including evidence that patients and experts consider the content of the PRO measure relevant and comprehensive for the concept, population, and aim of the measurement application. This includes documentation of: (1) qualitative and/or quantitative methods used to solicit and confirm attributes (i.e., concepts measured by the items) of the PRO relevant to the measurement application (2) the characteristics of participants included in the evaluation (e.g., race/ethnicity, culture, age, gender, socio-economic status, literacy level) with an emphasis on similarities or differences with respect to the target population (3) justification for the recall period for the measurement application	
<u>3b Construct validity</u>	A PRO measure should have evidence supporting its construct validity, including documentation of empirical findings that support predefined hypotheses on the expected associations among measures similar or dissimilar to the measured PRO.	

Minimum Standard	Explanation	Notes/comments
3c Responsiveness	A PRO measure for use in longitudinal research studies should have evidence of responsiveness, including empirical evidence of changes in scores consistent with predefined hypotheses regarding changes in the measured PRO in the target population for the research application.	
4. Interpretability of scores	A PRO measure should have documentation to support interpretation of scores, including what low and high scores represent for the measured concept.	
5. Translation of the PRO measure	A PRO measure translated to one or more languages should have documentation of the methods used to translate and evaluate the PRO measure in each language. Studies should at least include evidence from qualitative methods (e.g., cognitive testing) to evaluate the translations.	
6. Patient and investigator burden	PRO measures must not be overly burdensome for patients or investigators. The length of the PRO measure should be considered in the context of other PRO measures included in the assessment, the frequency of PRO data collection, and the characteristics of the study population. The literacy demand of the items in the PRO measure should usually be at a 6th grade education level or lower (i.e., 12-year-old or lower); however, it should be appropriately justified for the context of the proposed application.	

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Further Reading

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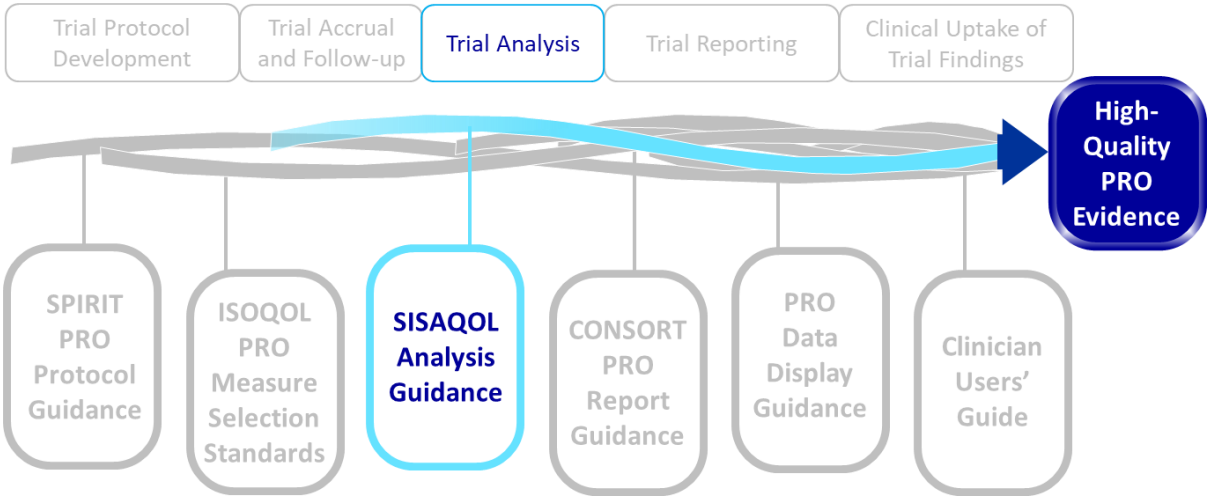
Chapter 4. Analyzing PRO Data



Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints Data (SISAQOL) Consortium

The European Organization for the Research and Treatment of Cancer (EORTC) formed the SISAQOL Consortium to set international standards in analyzing patient-reported outcomes and quality of life data from cancer clinical trials. SISAQOL provides a taxonomy of research objectives, outlines appropriate statistical methods for these objectives, and advises on handling missing data. Although SISAQOL focused on cancer clinical trials, many issues discussed here may also be applied to other health conditions, which warrants further scrutiny.

This chapter summarizes the preliminary SISAQOL recommendations; work is continuing via the SISAQOL-IMI initiative.

View SISAQOL Standards article

View the Checklist for the SISAQOL Analysis Guidance for Clinical Trials

References

Acknowledgements

Why is This Resource Needed?

To ensure a consistent and methodologically appropriate PRO data analysis

Recommends statistical approaches for analyzing PRO data

PRO data have unique properties compared to other clinical trial data.

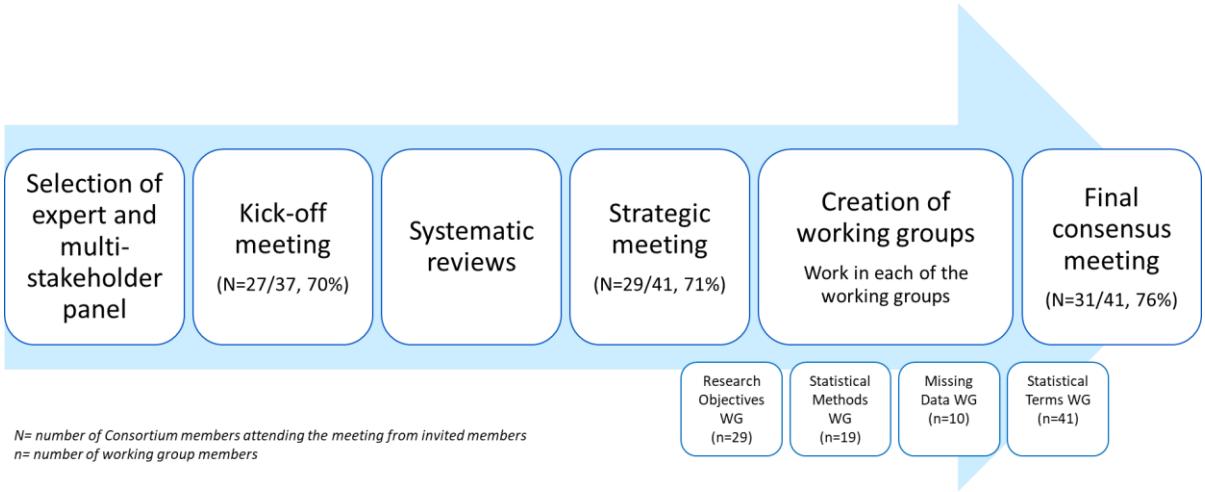
- Multidimensional – composed of different domains yielding multiple outcomes
- Longitudinal – data are collected repeatedly over time
- Missing data – occurs more frequently and have stronger clinical implications due to voluntary patient participation

Major hurdles in applying standardized statistical methods are:

- Unclear PRO objectives
- Inconsistent terminology

Methods for Resource Development

The SISAQOL Consortium was established from a group of international stake-holders experienced with PROs in cancer clinical trials to develop international consensus recommendations on the analysis of PRO data. The initial SISAQOL recommendations are based on discussions with stakeholder groups and (systematic) literature reviews of PRO analysis in cancer clinical trials. Four working groups were assembled: (1) research objectives, (2) statistical methods, (3) standardization of statistical terms, and (4) management of missing data. Final outputs from each working group were used as proposed statements for the SISAQOL recommendations. A consensus meeting was held to ratify the proposed recommendation statements, which informed the final SISAQOL recommendations.



SISAQOL Recommendations

Overview

The recommendations made by SISAQOL fall into three main categories: Taxonomy of research objectives, statistical methods, and missing data. It is important to note that the SISAQOL work is currently ongoing with SISAQOL-IMI and these recommendations will be updated in the future. The recommendations below are based on the initial SISAQOL work published in Lancet Oncology by Coens, Pe et al. (2020).

Taxonomy of Research Objectives

The first of these are recommendations regarding the **research objectives**. When developing a PRO objective, the PRO domain(s) and time frame of interest should be pre-specified. Additionally, four key attributes need to be considered when developing a PRO objective so that it can be aligned with an appropriate statistical method:

- Broad PRO research objectives: What is the overall goal of including PROs in the RCT? Is it to demonstrate *treatment efficacy/clinical benefit* (*confirmatory*)? Or is the goal to *describe patient perspective*, without drawing strong conclusions about treatment efficacy/clinical benefit (*exploratory/ descriptive*)?
- Between-arm PRO objective: For a treatment efficacy/clinical benefit (confirmatory) objective, is the goal to demonstrate that the treatment arm is *superior* to the reference arm? Or is the goal to demonstrate that the treatment arm is *equivalent* or *non-inferior* to the reference arm? Note that a non-significant superiority result should not be interpreted as evidence of equivalence or non-inferiority.
- Within-treatment group assumption: What is the assumption regarding how patients will report their experience in this trial? Will patients *improve, worsen, or remain stable* relative to their baseline (e.g., before randomization)? Or are there no assumptions (i.e., overall effect)?
- Within-patient/within-treatment PRO objective: What kind of PRO endpoint will be meaningful for this trial? Is it a *time to event*, *magnitude of change* at a specific time point, *responder* at a specific time point, or other?

For more detail, please refer to the Checklist for the SISAQOL Analysis Guidance for Clinical Trials.

Statistical Methods

The second category of SISAQOL recommendations relates to aligning the **appropriate statistical methods** with the research objective. Since there is no single analysis method that can address all clinical trial design and analytical concerns, set criteria to evaluate what *appropriate* statistical methods for a given PRO objective are needed.

Two essential statistical properties are:

- The ability to perform a comparative test (statistical significance)
- The ability to produce interpretable treatment effect estimates (clinical relevance)

Highly desirable criteria include:

- The ability to adjust for covariates, including baseline PRO score
- Handling missing data with the least restrictions
- Handling clustered data (repeated assessments)

These criteria informed the selection of specific statistical methods for each PRO objective. It should be noted that these recommendations are under further development as part of the SISAQOL-IMI initiative.

For more detail, please refer to the Checklist for the SISAQOL Analysis Guidance for Clinical Trials.

Missing Data

Finally, recommendations are provided for dealing with **missing PRO data.** To evaluate the extent of missing data, the PRO analysis population and missing data rates should be reported in a standardized way. Additionally, managing missing data, including collecting reasons for missing data, is critical to minimize the potential bias of the trial findings.

For more detail, please refer to the Checklist for the SISAQOL Analysis Guidance for Clinical Trials.

Implications of Using the SISAQOL Guidance

- Improved PRO analysis in clinical trials will enable robust evidence to inform patient choice, aid clinical decision making, and inform policy
- Clear PRO objectives should be specified at the study design phase
    - Consider design in relation to SPIRIT-PRO Initiative
- More standardized PRO analysis will lead to easier and better cross-trial comparison of PRO results, improving the value of such outcomes
    - Standardization recommendations still ongoing as part of SISAQOL-IMI
- Foster better collaboration and understanding between clinicians, patients, and methodologists on statistical analysis and interpretation
- Better PRO analysis will facilitate high-quality reporting, including clear and comprehensible description of the methods used
    - Consider reporting in relation to CONSORT-PRO

Checklist for the SISAQOL Analysis Guidance for Clinical Trials

Consideration	Recommended content	Notes/ comments
Part 1: General Considerations		

For each PRO scale or domain to be analyzed, specify *a priori* whether the research objectives are:	- **Confirmatory** *(see Part 2a below)*
	  ○ The broad goal is typically to demonstrate treatment efficacy or clinical benefit by providing formal comparative conclusions between treatment groups
	  ○ An *a priori* hypothesis is needed
	  ○ Statistical testing is required, so correction for multiple testing is needed
	  ○ Conclusions regarding comparisons between treatment arms are possible
	
	- **Exploratory/descriptive** *(see Part 2b below)*
	  ○ The broad goal is typically to describe the patient perspective or to explore the PRO data and use its findings to inform future studies. These outcomes cannot be used to draw comparative conclusions or used as support for treatment efficacy or clinical benefit
	  ○ No *a priori* hypothesis needed
	  ○ No statistical comparisons between treatment arms
	  ○ Multiple testing is not an issue
	
	- Regardless of the research objective, **missing data** needs to be addressed (*see Part 3 below)*
	
	- For all statistical models, **assumptions** should be checked and must hold *(see Coens et al, 2020)*	

Consideration	Recommended content	Notes/ comments

If applicable, specify the within-patient/within-treatment assumption and relevant endpoint for each PRO domain or item of interest	- When within-group assumption is **improvement/worsening***:*
	  ○ Time to improvement/worsening
	  ○ Magnitude of improvement/worsening at time *t*
	  ○ Proportion of responders with improvement/worsening at time *t*
	- When within-group assumption is **time to (end of) maintenance:**
	  ○ Time to (end of) maintenance
	  ○ Proportion of responders with maintenance at time *t*
	- When within-group assumption is **overall effect**
	  ○ Overall PRO score over time
	  ○ Response patterns/profiles	

Clearly differentiate the ITT population, the PRO study population, and the PRO analysis population	- **Intent-to-treat** (ITT) **population:** all patients randomized to the allocated treatment - **PRO study population:** all patients who consented and were eligible to participate in the PRO data collection (ideally but not necessarily the same as the ITT population) - **PRO analysis population:** patients included in the primary PRO analysis; should be as close as possible to the PRO study population; exists only in relation to a defined PRO analysis	
Part 2a: CONFIRMATORY Research Objectives		
Specify one of the following between-arm objectives for each PRO domain or item of interest	- **Superiority** of the experimental arm relative to the control arm - **Equivalence** of the trial arms - **Non-inferiority** of the trial arms	

Recommended statistical models	For **time-to-event** objectives: improvement, (end of) stable state, or worsening
	  - Cox proportional hazards models are recommended
	
	For **magnitude-of-event** at time *t* objectives: improvement or worsening
	  - If design is baseline + more than 1 follow-up: linear mixed models (time as discrete) are recommended	

