Analyzing Patient-Reported Outcomes from Clinical Trials: Insights for Biostatisticians from **The PROTEUS Consortium**

Funded by the Patient-Centered Outcomes Research Institute, Genentech, and Pfizer

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Professor Emeritus
The University of Sydney, Australia

Overview

- Challenges that patient-reported outcomes (PROs) raise for biostatisticians
- Relevance of PROTEUS to biostatisticians

Patient-Reported Outcomes (PROs)

"A PRO is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else."

In other words:

Patients' reports of how they feel, function, live their lives, and survive

https://www.fda.gov/media/77832/download

Haywood et al. DOI 10.1007/978-981-10-4068-9

https://www.fda.gov/about-fda/clinical-outcome-assessment-coa-frequently-asked-questions#COADefinition

Challenges that PROs Raise for Biostatisticians

- PRO data are complex
  - Multidimensional – e.g. different symptoms, aspects of function, health-related quality of life
  - Longitudinal – repeated measures
  - Missing PRO data are common, informative missing data create challenges to interpretation
- Protocols and statistical analysis plans often lack key detail on PROs
  - Unclear PRO objectives
  - Various approaches to analyzing data, including missing data; which ‘best’?
  - Inconsistency in terminology regarding statistical methods/models and missing data, create challenges to communication

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Got it! So what is PROTEUS and why is it relevant to me as a biostatistician?

Patient-Reported Outcomes Tools: Engaging Users & Stakeholders

TheProteusConsortium.org

The PROTEUS Consortium

- **OBJECTIVE**

  Ensure that patients, clinicians, and other decision-makers have high-quality PRO data from clinical trials to make the best decisions they can about treatment options

- **APPROACH**

  Partner with key stakeholder groups to disseminate and implement tools that have been developed to optimize the use of PROs in clinical trials

- **TheProteusConsortium.org** for more information and resources

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The PROTEUS Consortium's Objective

- Ensure that patients, clinicians, and other decision-makers have high-quality PRO data from clinical trials

- Requires a **SMART** approach:

  Specifying the PRO methods appropriately

  Measuring the PROs effectively

  Analyzing the PRO data properly

  Reporting the PRO results clearly

  Translating the PRO findings in practice

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Relevance to Biostatisticians

- Biostatisticians play a key role in trial protocol design and statistical analysis planning, and in analysis, reporting and visualization of the data and results
- Biostatisticians are therefore key stakeholders for implementing the six tools recommended by the PROTEUS Consortium
- The remainder of this slide set introduces these six tools and summarizes the components relevant to biostatisticians
- For further explanation about each tool, visit: **TheProteusConsortium.org**

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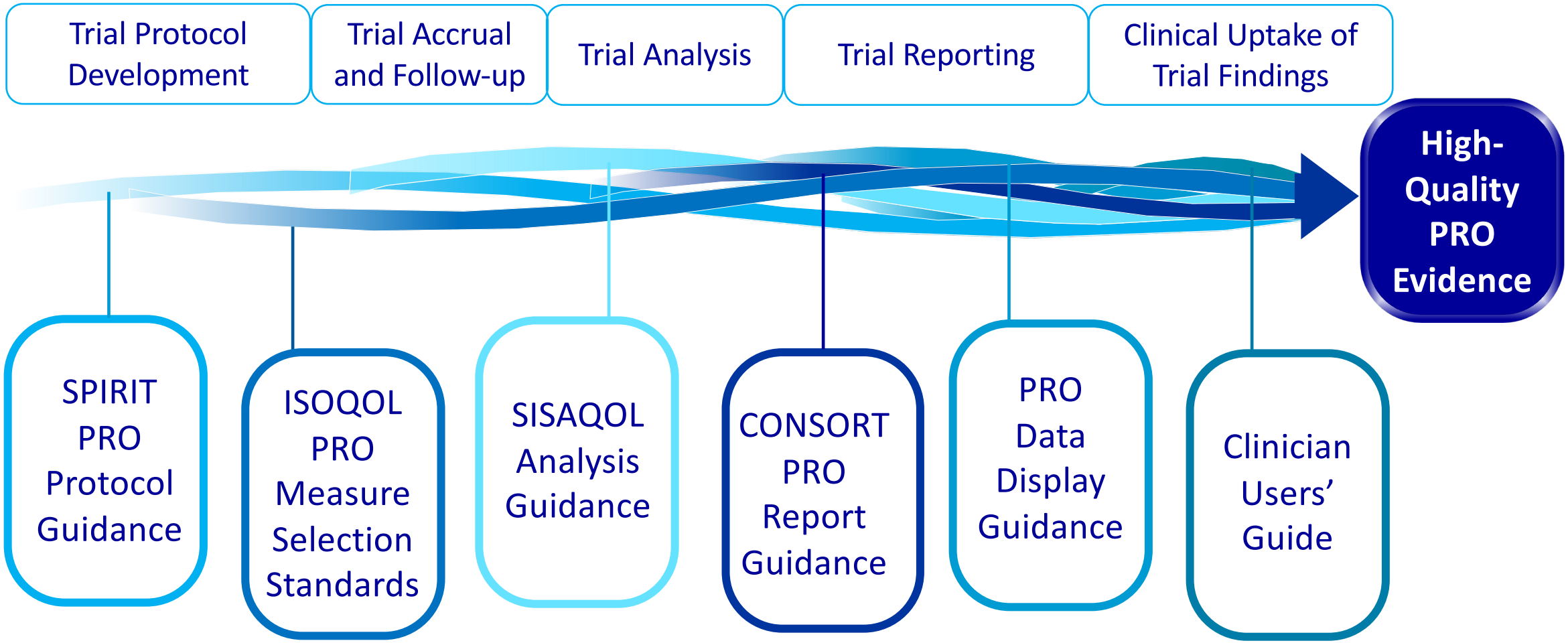
PROTEUS Roadmap