Consideration	Recommended content	Notes/ comments
	- If design is baseline + 1 follow-up only: linear regression is recommended Note: Caution is needed because many statistical programs (e.g., SAS) use complete case analysis for linear regression and inferences are valid only when missing data are missing completely at random For **proportion of responders** at time *t* - The SISAQOL recommendations on this point are not yet finalized. This work continues in SISAQOL-IMI For **overall PRO score over time** - The SISAQOL recommendations on this point are not yet finalized. This work continues in SISAQOL-IMI	
Part 2b: DESCRIPTIVE/EXPLORATORY Research Objectives		
For **time-to-event** objectives: improvement, (end of) stable state, or worsening	Cox proportional hazards models are recommended Options for descriptive objectives are: - Median time to improvement / (end of) stable state / worsening - Probability of improvement / (end of) stable state / worsening at a specific time point - Hazards ratio (with CI)	
For **magnitude-of-event** at time *t* objectives: improvement or worsening	- If design is baseline + more than 1 follow-up: linear mixed models (time as discrete) are recommended - If design is baseline + 1 follow-up only: linear regression is recommended Note: Caution is needed because many statistical programs (e.g., SAS) use complete case analysis for linear regression and inferences are valid only when missing data are missing completely at random Additional options for descriptive objectives are: - Mean magnitude at baseline and time *t* (with CI): improvement / (end of) stable state / worsening - Mean magnitude of improvement / (end of) stable state / worsening at time *t* (with CI)	
For **response patterns/ profiles**	For descriptive/exploratory objectives *only*: A linear mixed model (omnibus test; time as discrete variable; time*group interaction) is recommended	

over time objectives	Options for descriptive objectives are: - Mean magnitude at baseline and at every time point within a time frame (with CI) - Mean change at every time point within a time frame (with CI) - Mean profile over time (with CI)	
Part 3: Missing Data Considerations		
General considerations and definition of missing data	Statistical reports from clinical trials should specify the proportion of missing data, the reasons for missing data, and the analytic approaches used to address missing data Note: Missing data that are considered meaningful for analysis (would contribute to the PRO findings) can affect the interpretability of PRO findings (e.g., by reducing the sample size [non-informative missing data], distorting the treatment estimate [informative missing data], or both).	
Calculate the completion rate (variable denominator rate)	**PRO completion rate** = the number of patients *on PRO assessment* submitting a valid PRO assessment at the designated time point as a proportion of the number of patients *on PRO assessment* at the designated time point - Absolute numbers for numerator and denominator should also be reported at every time point - On PRO assessment: patients still expected to provide PRO assessments at that time point - After death, patients are considered off PRO assessment and no longer included in the denominator	
Calculate the available data rate (fixed denominator rate)	**Available PRO data rate** = the number of patients *on PRO assessment* submitting a valid PRO assessment at the designated time point as a proportion of the number of patients *in the PRO study population* - Absolute numbers for numerator and denominator should also be reported at every time point	
Record the reasons for missing data	To assess the impact of missing data on PRO findings, a case report form to collect reasons for missing data in a standardized way should be included in every trial	
Handle item-level missing data according to the scoring algorithm	- Item-level missing data within a scale should be handled according to the instrument scoring algorithm (when available) - If changes in official scoring algorithms for the PRO measure occur, the resulting updated guidelines from the developers should be followed	
State methods for handling missing	- The approach for handling missing data at the item- and scale- levels should be specified *a priori*	

PRO data in statistical analysis	- Depending on the reason and amount of missing data, the approach to handling missing data may include: ○ Sensitivity analyses (specified *a priori*) to test the robustness of the conclusions using a different set of assumptions regarding missing data ▪ At least two different approaches to handle missing data are recommended to assess the impact of missing data across various assumptions ○ Methods that use all available data are recommended as they make weaker assumptions about missing data compared to complete case analysis ○ Explicit simple imputation methods are not recommended unless justified within the context of the clinical trial ○ Approaches that ignore missing data and only include patients with complete data in analysis are not recommended (e.g., complete case analysis)	

Abbreviations: confidence interval (CI), health-related quality of life (HRQOL), patient-reported outcomes (PRO)

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Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data (SISAQOL-IMI). Accessed at https://www.sisaqol-imi.org/

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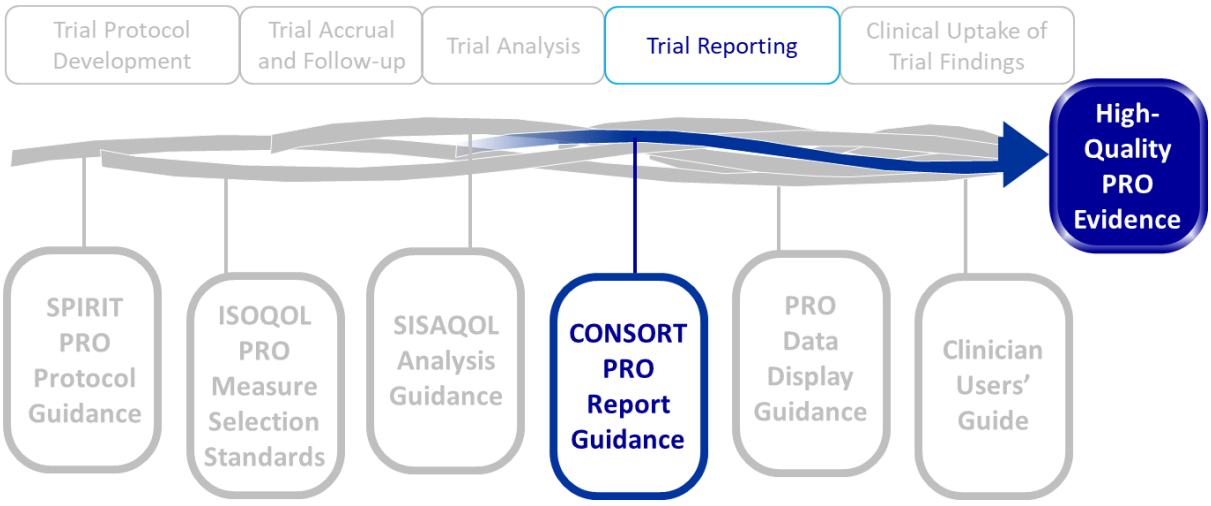
Please Note: When referencing information included in this Chapter, we recommend citing the primary sources rather than this Handbook.

Chapter 5. Reporting PRO Findings



Consolidated Standards of Reporting Trials PRO Extension (CONSORT PRO)

The CONSORT guidance (Consolidated Standards of Reporting Trials) provides recommendations for publications reporting clinical trial results (Schulz et al., 2010). In 2013, a PRO-specific extension was published that addresses the specific elements related to PRO endpoints that should be included in clinical trial publications.

This chapter summarizes the recommendations for reporting PRO components of research studies.

View the CONSORT PRO article

View the Checklist for the CONSORT PRO Reporting Guidance

References

Acknowledgements

Why is This Resource Needed?

To ensure that the PRO methods and results are clearly described in clinical trial publications

Identifies the relevant information to include in clinical trial publications with PRO endpoints

CONSORT PRO Summary of Reporting Guidance

The CONSORT PRO guidance constitutes an extension to the CONSORT statement that guides the reporting of clinical trials in general. The key items relevant to the reporting of PROs include the following:

Abstract

- Identify PRO as primary or secondary outcome

Background

- State PRO hypothesis, specifying domains, if applicable

Methods

- Provide/cite evidence of PRO instrument validity and reliability
- Summarize study procedures for PRO data collection
- State statistical approaches for dealing with missing PRO data

Discussion

- Address PRO-specific limitations and implications for generalizability in clinical practice

Why We Need PRO Reporting Guidance

- Clinicians, patients, and policy makers value PRO information
- Existing reporting guidelines are not adhered to
- Poor reporting hampers the use of PRO data in clinical practice and undermines the clinicians' ability to use PRO data in their practice to benefit patients
- Improved reporting of PRO data should facilitate robust interpretation of the results from clinical trials and inform patient care

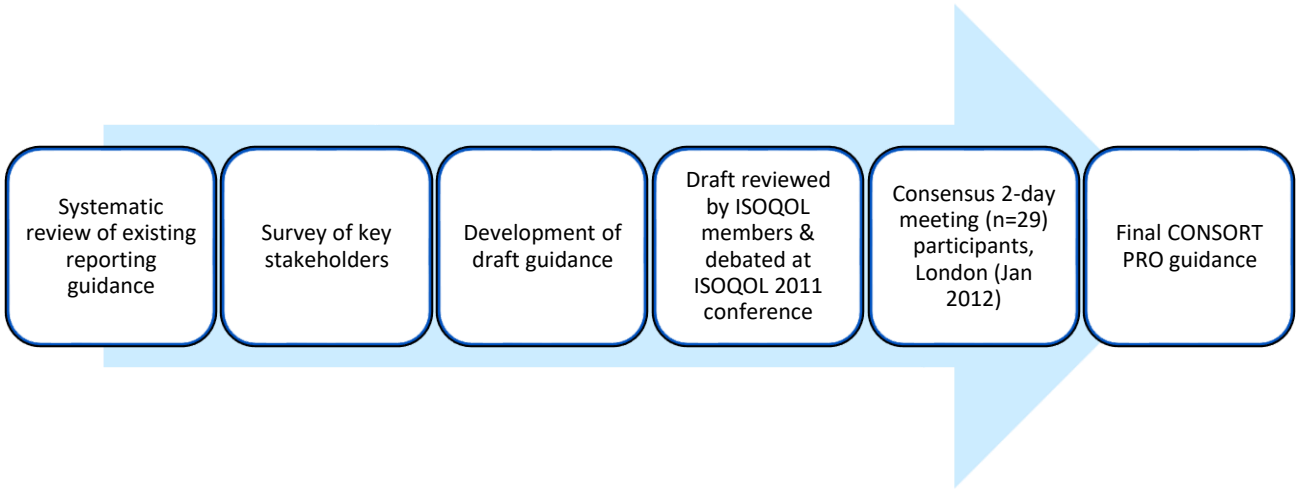
Objective of Resource

The CONSORT (Consolidated Standards of Reporting Trials) Statement aims to improve the reporting of randomized controlled trials, but lacks guidance on the reporting of PROs. CONSORT PRO provides evidence-based extensions to the CONSORT statement for reporting PROs in clinical trials and elaborations on the CONSORT 2010 statements specifically as applied to PROs.

It is recommended that PRO data be presented in the primary clinical trial publication, as this will help ensure PROs are considered alongside other clinical outcomes.

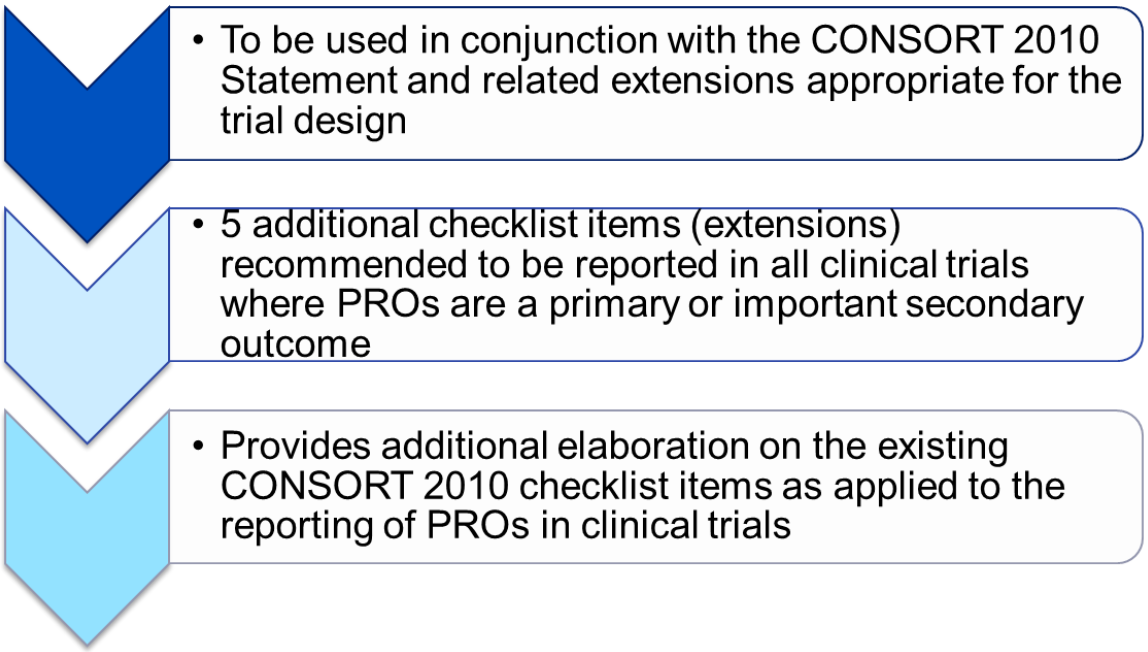
Methods for Resource Development

The below figure illustrates the development process for the CONSORT PRO Guidance.



CONSORT PRO Reporting Guidance

Overview



CONSORT PRO Extensions and Elaborations

The CONSORT PRO Reporting Guidance identifies 5 additional items (extensions) to be reported in all RCTs in which PROs are a primary or important secondary outcome. An extension was deemed unnecessary for six existing CONSORT checklist items and therefore were elaborated for PRO endpoints. Below is a list of the CONSORT 2010 item and the corresponding PRO Extension and Elaborations

2013 item with a brief explanation. Please see Calvert et al. (2013) for the full explanation and real-world examples.

Abstract Item 1b

CONSORT 2010:	PRO Extension 2013:
Structured summary of trial design, methods, results, and conclusions.	The PRO should be identified in the abstract as a primary or secondary outcome.

Explanation:

Identifying the PRO as a primary or secondary outcome in the abstract will facilitate indexing and identification of studies to inform clinical care and evidence synthesis.

Introduction Item 2a

CONSORT 2010:	PRO Elaboration 2013:
Scientific background and explanation of rationale.	The relevant background and rationale for why PROs were assessed in the clinical trial should be briefly described.

Explanation:

The Background or Methods section should provide the rationale for including PROs and why the specific outcomes were selected, thus providing appropriate context for the PRO-specific objectives and hypotheses.

Introduction Item 2b

CONSORT 2010:	PRO Extension 2013:
Specific objectives or hypotheses.	The PRO hypothesis should be stated and relevant domains identified, if applicable.

Explanation:

Without a prespecified hypothesis there is risk of multiple statistical testing and selective reporting of significant results.

Methods Item 6a Extension

CONSORT 2010:	PRO Extension 2013:
Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed.	Evidence of PRO instrument validity and reliability should be provided or cited, if available.

Explanation:

Clinical use of PRO data requires that the trial results are robust, which depends on a valid and reliable PRO measure being used appropriately.

Methods Item 6a Elaboration

CONSORT 2010:	PRO Elaboration 2013:
Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed.	Details of the mode of PRO completion (in particular if a proxy completed the questionnaire on behalf of the patient), and the method of data collection (paper, telephone, electronic, other) should also ideally be provided particularly when the PRO is the primary outcome.

Explanation:

Different methods of data collection may affect the results and lead to potential bias if used differentially between intervention groups.

Methods Item 12a

CONSORT 2010:	PRO Extension 2013:
Statistical methods used to compare groups for primary and secondary outcomes.	Statistical approaches for dealing with missing data should be explicitly stated.

Explanation:

The level of missing PRO data is often high and can lead to reduced power, is a potential source of bias, and can result in misleading results.

Results Item 13a

CONSORT 2010:

For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome.

PRO Elaboration 2013:

The number of participants reporting PRO data at baseline and at subsequent time points should be made transparent.

Explanation:

The flow of participants through the trial in relation to PROs, including information on the reason for missing PRO data, should be reported to help readers interpret the PRO results and assess potential for bias.

Results Item 15

CONSORT 2010:

Table showing baseline demographic and clinical characteristics for each group.

PRO Elaboration 2013:

Including baseline PRO data when collected.

Explanation:

Baseline PRO data may be used by clinicians and policy makers to assess the relevance and generalizability of trial findings.

Results Item 17a

CONSORT 2010:

For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval).

PRO Elaboration 2013:

For multidimensional PROs, results from each domain and time point specified for analysis.

Explanation:

The potential for selective reporting of PROs is increased because study measures often contain multiple scales and items. In general, all PRO results should be presented alongside other outcome data to facilitate the clinical integration of the important findings with other prespecified outcomes.

Discussion Items 20/21

CONSORT 2010:	PRO Extension 2013:
Item 20. Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses. Item 21. Generalizability (external validity, applicability) of the trial findings.	PRO specific limitations and implications for generalizability of study findings and clinical practice.

Explanation:

Readers need to be able to assess generalizability and any potential sources of bias.

Discussion Item 22

CONSORT 2010:	PRO Elaboration 2013:
Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence.	PRO data should be interpreted in relation to clinical outcomes including survival data, where relevant.

Explanation:

The clinical significance of PRO results is often not discussed in clinical trial reports but should be interpreted in relation to other important clinical outcomes such as survival, especially in trials for which there are clinically relevant trade-offs between PROs and survival outcomes.

Implications of Using CONSORT PRO Guidance

- Improved PRO reporting in clinical trials will enable robust evidence to inform patient choice, aid clinical decision making, and inform health policy
- Active implementation by journals, authors, and reviewers may lead to improved reporting
- Endorse CONSORT PRO and other reporting guidelines
- PRO reporting is intrinsically linked to study design. Consider design in relation to:
    - FDA Guidance on PROs
    - SPIRIT Initiative

Checklist for the CONSORT PRO Reporting Guidance

Section/Topic	CONSORT-PRO Item	Recommended Content	Page Addressed
Title and Abstract			
	P1b	The PRO should be identified in the abstract as a primary or secondary outcome.	
Introduction			
Background and objectives	2a	The scientific background and explanation of rationale of PRO assessment should be included.	
	P2b	The PRO hypothesis should be stated, and relevant domains identified, if applicable.	
Methods			
Participants	4a	PRO-specific criteria are required only if PROs were used for eligibility or stratification.	
Outcomes	P6a	Evidence of PRO instrument validity and reliability should be provided or cited if available including the person completing the PRO and methods of data collection (paper, telephone, electronic).	
Sample size	7a	Sample size determination is required only if PRO is a primary study outcome.	
Randomization			
Statistical methods	P12a	Statistical approaches for dealing with missing data are explicitly stated.	
Results			
Participant flow	13a	The number of PRO outcome data at baseline and at subsequent time points should be transparent.	
Baseline data	15	PRO data in the table showing baseline demographic and clinical characteristics for each group should be included.	
Numbers analyzed	16	For each group, the number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups) is required for PRO results.	
Outcomes and estimation	17a	The estimated effect size and its precision such as 95% confidence interval should be presented for multidimensional PROs from each domain and time point.	
Ancillary analyses	18	Results of any other PRO analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory, should be presented, where relevant.	
Discussion			
Limitations	P20/21	PRO-specific limitations and implications for generalizability and clinical practice should be presented.	
Interpretation	22	PRO data should be interpreted in relation to clinical outcomes including survival data, where relevant.	

References

Calvert M, Blazeby J, Altman DG, Revicki DA, Moher D, Brundage MD, CONSORT PRO Group. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. *JAMA*. 2013;309:814-822.

Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340:c332. doi:10.1136/bmj.c332

Further Reading

Brundage M, Bass B, Davidson J et al. Patterns of reporting health-related quality of life outcomes in randomized clinical trials: implications for clinicians and quality of life researchers. *Qual Life Res*. 2011; 20(5): 653-664.

Brundage M, Blazeby J, Revicki D et al. Patient Reported Outcomes in Randomized Clinical Trials: Development of ISOQOL Reporting Standards. *Qual Life Res* 2012; 22(6): 1161-75.

Calvert M, Kyte D, Mercieca-Bebber R, et al, for the SPIRIT-PRO Group. Guidelines for inclusion of Patient-Reported Outcomes in Clinical Trial Protocols The SPIRIT-PRO Extension. *JAMA* 2018;319(5):483-494.

Moher D, Hopewell S, Schulz KF et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010; 340:c869.

Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010; 340:c332.

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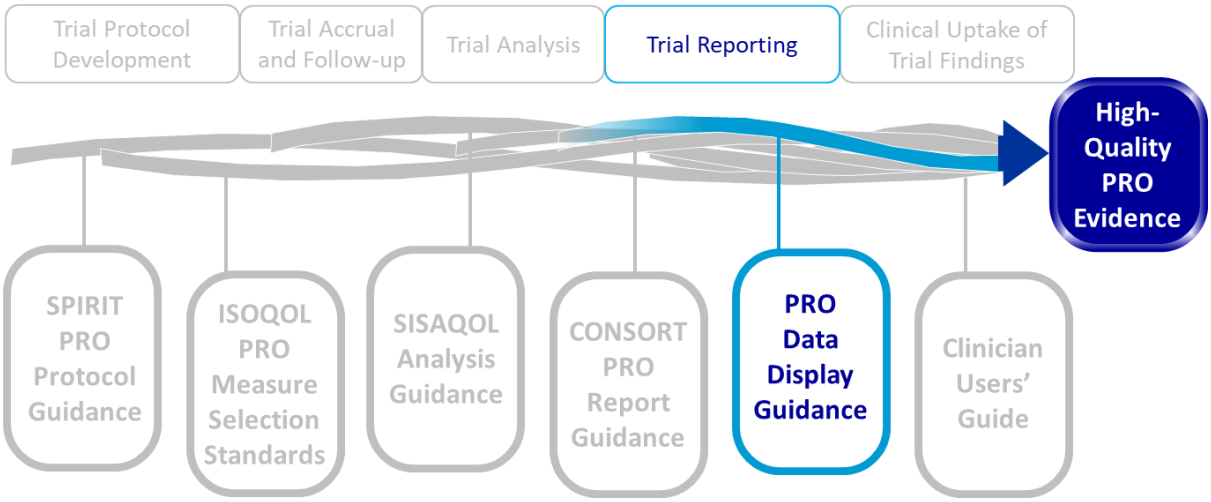
Chapter 6. Graphically Displaying PRO Data



Stakeholder-Driven, Evidence-Based Standards for Presenting PRO data to Patients and Clinicians/Researchers

A specific issue related to the reporting of PRO clinical trial results is the best way to graphically report the findings so that patients and clinicians can easily and accurately interpret the PRO findings. To address this issue, stakeholder-driven, evidence-based recommendations for how to display PRO data to promote understanding and use have been developed.

This chapter summarizes the recommendations for graphically displaying PRO data, for use by clinicians and/or patients.

View PRO Data Display article

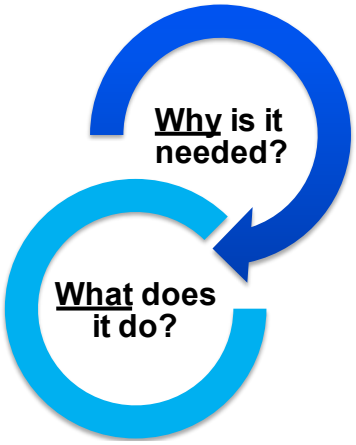
View the Checklists for PRO Data Display:

- Research Results Presented to Patients
- Research Results Presented to Clinicians/Researchers

References

Acknowledgements

Why is This Resource Needed?



To promote consistent presentation of PRO data so that clinicians and patients can understand what PRO scores mean

Provides evidence -based recommendations for presenting PRO data clearly to patients and clinicians/researchers

The impetus for developing these recommendations was evidence showing that while both patients and clinicians endorse the value of PROs, they also report challenges interpreting the meaning and implications of PRO data, such as those produced within a clinical trial. These challenges result, in part, from the lack of standardization in how PRO measures are scored and scaled, and in how the data are reported. For example, on some PRO measures, higher scores are always better; on other PRO measures, higher scores reflect “more” of the outcome and are therefore better for function domains but worse for symptoms. Some PRO measures are scaled from 0 to 100, with the best and worst outcomes at the extremes, whereas others are normed to, for example, a general population average of 50. There are also variations in how PRO results are reported—in some cases as mean scores over time, in other cases as the proportion of patients meeting a responder definition (i.e., improved/stable/worsened). These challenges in interpreting PRO results limit patients’ and clinicians’ use of the data in clinical practice.

Objective of Resource

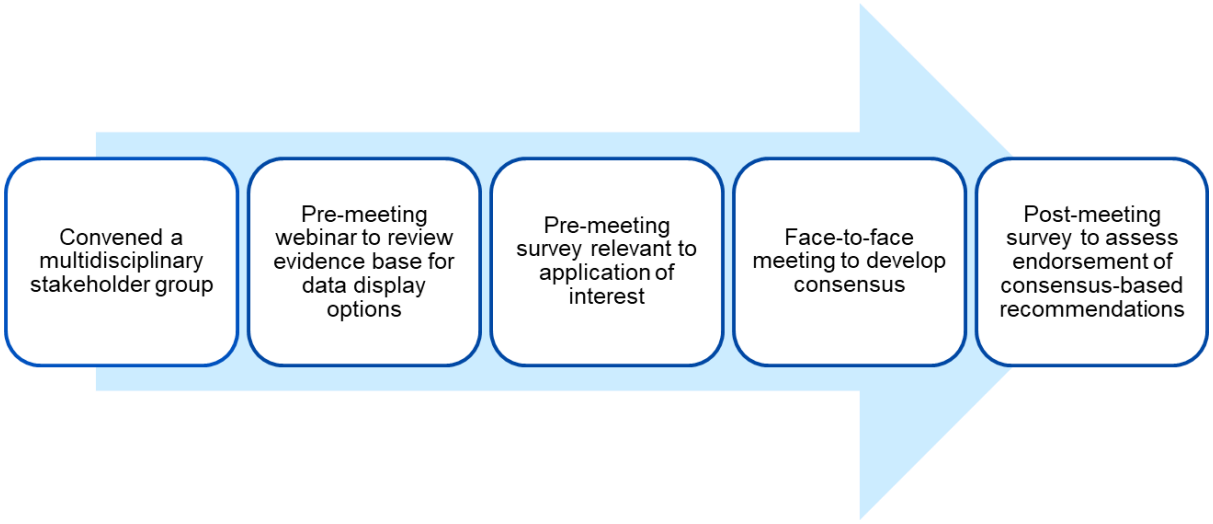
This resource is designed to provide evidence-based recommendations for PRO data display to facilitate ease of interpretation for presenting results to:

- Patients (e.g., educational materials and decision aids)
- Clinicians/researchers (e.g., peer-reviewed publications)

The resource also provides recommendations for display of individual patient PRO data within clinical practice settings, but these are not covered in this Handbook. If you are interested in learning more about recommendations for displaying individual patient PRO data, please see Snyder et al. (2019).

Methods for Resource Development

This PRO data display resource was developed using a modified Delphi process to establish consensus on evidence-based recommendations for graphically displaying PRO data among a multi-disciplinary group of stakeholders, which included clinicians, patients/caregivers, academics, and journal editors.