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“6 Tools-1 Paper Paper”

Short Communication

CLINICAL TRIALS

Clinical Trials
1–8


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SAGE

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

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

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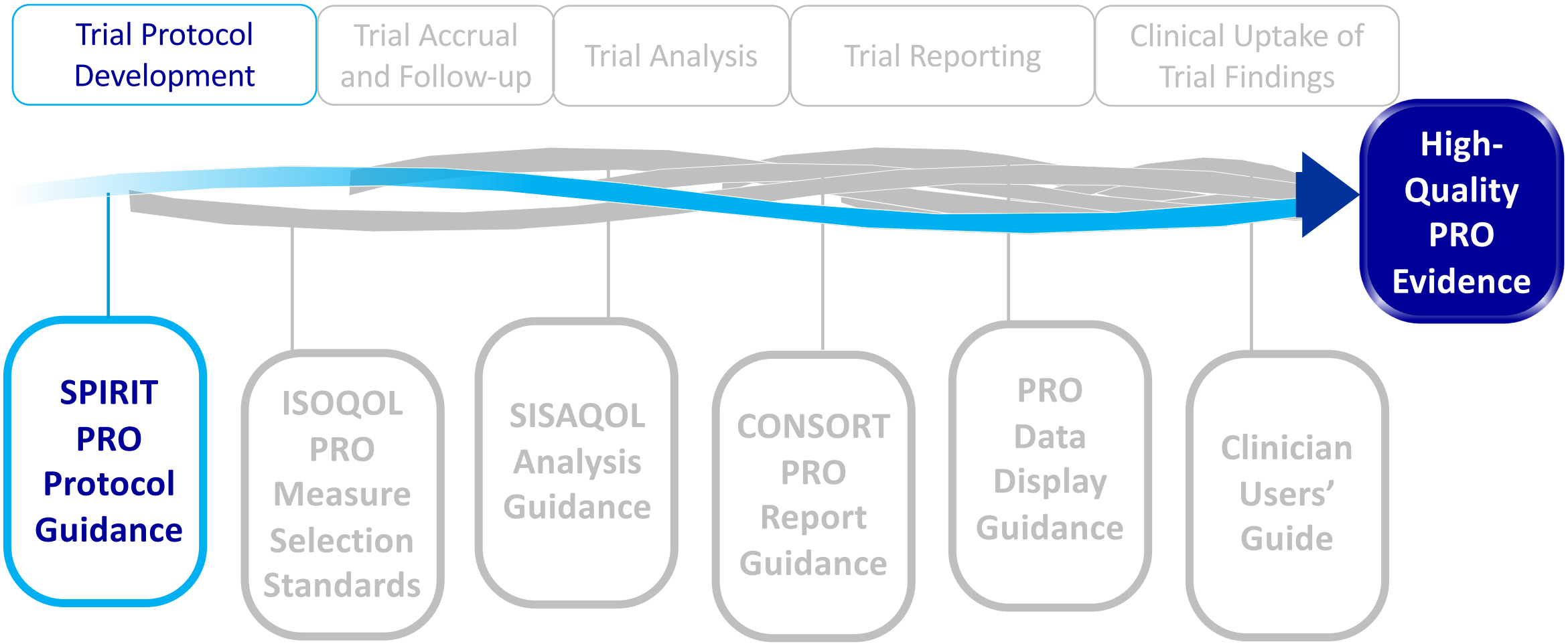
Tools Relevant to Biostatisticians in black

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

Specifying PRO Methods Appropriately



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Clinical Review & Education

JAMA | Special Communication

Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols
The SPIRIT-PRO Extension

Melanie Calvert, PhD; Derek Kyte, PhD; Rebecca Mercieca-Bebber, PhD; Anita Slade, PhD; An-Wen Chan, MD, DPhil; Madeleine T. King, PhD; and the SPIRIT-PRO Group

IMPORTANCE 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. The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement was published in 2013 and aims to improve the completeness of trial protocols by providing evidence-based recommendations for the minimum set of ite
not provide PRO-specific guidance.