Parameters for Recommendations

The following parameters informed the PRO data display considerations:

1. recommendations should work on paper (static presentation)
2. presentation in color is possible (but it should be interpretable in grayscale)
3. additional functionality in electronic presentation is possible (but not part of standards)

Additional guiding principles were also established:

1. displays should be as simple and intuitively interpretable as possible
2. it is reasonable to expect that clinicians will need to explain the data to patients
3. education and training support should be encouraged to be available

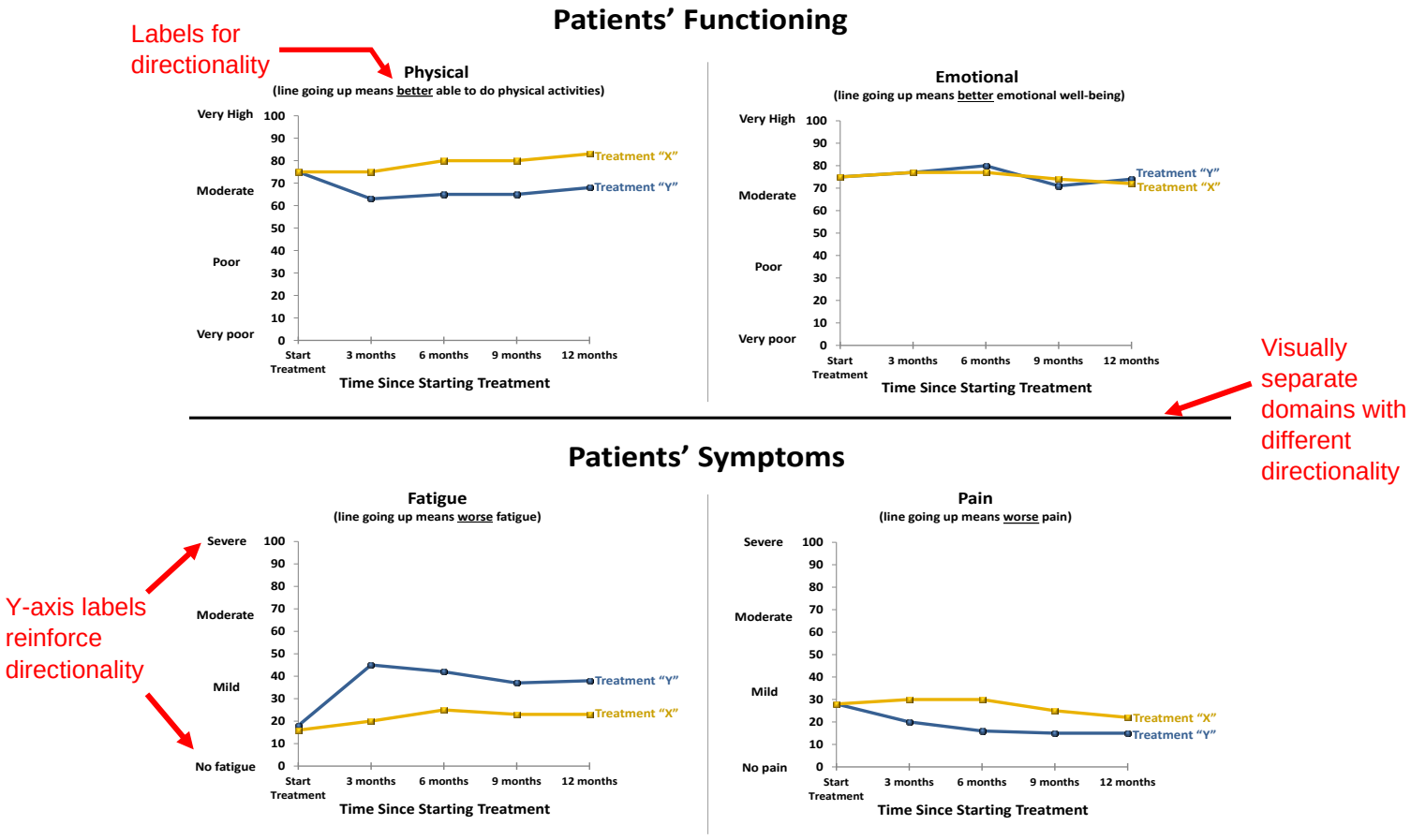
Overview of PRO Data Display Recommendations

In this section, we include several graphs/charts illustrating how to implement the PRO data display recommendations. Graphs/charts in color illustrate recommendations for how to display PRO data to patients, whereas black-and-white figures illustrate recommendations for PRO data display to clinicians or researchers. These graphs shown in black-and-white are common for journal publications, and for printers that clinicians and researchers may have access to.

Directionality

One of the key issues to address in the presentation of PRO data is how to display variations in directionality – that is, how to aid interpretation when higher scores are better for some domains, such as, physical function, but worse for other domains, such as pain.

There are two general recommendations for addressing directionality. First, the graphic should include exceptionally clear labeling, titling, and annotations to help viewers understand whether higher scores are better or worse. Second, domains that differ in scoring directionality should be presented separately.

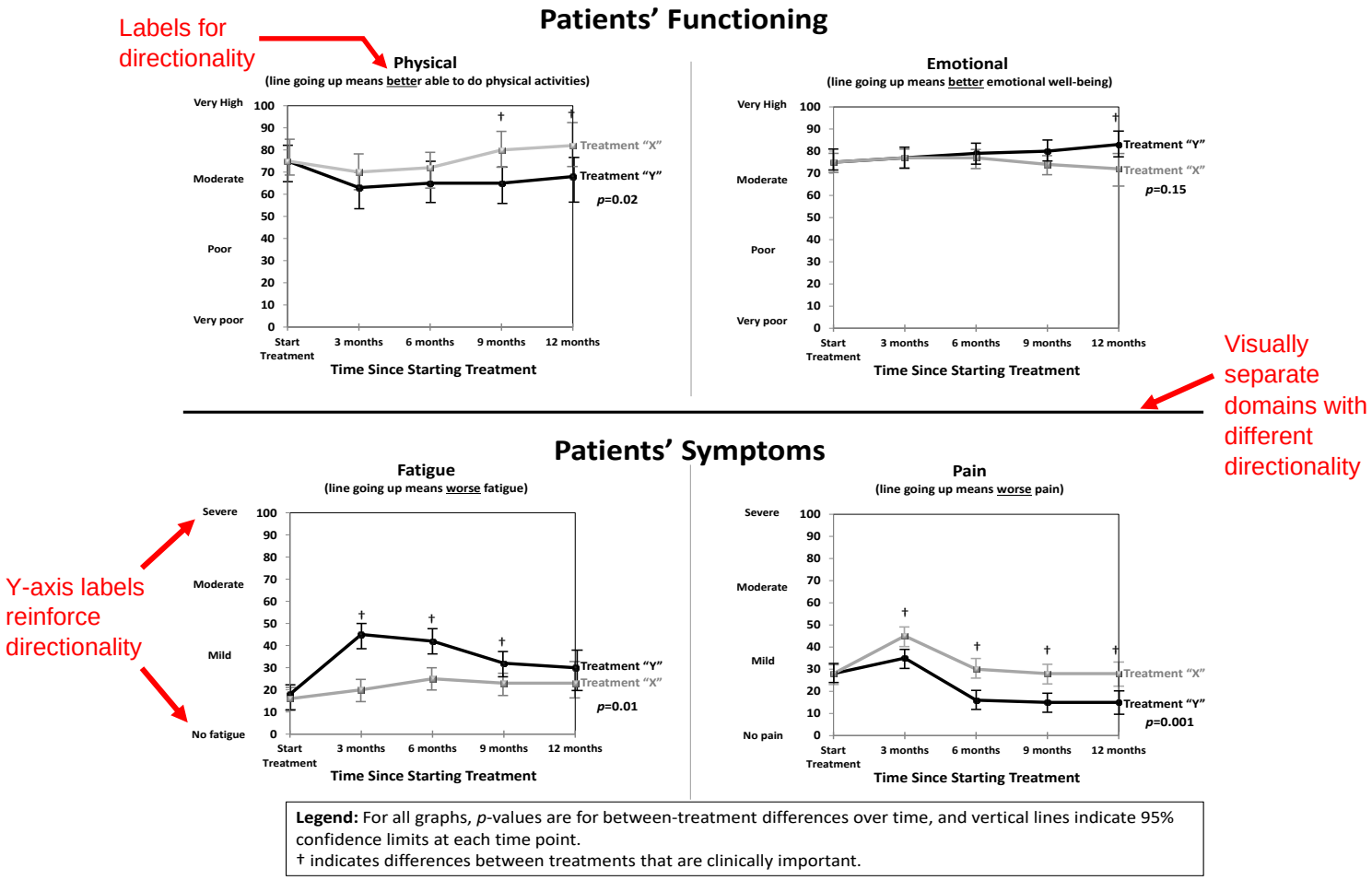


The above illustration shows an example of how to display data to patients. Please note a few key aspects of these graphs.

First, we use a line graph of average scores over time, which was the preferred approach for showing longitudinal data. Different colors are used for the two treatment arms, and the lines are labeled directly, rather than using a legend.

As for directionality, you can see that under each domain title, a header describes whether a line going up indicates improvement or worsening. The functional domains where higher scores are better are clearly separated from the symptom domains

where higher scores are worse. Finally, we have included descriptive labels on the y-axis to help with directionality, as well as to help convey score meaning.



Legend: For all graphs, *p*-values are for between-treatment differences over time, and vertical lines indicate 95% confidence limits at each time point.
† indicates differences between treatments that are clinically important.

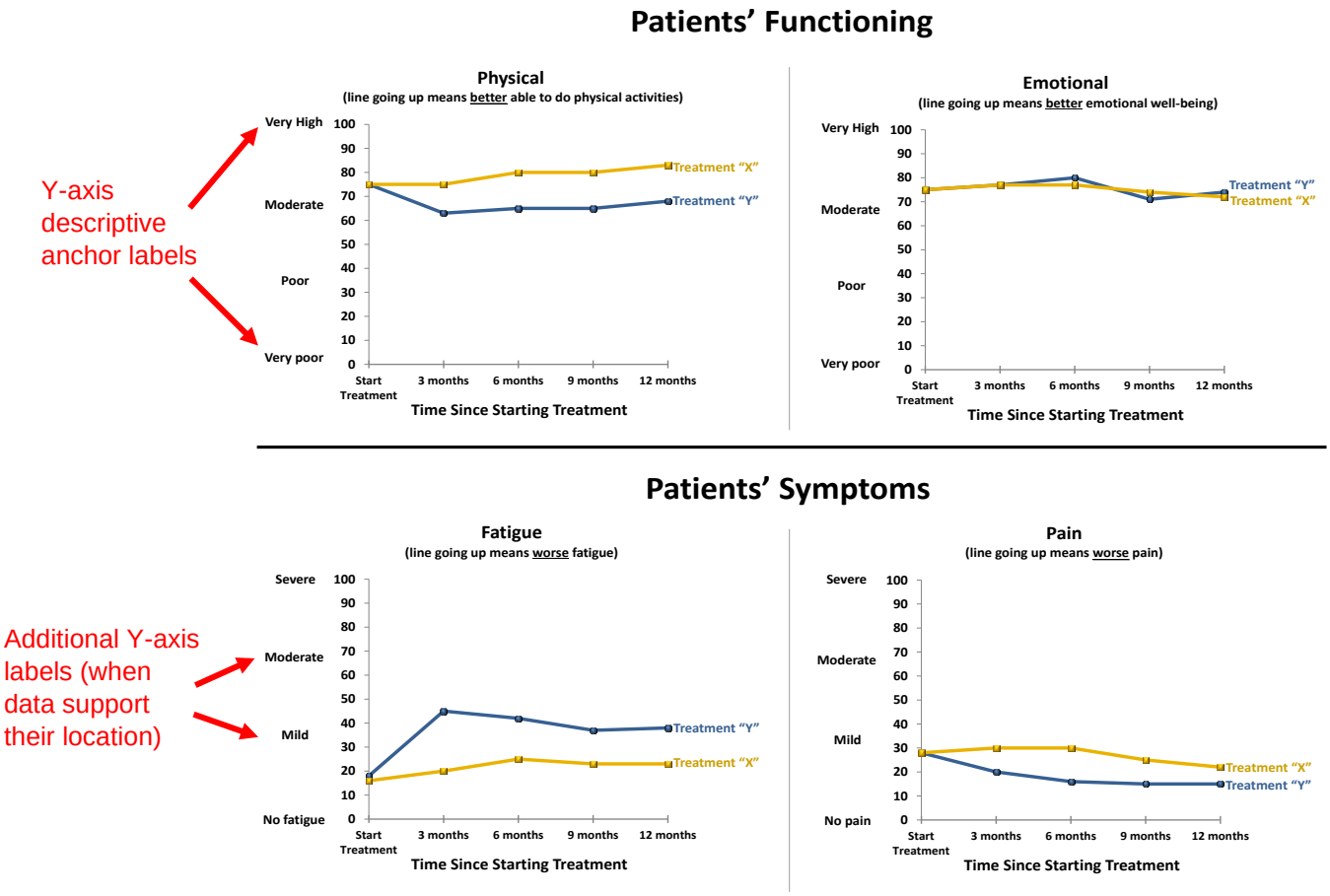
The figure above shows an example of how to display data to clinicians or researchers. Again, we use line graphs of average scores over time, but these versions include additional statistical and other details we will describe later. Similar to the patient graphic, the lines are labeled directly, rather than using a legend.

The same labeling, titling, and annotations are also included here, such as the headers under the domain names, the separation of domains with different scoring directionality, and the y-axis labels.

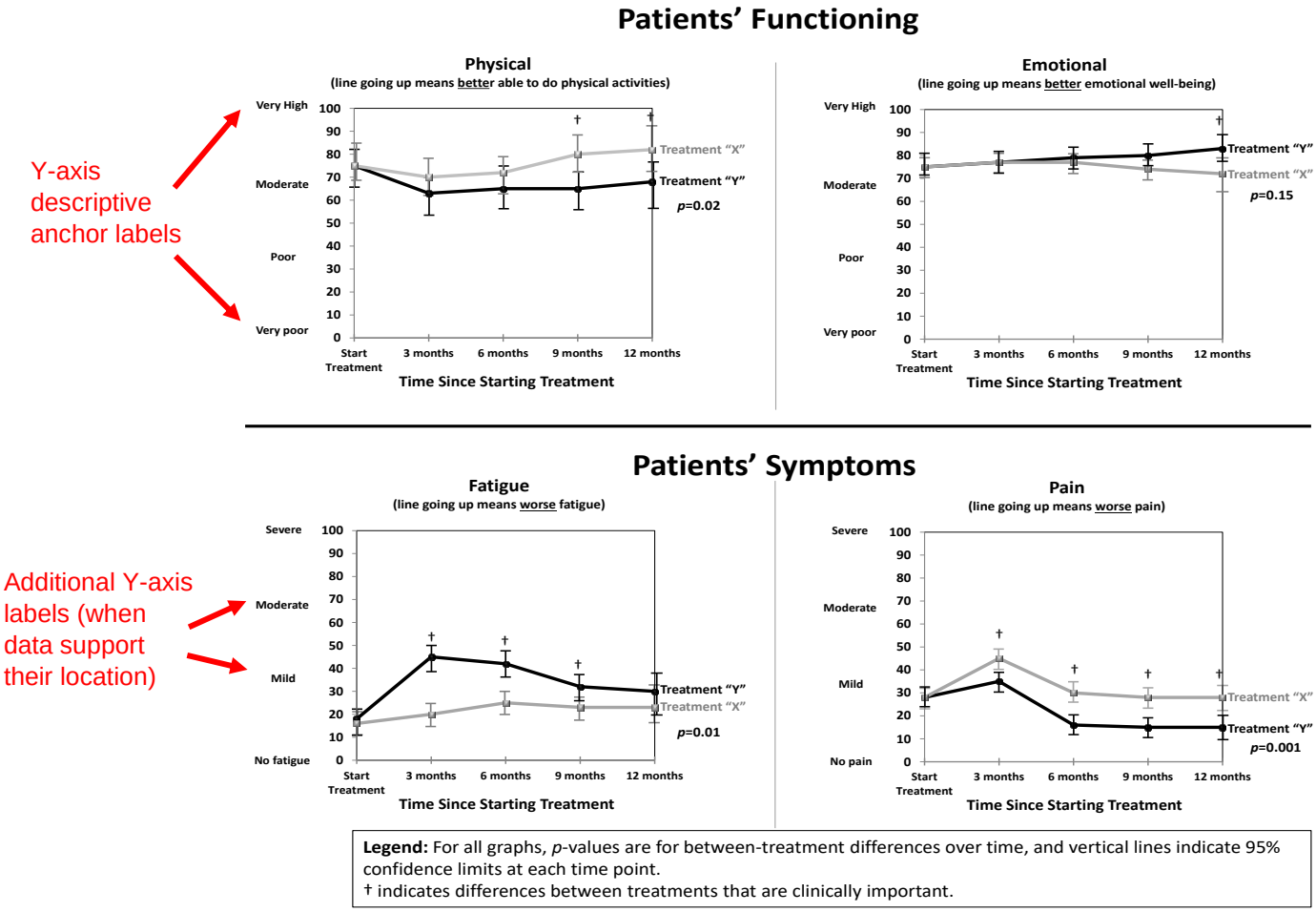
Conveying Score Meaning

The next recommendations relate to conveying score meaning. That is, how to understand whether a score is good or bad, or what level of function or symptoms is represented.

The recommendations suggest including descriptive labels along the y-axis – to the extent that this information is known. In displaying the data, inclusion of reference values for comparison populations may also be considered.



Above is an illustrative example for displaying PRO data to patients, highlighting the descriptive labels along the y-axis. As noted previously, the labels along the y-axis should only be included when there is evidence to support where on the scoring continuum the labels should be placed. The Consensus Panel acknowledged that it would be easier to place the anchor labels, for example, "*none*" and "*severe*", at the extreme ends of the continuum and that it might be more difficult to place the middle labels, for example, "*mild*" and "*moderate*".



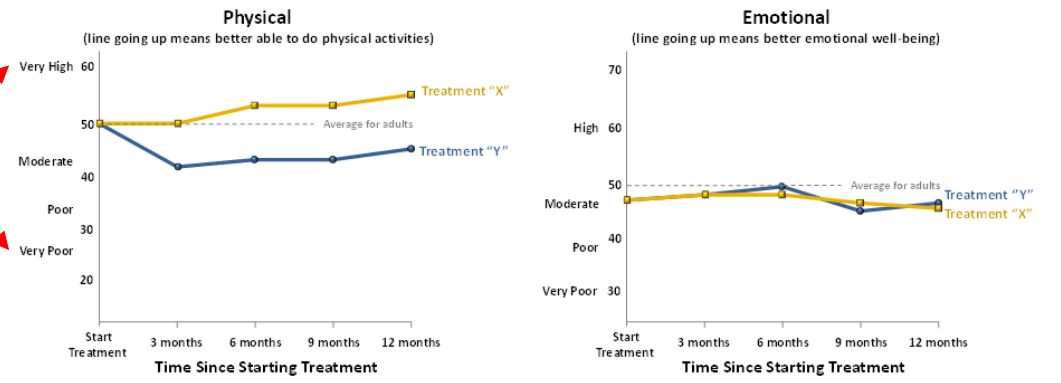
Legend: For all graphs, *p*-values are for between-treatment differences over time, and vertical lines indicate 95% confidence limits at each time point.
† indicates differences between treatments that are clinically important.

This is the clinician/researcher example illustration. The same considerations regarding the y-axis labels apply, with potentially greater knowledge and ability to include the anchor labels compared to the middle labels.

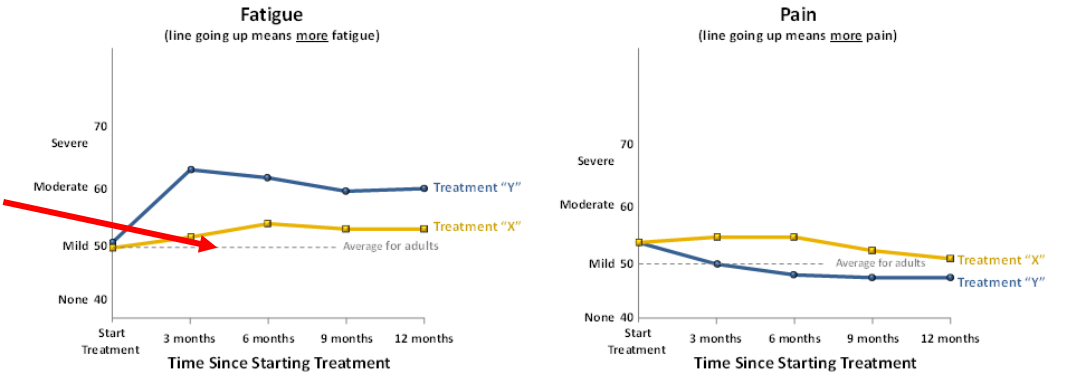
Normed Scoring

The next recommendations address normed scoring. As a reminder, some PRO measures are normed with, for example, a score of 50 representing the general population average. The Consensus Panel recommended displaying the scores based on the questionnaire's scoring metric, whether it is normed or not. Displaying the actual norm is optional.

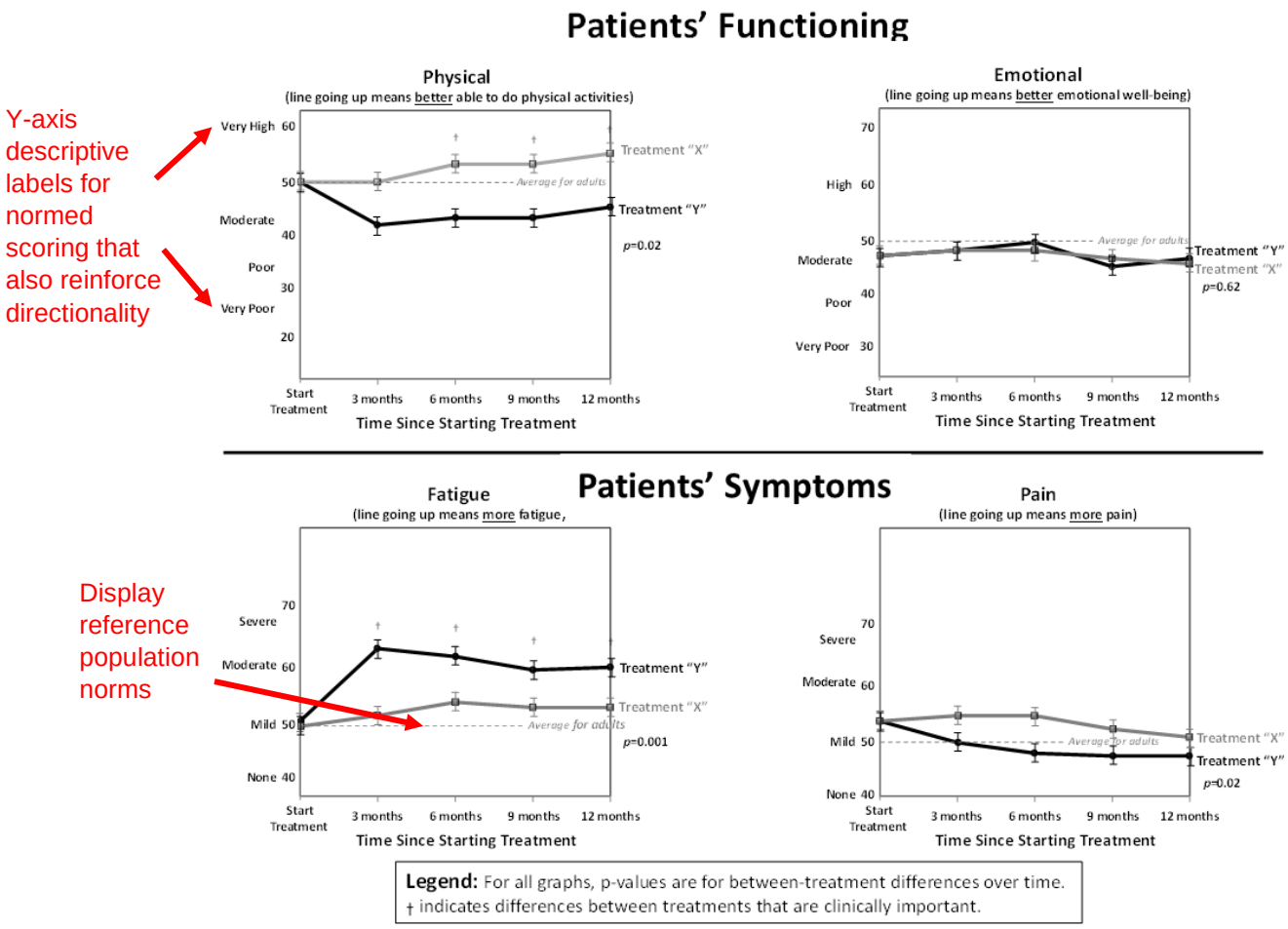
Y-axis descriptive labels for normed scoring that also reinforce directionality



Display reference population norms



The example above shows normed scoring for display to patients. In this case, it does display the general population average of 50 and includes the y-axis descriptive labels. As with the non-normed scoring, the decision of where to position these labels should be evidence-based.



Y-axis descriptive labels for normed scoring that also reinforce directionality

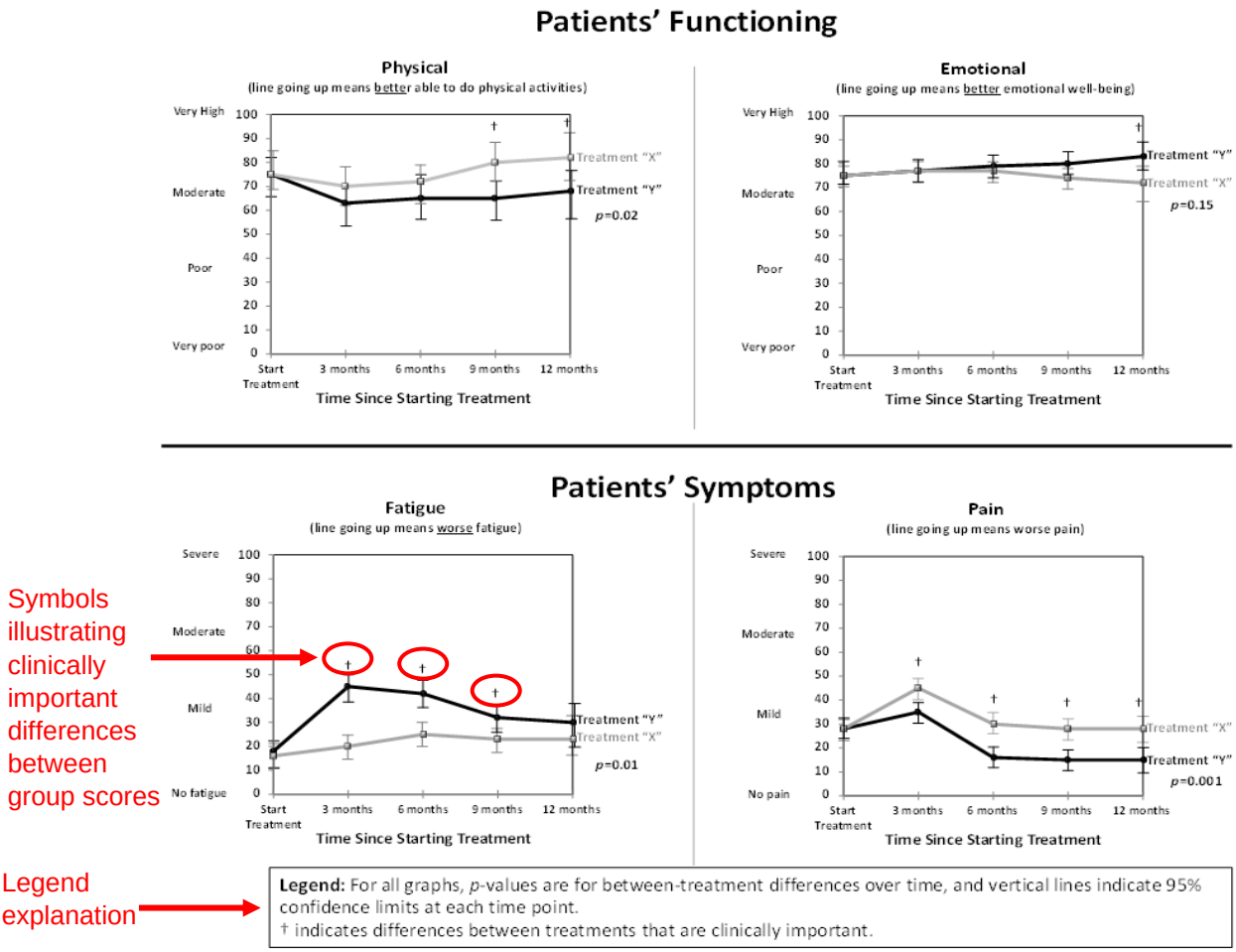
Display reference population norms

The illustration above provides an example of how to present normed scoring to clinicians/researchers and includes the same annotations as the example for patients.