OBJECTIVE To develop international, consensus-based, PRO-
(the SPIRIT-PRO Extension).

Editorial page 450

Supplemental content

CME Quiz at jamanetwork.com/learning

Calvert et al, JAMA 2018, 319(5), 483-494

Open access Communication

BMJ Open SPIRIT-PRO Extension explanation and elaboration: guidelines for inclusion of patient-reported outcomes in protocols of clinical trials

Calvert et al, BMJ Open 2021;11:e045105.

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Use SPIRIT-PRO with General Protocol Writing Guidance

RESEARCH AND REPORTING METHODS | Annals of Internal Medicine

SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials

An-Wen Chan, MD, DPhil; Jennifer M. Tetzlaff, MSc; Douglas G. Altman, DSc; Andreas Laupacis, MD; Peter C. Gøtzsche, MD, DrMedSci; Karmela Krleža-Jerić, MD, DSc; Asbjørn Hróbjartsson, PhD; Howard Mann, MD; Kay Dickersin, PhD; Jesse A. Berlin, ScD; Caroline J. Doré, BSc; Wendy R. Parulekar, MD; William S.M. Summerskill, MBBS; Trish Groves, MBBS; Kenneth F. Schulz, PhD; Harold C. Sox, MD; Frank W. Rockhold, PhD; Drummond Rennie, MD; and David Moher, PhD

The protocol of a clinical trial serves as the foundation for study planning, conduct, reporting, and appraisal. However, trial protocols and existing protocol guidelines vary greatly in content and quality. This article describes the systematic development and scope of SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013, a guideline for the minimum content of a clinical trial protocol.

The 33-item SPIRIT checklist applies to protocols for all clinical trials and focuses on content rather than format. The checklist recommends a full description of what is planned; it does not prescribe how to design or conduct a trial. By providing guidance for key content, the SPIRIT recommendations aim to facilitate the drafting of high-quality protocols. Adherence to SPIRIT would also enhance the transparency and completeness of trial protocols for the benefit of investigators, trial participants, patients, sponsors, funders, research ethics committees or institutional review boards, peer reviewers, journals, trial registries, policymakers, regulators, and other key stakeholders.

Ann Intern Med. 2013;158:200-207. www.annals.org
For author affiliations, see end of text.
This article was published at www.annals.org on 8 January 2013.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

Standard Protocol Items: Recommendations for Interventional Trials

www.spirit-statement.org

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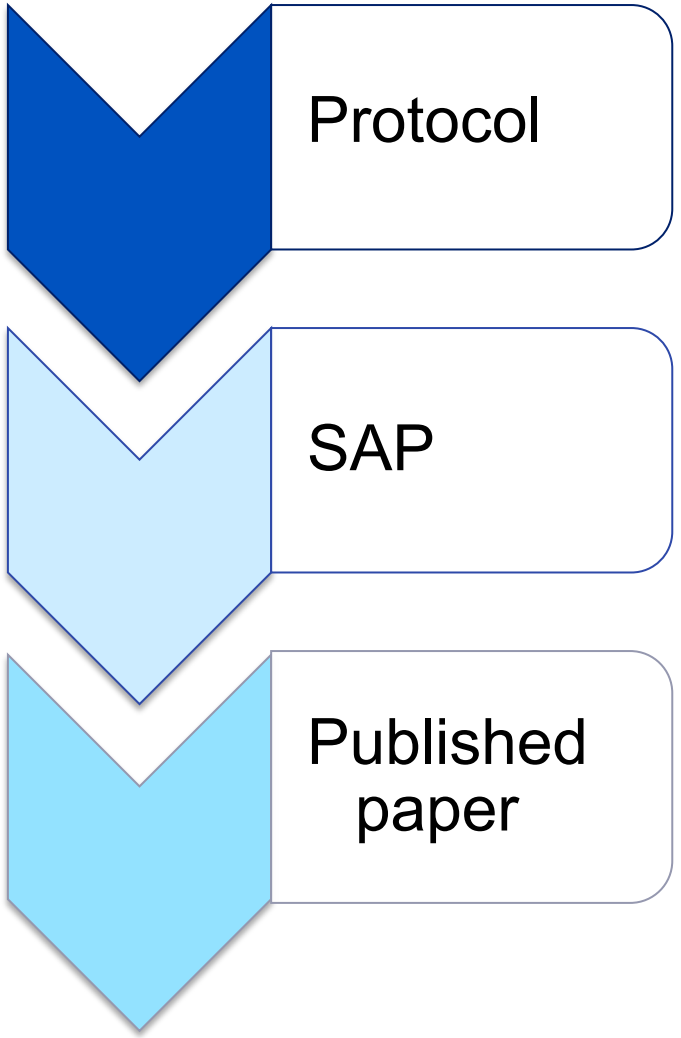
What SPIRIT-PRO Adds to SPIRIT 2013