Clinically Important Differences

The recommendations for PRO data display also address how to indicate whether differences between treatment/intervention arms are clinically important. Although the Consensus Panel agreed it is important for patients to know whether differences are clinically important, there was insufficient evidence to inform how best to convey this information to patients.

For clinicians and researchers, the recommendation is to use a symbol to indicate which differences are clinically important. However, an asterisk should not be used given that it is commonly used to indicate statistical significance in academic journals.



Symbols illustrating clinically important differences between group scores

Legend explanation

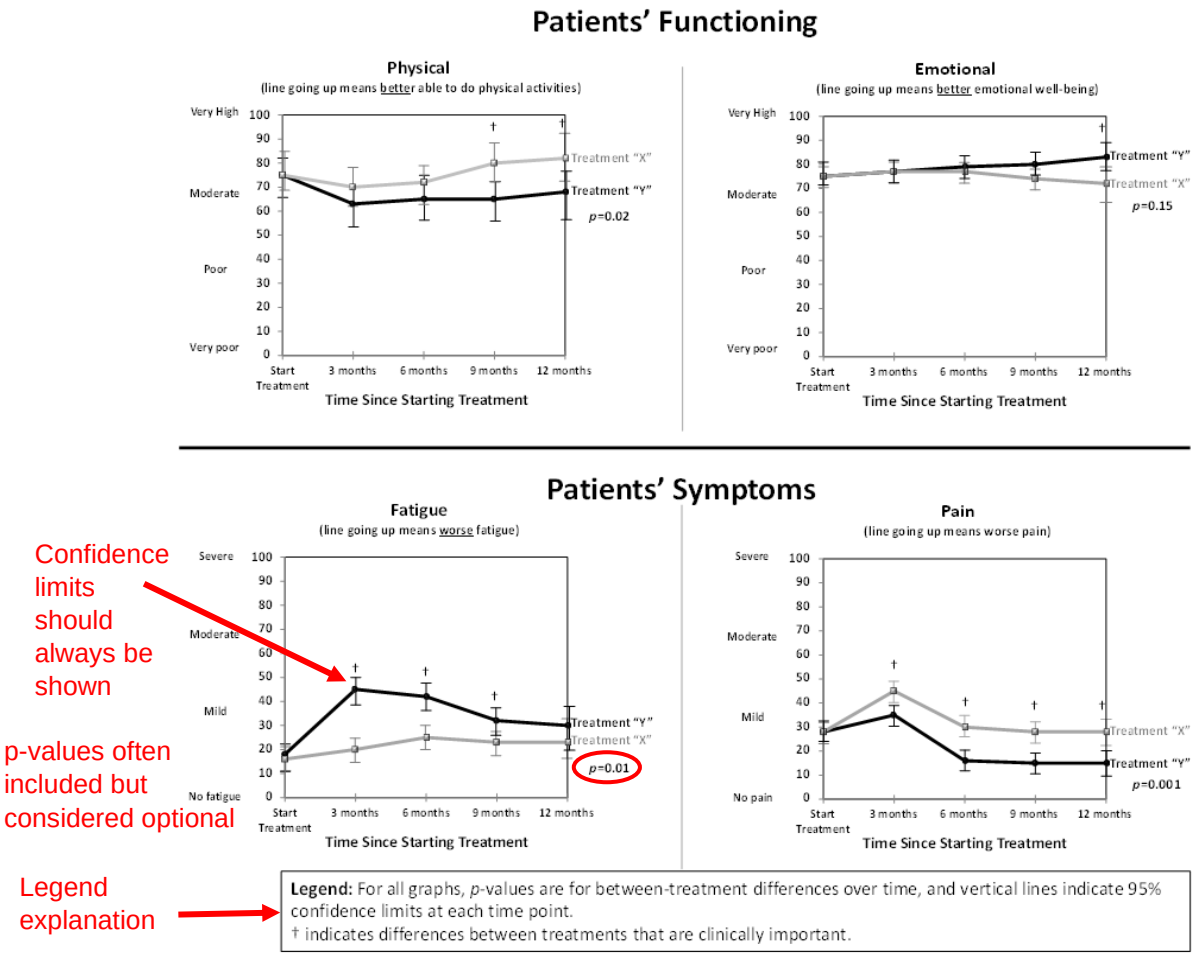
Legend: For all graphs, *p*-values are for between-treatment differences over time, and vertical lines indicate 95% confidence limits at each time point.
† indicates differences between treatments that are clinically important.

In the example above for clinicians/researchers, a cross is used to indicate the time points where the differences are clinically important, and the meaning of this symbol is included in the figure legend.

Conveying Statistical Significance (for clinicians and researchers only)

Finally, while evidence suggests that many patients do not want statistical information included as they find it confusing, many clinicians and researchers were interested in statistical information. For this reason, recommendations regarding how to convey statistical significance only apply for PRO data display to clinicians/researchers.

The consensus-based recommendations are to include confidence intervals in all cases and note that p-values may also be appreciated.

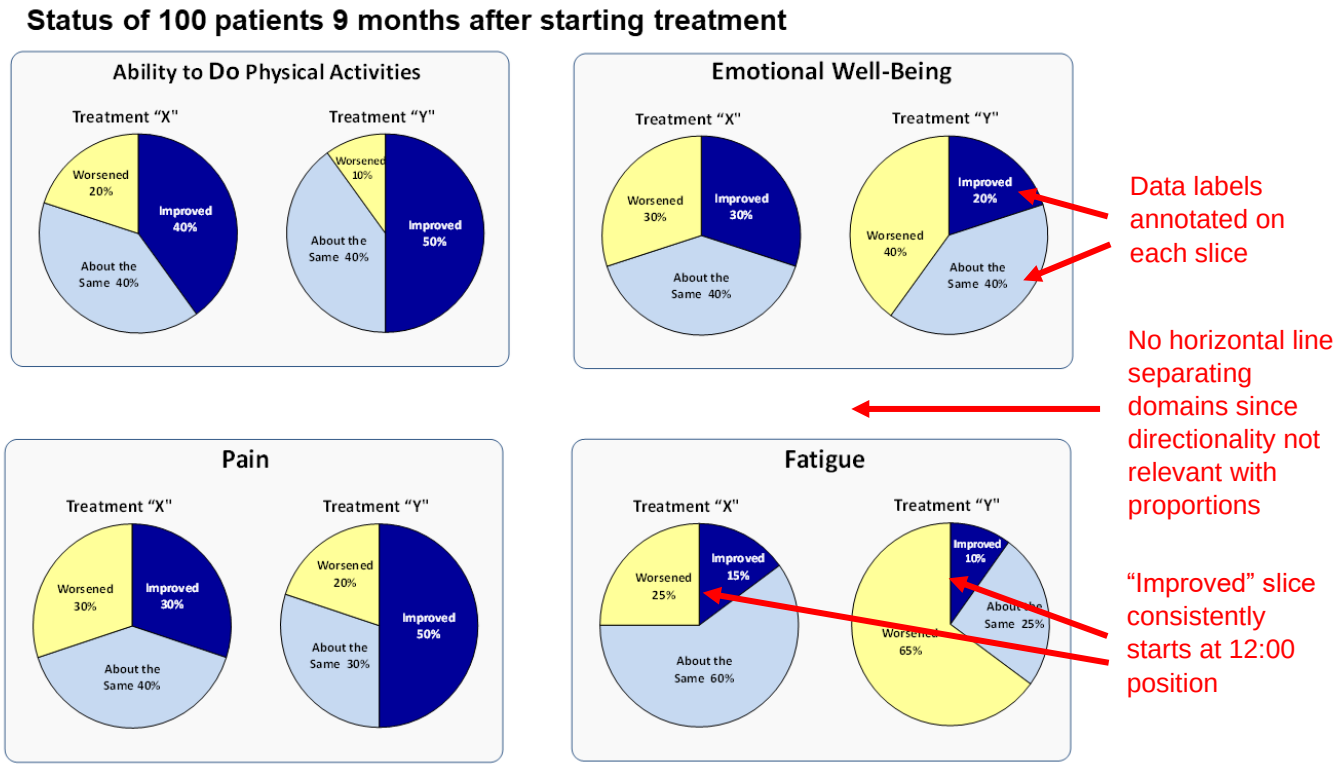


The example for clinicians and researchers above shows the confidence intervals indicating statistical significance at each time point, and a p-value for the overall difference between groups over time. Both the confidence limits and p-value are explained in the figure legend.

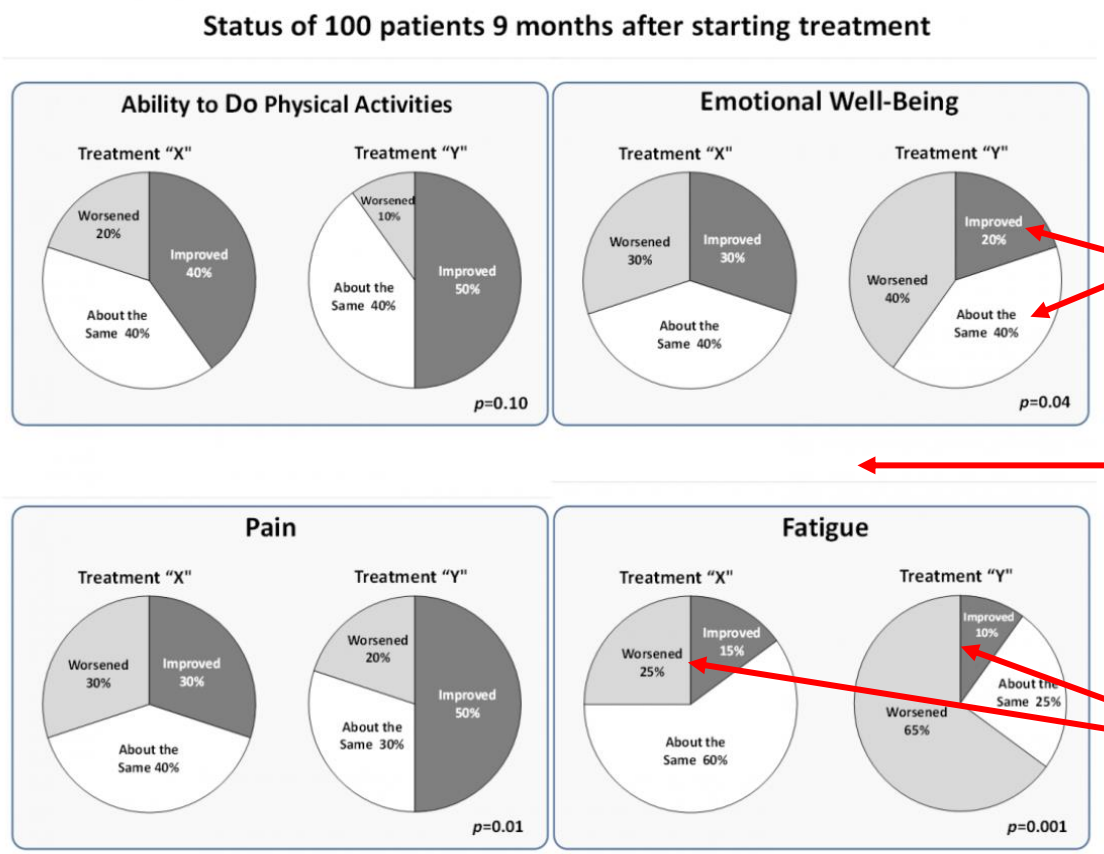
Proportions Changed

Finally, in some instances, clinical trials report the proportion of patients in each arm meeting a responder definition. That is, the proportion of patients who improved, stayed the same, or worsened by some change-score criterion. In cases where a proportion needs to be displayed, the recommendation is to use pie charts for PRO data display to patients. For clinicians and researchers, bar charts, pie charts, or stacked bar charts are reasonable options.

Notably, the evidence supports showing two pie charts with only three slices per pie chart. Showing more than two pie charts or showing more than three slices per pie chart may be more difficult to interpret.



These are example pie charts designed for patients, highlighting specific attributes that aid interpretation of the PRO data display. Each pie slice is labeled directly with the specific percentage and whether improvement, no change, or worsening is represented, negating the need for a legend. Also, the improved pie slice consistently starts at the 12:00 position.



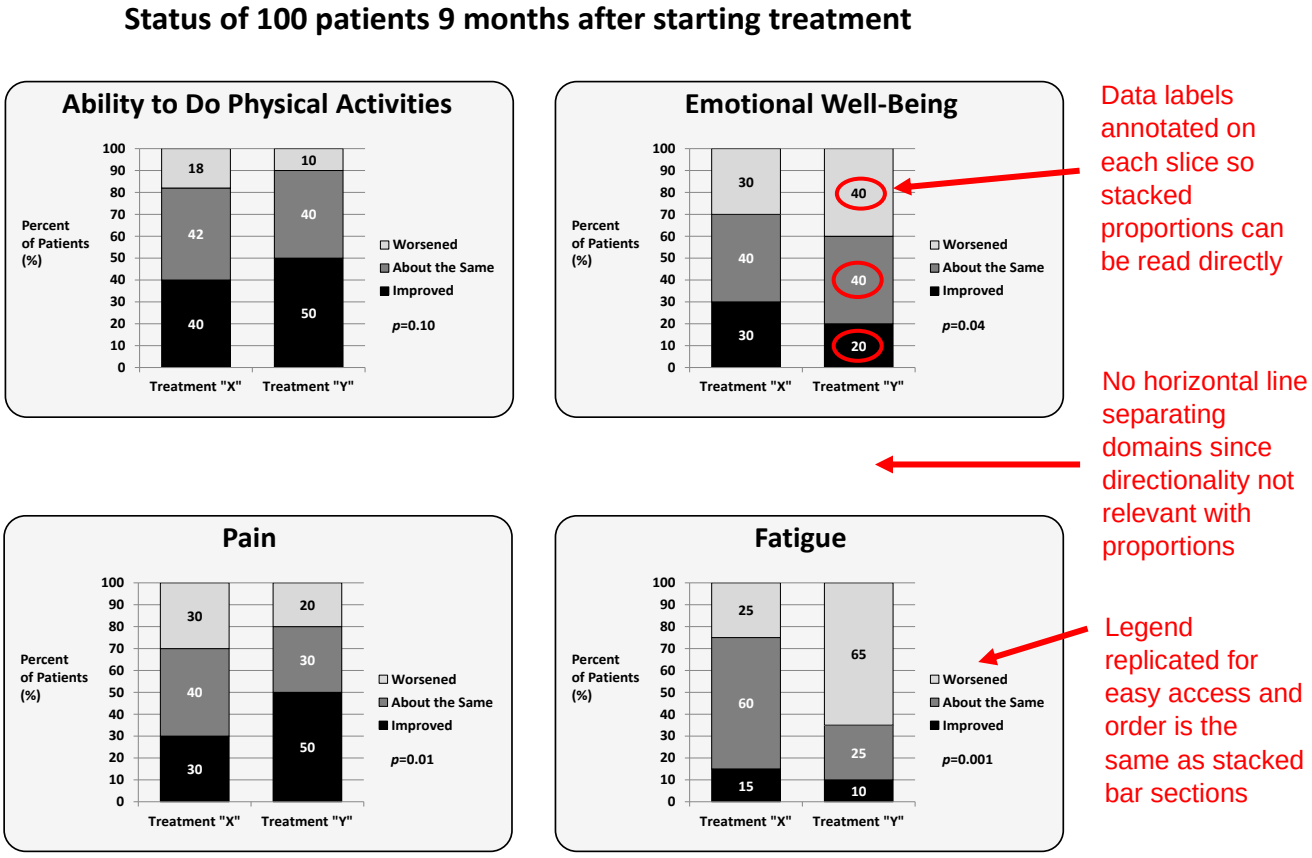
Data labels annotated on each slice

No horizontal line separating domains since directionality not relevant with proportions

"Improved" slice consistently starts at 12:00 position

Recommendations for clinicians are similar to those for patients, with the addition of p-values for statistically significant between-arm differences in proportions.

Given that directionality is not an issue with pie charts, there is no separation between the function and symptom domains.



As noted earlier, stacked bar-charts are also appropriate for displaying these responder data to clinicians and researchers. Note that, again, data labels are used to annotate the proportions, and an easily accessible legend is replicated and presented in the same order as the stacked bars.

Checklist for PRO Data Display: Research Results Presented to Patients

Issue	Consensus Statement	Notes/ comments
Directionality of PRO Scores	The Consensus Panel warned against trying to change current instruments–even if only how the data are displayed (e.g., "flipping the axes" where required for symptom scores so that lines going up are always better). PRO data presentation should avoid mixing score direction in a single display.	
Conveying Score Meaning	Descriptive labels (e.g., none/mild/moderate/severe) along the y-axis are helpful and should be used when data supporting their location on the scale are available. In addition to the descriptive y-axis labels, reference values for comparison populations should be considered for inclusion if they are available.	
Normed Scoring	PRO data presentation needs to accommodate instruments the way they were developed, with or without normed scoring. One can decide if/when to show the reference population norm visually (e.g., with a line on the graph), understanding that displaying it might provide additional interpretive value, but potentially at the cost of greater complexity. Comparison to the norm might be less relevant in the context where the primary focus is the choice between treatments. If a norm is displayed: • It is necessary to describe the reference population and label the norm as clearly as possible (recommend "average" rather than "norm") • It also requires deciding what reference population to show (to the extent that options are available). • It will need to be explained to patients that this normed population may not be applicable to a given patient.	
Clinically Important Differences	Patients may find information regarding clinically important differences between treatments to be confusing, but it is important for them to know what differences "matter" if they are going to make an informed decision.	
Proportions Changed	Pie charts are the preferred format for displaying proportion meeting a responder definition (improved, stable, worsened), so long as the proportion is also indicated numerically.	

Checklist for PRO Data Display: Research Results Presented to Clinicians/Researchers

Issue	Consensus Statement	Notes/ comments
Directionality of PRO Scores	PRO data presentation should avoid mixing score direction in a single display. In cases where this is not possible, authors should consider changing the directionality in the display to be consistent. There is a need for exceptionally clear labeling, titling, and other annotations.	
Conveying Score Meaning	Descriptive labels (e.g., none/mild/moderate/severe) along the y-axis are helpful and should be used when data supporting their location on the scale are available. In addition to the descriptive y-axis labels, reference values for comparison populations should be considered for inclusion if they are available.	
Normed Scoring	PRO data presentation needs to accommodate instruments the way they were developed, with or without normed scoring. One can decide if/when to show the reference population norm visually (e.g., with a line on the graph), understanding that displaying it might provide additional interpretive value, but potentially at the cost of greater complexity. Display of the norm might be less relevant in the context where the primary focus is the choice between treatments. If a norm is displayed: • It is necessary to describe the reference population and label the norm as clearly as possible (recommend "average" rather than "norm") • It also requires deciding what reference population to show (to the extent that options are available).	
Clinically Important Differences	Clinically important differences between treatments should be indicated with a symbol of some sort (described in a legend). The use of an asterisk is not recommended (as it is often used to indicate statistical significance). If there is no defined clinically important difference, that also needs to be in the legend and/or the text of the paper.	
Conveying Statistical Significance	The data suggest that clinicians and others appreciate p-values; however, the Consensus Panel recognizes a move away from reporting them (and toward the use of confidence limits to illustrate statistical significance). Regardless of whether p-values are reported, confidence intervals should always be displayed.	
Proportions Changed	Reasonable options include bar charts, pie charts, or stacked bar charts.	

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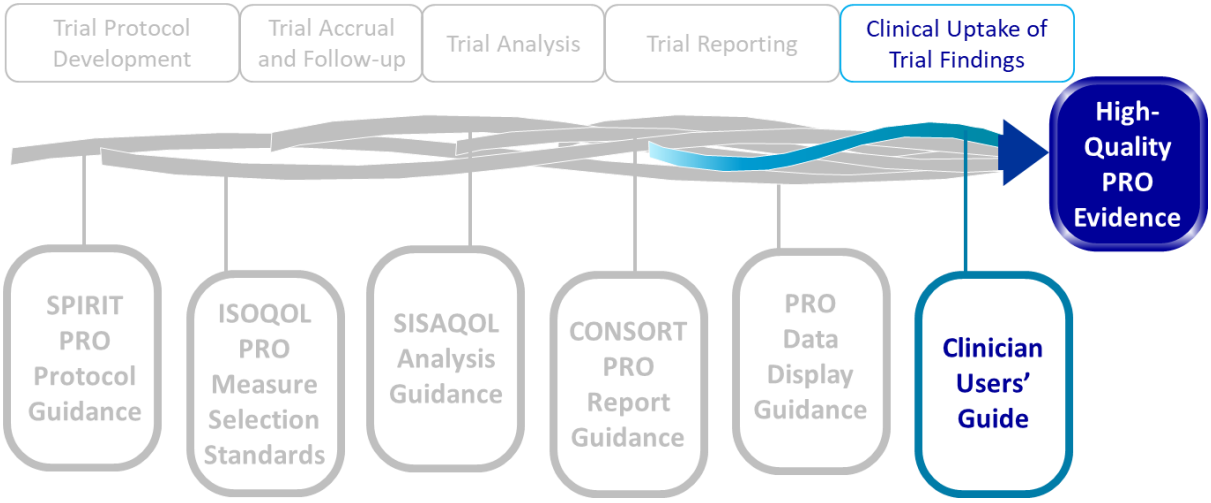
Chapter 7. Interpreting PRO Papers



Clinician's Checklist for Reading and Interpreting an Article that Includes PROs

The Clinician's Checklist for interpreting journal articles that include PROs provides clinicians who are not experts in PRO research with guidance on how to evaluate whether PRO findings are useful for their clinical practice.

This chapter summarizes the checklist items for clinicians to consider when evaluating articles with PROs.

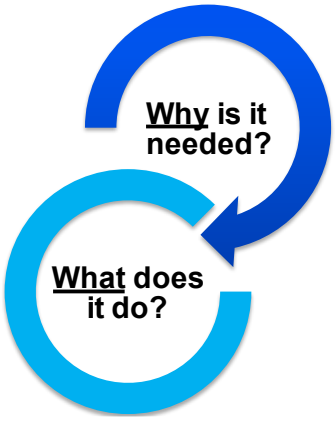
View Clinician Users' Guide for Evaluating Studies with PROs article

View Checklist for the Clinician Users' Guide for Evaluating Studies with PROs

References

Acknowledgements

Why is This Resource Needed?



To help clinicians assess the quality of PRO research studies and determine whether findings are useful for clinical practice

Provides a checklist to evaluate the quality of studies that use PROs

In order to use PRO results to inform patient care, clinicians need to be able to evaluate published literature that includes PROs. However, clinicians face some barriers in applying PRO findings in clinical practice, including:

- a lack of education and training on the measurement and interpretation of PROs
- the wide variety of PRO measures available
- variation in how PRO findings are reported in the literature

Objective of Resource

The objective of this resource is to help practicing clinicians apply results of clinical research studies that include PROs in their patient care by providing a brief checklist to help them review published research studies that include PROs.

Methods for Resource Development

This Clinician's Checklist builds on guidelines published by Guyatt et al. (1997). Key elements to consider when reading a published study using PROs include:

- Assessment strategy and study design
- Performance of the PRO tool
- Validity of results
- Context of results
- Generalizability to one's own clinical setting and patient population

Clinician's Checklist to Evaluate Studies Using PROs

The items in the clinician's checklist address the key elements mentioned above to help clinicians evaluate a study with PROs.

1. Was the PRO assessment strategy appropriate?

Consideration	Explanation
a. PRO hypothesis stated?	*A priori* hypothesis explicit for PROs
b. PRO measures described?	PRO measures used, and timing/follow-up of subjects
c. PRO content appropriate?	Investigators measured aspects of patients' lives that patients consider important PRO domains correspond to anticipated effects of disease and treatment All important aspects of patient-reported outcomes included

Elements that are important to the conceptualization and design of any clinical research study apply equally to studies that include PROs. The research question, study design, patient population, and primary/secondary outcomes should be clearly

identified within the scientific article. The research article should also clearly specify whether any primary and/or secondary outcomes are measured from the patient perspective, using PRO measures. A rationale for PRO assessment should be included and relevant PRO findings from previous studies should be described, especially if the PRO is a primary outcome. PRO hypotheses should be stated explicitly *a priori*.

The PRO measurement strategy should be described, including the timing of initial and follow-up assessments; this timing should be consistent with knowledge about the expected trajectory of patient outcomes over time in the patient population and, if possible, based on any information regarding the timing of treatment-related changes in patient health status. Pre-treatment "baseline" PRO assessment is critical and follow-up assessment time points should be appropriate to capture differences specified in the hypothesis.

The PRO measure content should correspond to the extent and breadth of problems observed in the patient population. To evaluate this, the reader should determine whether the PRO measure captures the expected effects of treatment on patient outcomes. Although there is often pressure to measure only symptoms and adverse effects in research studies, it is important to evaluate the "reach" of these symptoms to the patient's day-to-day functioning. For example, a phase II trial may have a more restricted focus on symptoms, but a phase III study should have a more comprehensive assessment of the effect of treatment on patient functioning. The reader should check to see whether important aspects of PROs have been omitted, because their omission could lead to incorrect conclusions.

2. Did they measure PROs effectively?

Consideration	Explanation
a. Evidence for reliability, validity?	The PRO instruments appear to work as intended; evidence of internal consistency and/or test retest reliability, and construct validity are cited or are well established
b. Were missing data handled appropriately?	Similar number of questionnaires completed by respondents in all treatment groups at every time point Missing data management strategy described Presence of data analysis plan for handling death, if frequent

When reading a research article, the reader should determine whether there is sufficient evidence cited to suggest that the PRO measures used are valid and reliable. The Methods section should cite evidence of the PRO measure's internal consistency reliability, test-retest reliability, and construct validity, ideally in the clinical population of interest. There should also be evidence that the questionnaire is responsive to expected changes in health status over time. In addition, the authors should describe how they handled missing data and report the extent and pattern of missing PRO data. If a substantial incidence of death was anticipated, the method of

handling death should be stated. The absence of any aforementioned elements should lead the reader to question the study findings, particularly if the conclusions suggest no treatment effect or no difference between groups.

3. Should I believe the results?

Consideration	Explanation
a. Internal validity	Findings established; observed effects likely to be caused by intervention If non-treatment factors affect PRO, risk adjustment needed

The PRO results should be clearly described. The study's internal validity should be established, addressing whether the observed effects likely result from the intervention. To do so, the authors should assess differences between treatment groups at baseline and ensure that known confounding variables have been measured. When non-treatment factors are known to affect PRO scores, a system for risk adjustment should be applied to ensure fair comparison between groups. Results should be presented for important patient subgroups that might be expected to show heterogeneity of treatment effects. Ideally, these subgroups should be identified *a priori* or results should be qualified as exploratory.

To evaluate the internal validity of a study, the reader should assess whether it seems likely that the observed results can be attributed to the intervention rather than to other factors, whether a risk adjustment strategy was used successfully, and finally, whether they believe the effects are clinically plausible.

4. Were the results placed in a clinical context?

Consideration	Explanation
a. Was the clinical meaning of results explained?	Magnitude of effect on PROs described Clinical importance of observed differences in PRO scores demonstrated
b. Will the results help me in caring for my patients?	Benefits and harms recognized and reconciled, including potential trade-offs between quality and quantity of life Description of what a clinician should do with the results; study information helps clinicians communicate with patients about treatment options; applicability of group results to individual patient

The clinical significance of PRO results must be discussed explicitly, including whether the observed change was large enough to be noticeable to the patient or to compel a treatment change. PROs can provide comprehensive information about

both positive and negative effects of disease and treatments. If an intervention has both positive and negative effects, the discussion should balance benefits and harms. This is especially important when there are trade-offs between quality and quantity of life, such as when a treatment extends life but decreases quality of life (e.g., toxic chemotherapy). Given a study's PRO results, it may or may not be obvious what management option a clinician would consider. If the article includes recommendations from the authors, this increases the likelihood that the study findings will be translated to practice change.

The reader should identify the magnitude of effect on the PROs and determine whether it is large enough to motivate changes in patient care. The reader should consider potential trade-offs involving the benefits and harms suggested by the study findings.

5. Do the results apply to my patients?

Consideration	Explanation
a. External validity to clinician's practice	Study population is similar enough to clinician's patient population to apply to practice

External validity of the findings is important to clinicians if they are going to engage in a dialogue with patients about treatment options. The reader should judge how well the study simulates clinical practice in general, and whether or not the results are generalizable to his or her own patient population. Ideally, study authors will address the generalizability of study results, including PROs, to help clinicians with this task.

Checklist for Clinicians for Evaluating Studies with PROs

Consideration	Explanation	Notes/ comments
1. Was the PRO assessment strategy appropriate?		
a. PRO hypothesis stated?	*A priori* hypothesis explicit for PROs	
b. PRO measures described?	PRO measures used, and timing/follow-up of subjects	
c. PRO content appropriate?	Investigators measured aspects of patients' lives that patients consider important PRO domains correspond to anticipated effects of disease and treatment All important aspects of patient-reported outcomes included	
2. Did they measure PRO effectively?		
a. Evidence for reliability and validity?	The PRO instruments appear to work as intended: evidence of internal consistency and/or test retest reliability, and construct validity are cited or are well established	
b. Were missing data handled appropriately?	Similar number of questionnaires completed by respondents in all treatment groups at every time point Missing data management strategy described Presence of data analysis plan for handling death, if frequent	
3. Should I believe the results?		
a. Internal validity	Findings established; observed effects likely to be caused by intervention If nontreatment factors affect PRO, risk adjustment used	
4. Were the results placed in clinical context?		
a. Was clinical meaning of results explained?	Magnitude of effect on PROs described Clinical importance of observed differences in PRO scores demonstrated	
b. Will the results help me in caring for my patients?	Benefits and harms recognized and reconciled, including potential trade-offs between quality and quantity of life Description of what a clinician should do with the results; study information helps clinician communicate with patients about treatment options; applicability of group results to an individual patient.	
5. Do the results apply to my patients?		
a. External validity to clinician's practice	Study population is similar enough to clinician's patient population to apply to practice	

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Acknowledgements

The SPIRIT-PRO Group

Group executive

Melanie Calvert, PhD, Chair[1]
Madeleine King, PhD, Co-chair[2]
Derek Kyte, PhD[1]
Rebecca Mercieca-Bebber, PhD[2]
Anita Slade, PhD[1]
An-Wen Chan, MD, DPhil[3]

1. University of Birmingham, UK
2. University of Sydney, Australia
3. University of Toronto, Canada

Group members

Amanda Hunn[1]
Andrew Bottomley, PhD[2]
Antoine Regnault, PhD[3]
Carolyn Ells, PhD[4]
Daniel O'Connor, PhD[5]
Dennis Revicki, PhD[6]
Donald Patrick, PhD[7]
Doug Altman, DSc[8]
Ethan Basch, MD[9]
Galina Velikova, PhD[10]
Gary Price, Patient Partner, UK
Heather Draper, PhD[11]
Jane Blazeby, MD[12]
Jane Scott, PhD[13]
Joanna Coast, PhD[12]
Josephine Norquist, PhD[14]
Julia Brown, MSc[10]
Kirstie Haywood, PhD[11]
Laura-Lee Johnson, PhD[15]
Lisa Campbell, MD[5]
Lori Frank, PhD[16]
Maria von Hildebrand, Patient Partner, UK
Michael Brundage, MD[17]
Michael Palmer, MSc[17]
Paul Kluetz, MD[15]
Richard Stephens[18]
Robert M Golub, MD[19]
Sandra Mitchell, PhD[20]
Trish Groves, MRCPsych[21]

1, Health Research Authority (HRA), UK ;
2, European Organization for Research and Treatment of Cancer (EORTC), Belgium;
3, Modus Outcomes, France;
4, Panel on Research Ethics (On behalf of the: Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada),Canada;
5, Medicines and Healthcare products Regulatory Agency (MHRA), UK;
6, Evidera, USA;
7, University of Washington, USA;
8, University of Oxford, UK;
9, University of North Carolina, USA;
10, University of Leeds, UK;
11, University of Warwick, UK;
12, University of Bristol, UK;
13, Janssen Global Services, Johnson and Johnson, UK;
14, Merck Sharp & Dohme Corporation, USA;
15, Food and Drug Administration (FDA), USA;
16, Patient-Centered Outcomes Research Institute (PCORI), USA;
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19, JAMA, USA;
20, National Cancer Institute, USA;
21, British Medical Journal (BMJ), UK

ISOQOL Best Practices for PROs in Randomized Clinical Trials PROtocol Checklist Taskforce

Antonia Bennett, PhD, University of North Carolina, USA;
Jane Blazeby, MD, University of Bristol, UK;
Andrew Bottomley, PhD, European Organization for Research and Treatment of Cancer (EORTC), Belgium;
Heather Draper, PhD, University of Warwick, UK;
Amylou Dueck, PhD, Mayo Clinic, USA;
Kirstie Haywood, PhD, University of Warwick, UK;
Derek Kyte, PhD, University of Birmingham, UK;
Rebecca Mercieca-Bebber, University of Sydney, Australia;
Sandra Mitchell, PhD, National Cancer Institute, USA;
Carol Moinpour, PhD, Fred Hutchinson Cancer Research Center, USA;
Josephine Norquist, PhD, Merck Sharp & Dohme Corporation, USA,
David Osoba MD, University of British Columbia, Canada;
Michael Palmer Queen's University MSc, Canada;
Jennifer Petrillo PhD, Novartis Pharmaceuticals, USA;
Andreas Pleil PhD, Pfizer, USA;
Antoine Regnault, PhD, Modus Outcomes, France;
Dennis Revicki, PhD, Evidera, USA;
Lothar Tremmel, PhD Incyte Corporation, USA;
Lari Wenzel, PhD, University of California, Irvine, USA

…and to ISOQOL members that completed the stakeholder survey

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The ISOQOL Scientific Advisory Task Force (SATF)

Neil Aaronson, PhD
University of Amsterdam
Sara Ahmed, PhD
McGill University
Michael Brundage, MD
Queens University
Zeeshan Butt, PhD***
Northwestern University
David Cella, PhD
Northwestern University
Peter Fayers, PhD
University of Aberdeen
David Feeny, PhD
University of Alberta
Richard Gershon, PhD
Northwestern University
Joanne Greenhalgh, PhD
University of Leeds
Ron Hays, PhD
University of California – Los Angeles
Pamela Hinds, PhD
National Children's Hospital, Wash. DC
William Lenderking, PhD
United BioSource Corporation
Jessica Lyons, MS
University of North Carolina
Lori McLeod, PhD
RTI Health Solutions
Carol Moinpour, PhD
Fred Hutchinson Cancer Research Center
Bryce B. Reeve, PhD
University of North Carolina
Dennis Revicki, PhD
United BioSource Corporation
Carolyn Schwartz, ScD
DeltaQuest Found. / Tufts Univ. Med. Sch.
Claire Snyder, PhD
Johns Hopkins University
Caroline Terwee, PhD
VU University Medical Center
Galina Velikova, MD, PhD
University of Leeds
Albert Wu, MD
Johns Hopkins University
Kathleen Wyrwich, PhD
United BioSource Corporation

The SISAQOL Consortium

Ethan Basch[1]
Andrew Bottomley[2]
Melanie Calvert[3]
Alicyn Campbell[4]
Charles Cleeland[5]
Kim Cocks[6]
Corneel Coens[2]
Laurence Collette[2]
David Collingridge[7]
Nancy Devlin[8]
Lien Dorme[2]
Amylou Dueck[9]
Hans-Henning Flechtner[10]
Carolyn Gotay[11]
Ingolf Griebsch[12]
Mogens Grønvold[13]
Laura Lee Johnson[14]
Madeleine King[15]
Paul Kluetz[14]
Michael Koller[16]
Daniel C Malone[17]
Francesca Martinelli[2]
Sandra A Mitchell[18]
Jammbe Z Musoro[2]
Daniel O' Connor[19]
Kathy Oliver[20]
Madeline Pe[2]
Elisabeth Piault-Louis[21]
Martine Piccart[22]
Chantal Quinten[23]
Jaap C Reijneveld[24]
Christoph Schürmann[25]
Jeff Sloan[26]
Ashley Wilder Smith[18]
Katherine M Soltys[27]
Rajeshwari Sridhara[14]
Martin Taphoorn[28]
Galina Velikova[29]

[1]Lineberger Comprehensive Cancer Center; University of North Carolina, North Carolina, USA
[2]European Organisation for Research and Treatment of Cancer, Belgium
[3]Centre for Patient Reported Outcomes Research, University of Birmingham, UK
[4]Patient Relevant Evidence, San Francisco, USA
[5]Dept. Of Symptom Research, MD Anderson Cancer Center; University of Texas, Texas, USA
[6]Adelphi Values, UK
[7]The Lancet Oncology, UK
[8]University of Melbourne, Australia
[9]Alliance Statistics and Data Center; Mayo Clinic, Arizona, USA
[10]Clinic for Child and Adolescent Psychiatry and Psycohtherapy; University of Magdeburg, Germany
[11]School of Population and Public Health; University of British Columbia, British Columbia, Canada
[12]Boehringer-Ingelheim, Germany
[13]Dept. Of Public Health; Bispebjerg Hospital, University of Copenhagen, Denmark
[14]US Food and Drug Administration, Maryland, USA
[15]School of Psychology and Sydney Medical School; University of Sydney, Australia
[16]Center for Clinical Studies; University Hospital Regensburg, Germany
[17]College of Pharmacy, University of Arizona, Arizona, USA
[18]National Cancer Institute, Maryland, USA
[19]Medicines and Healthcare products Regulatory Agency, UK
[20]International Brain Tumour Alliance, UK
[21]Genentech, San Francisco, USA
[22]Institut Jules Bordet; Université Libre de Bruxelles, Belgium
[23]European Centre for Disease Prevention and Control, Sweden
[24]VU University Medical Center, Dept. of Neurology & Brain Tumor Center, The Netherlands
[25]Institute for Quality and Efficiency in Health Care, Germany
[26]Alliance Statistics and Data Center; Mayo Clinic, Minnesota, USA
[27]Health Canada, Ontario, Canada
[28]Leiden University/Haaglanden Medical Center, The Netherlands
[29]Leeds Institute of Cancer and Pathology; University of Leeds, St. James's Hospital, UK

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CONSORT-PRO

CONSORT PRO Executive:

Prof. Michael Brundage (chair), Director, Cancer Care and Epidemiology, Cancer Research Institute, Queen's University, Canada

Prof. Melanie Calvert, Director, Centre for Patient Reported Outcomes Research, and Director, Birmingham Health Partners Centre for Regulatory Science and Innovation, U. of Birmingham, UK

Prof. Jane Blazeby, MRC ConDuCT Hub for Trials Methodology Research, School of Social and Community Medicine, University of Bristol, UK

Prof. Doug Altman, Director of Centre for Statistics in Medicine, University of Oxford, UK

Prof. Dennis Revicki, Outcomes Research, United BioSource Corporation, Bethesda, MD, USA

Prof. David Moher, Clinical Epidemiology Program, Ottawa Hospital Research Institute, Canada

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Collaborators:

International Society for Quality of Life Research

CONSORT Executive & EQUATOR Network

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University of Birmingham, UK, Queens University, Canada, University of Bristol, UK, University of Ottawa, Canada, University of Oxford, UK, United BioSource Corporation, Bethesda, MD, USA

Survey participants including: ISPOR, MRC HTMR, NIHR Research design service, SCT, European Clinical Trials Units, Journal Editors, Policy Makers

Meeting participants

PRO Graphical Display

PROJECT TEAM

Claire Snyder, PhD
Michael Brundage, MD, MSc
Elissa Bantug, MHS
Katherine Smith, PhD
Bernhard Holzner, PhD

STAKEHOLDER ADVISORY BOARD

Daniel Weber
Ethan Basch, MD
Neil Aaronson, PhD
Bryce Reeve, PhD
Galina Velikova, BMBS(MD), PhD
Andrea Heckert, PhD, MPH
Eden Stotsky-Himelfarb
Cynthia Chauhan
Vanessa Hoffman, MPH
Patricia Ganz, MD
Lisa Barbera, MD, MPA

INVITED PARTICIPANTS

Elizabeth Frank
Mary Lou Smith, JD
Arturo Durazo
Judy Needham
Shelley Fuld Nasso
Robert Miller, MD
Tenbroeck Smith, MA
Deborah Struth, MSN, RN, PhD(c)
Alison Rein, MS
Andre Dias, PhD
Charlotte Roberts, MBBS, BSc
Nancy Smider, PhD
Gena Cook
Jakob Bjorner, MD, PhD
Holly Witteman, PhD
James G. Dolan, MD
Jane Blazeby, MD, MSc
Robert M. Golub, MD
Christine Laine, MD, MPH
Scott Ramsey, MD, PhD

Funded by the Patient-Centered Outcomes Research Institute

Clinician Checklist

Collaborators: Albert W. WU, MD, FACP; Anna N. Bradford, PhD, MSW, LCSW; Vic Velanovich, MD; Mirjam A.G. Sprangers, PhD; Michael Brundage, MD, FRCP, MSc; and Claire Snyder, PhD

This article was reviewed by members of the International Society for Quality of Life Research (ISOQOL) and is endorsed by the ISOQOL Board of Directors.