- Protocols can lack key PRO content
- PRO data quality may be affected
- SPIRIT 2013 does not provide PRO-specific guidance

- Key aspects of statistical analysis plans (SAP) will be drawn from the protocol (e.g., objectives)
- Other issues relevant to SAP are included in SPIRIT-PRO

- Published PRO results can also lack key PRO content; ensuring the protocol is complete may improve this



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SPIRIT-PRO Items

Items in black are relevant to biostatisticians

- PRO-specific research question, rationale, relevant previous findings
- PRO-specific objectives or hypotheses
- PRO-specific eligibility criteria (if any)
- PRO concepts/domains and related analysis metric used to evaluate the intervention
- PRO measure description and psychometrics
- Data collection plan
- Available language versions
- Justification for proxy reporting (if relevant)
- Statistical methods, including any plans for addressing multiplicity and missing data
- Whether PRO data will be monitored to inform care

SPIRIT Item 7 - Objectives

SPIRIT 2013:

Specific objectives or hypotheses.

PRO Extension 2018:

State specific PRO objectives or hypotheses (including relevant PRO concepts/domains).

Explanation:

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.

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SPIRIT Item 12 - Outcomes

SPIRIT 2013:

Primary, secondary, and other outcomes, including the specific measurement variable, analysis metric, method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended.

PRO Extension 2018:

Specify the PRO concepts/ domains used to evaluate the intervention (eg, overall HRQOL, specific domain, specific symptom).

For each of these, specify the analysis metric (eg, change from baseline, final value, time to event) and the principal time point or period of interest.

Explanation:

These should closely align with the trial objectives and hypotheses.

Reduces risk of multiple statistical testing.

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SPIRIT Item 13 - Participant Timeline

SPIRIT 2013:

Time schedule of enrollment, interventions (including any run-ins and washouts), assessments, and visits for participants.

A schematic diagram is highly recommended.

PRO Extension 2018:

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:

Will assist staff and may help reduce missing data.

Pre-randomization helps ensure unbiased baseline assessment; if eligibility criterion, ensures data completeness.

Time windows ensure that PROs capture the effect of the clinical event(s) of interest.

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SPIRIT Item 14 - Sample Size

SPIRIT 2013:

Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations.

PRO Elaboration 2018:

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:

If PROs are primary: ideally, specify criteria for clinical significance (eg, minimal important difference) if known.

If PROs are secondary, specify whether the sample size provides sufficient power to test the principal PRO hypotheses.

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SPIRIT Item 18a - Data Collection Methods

PRO Extension (i) 2018:

Justify the PRO instrument, describe domains, no. items, recall period, instrument scaling/scoring (eg, 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.

Consider 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.

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SPIRIT Item 18b - Data Collection Methods

PRO Extension (i) 2018:

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

Explanation:

Missing data are particularly problematic for PROs:

- PRO data cannot be obtained retrospectively
- reduce effective sample size hence power for PRO analyses
- potential source of bias because participants with the poorest outcomes are often those who do not complete planned PRO assessments

** Not all missing PRO data are avoidable: patients have the right to decline questionnaire completion (e.g. feeling too unwell); deceased cannot complete*

Avoidable reasons: e.g. staff/patient oversight, technical errors/failure

Strategies: Avoid/manage oversight and errors. Collect and review reasons for missed assessments during trial conduct (this information is also valuable during analysis and write-up). Intervene to remediate where possible.

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Mercieca-Bebber et al , BMJ Open 2016;6(6):e010938.

SPIRIT 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:

Several domains and time points implies multiple hypothesis testing, inflates the probability of false-positive results (type I error).

Pre-specifying key PRO domain(s) and time point(s) helps (Item 12).

Protocol should either fully address or summarize and refer to where details can be found, eg, SAP.

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SPIRIT Item 20c - Statistical Methods

SPIRIT 2013

Definition of analysis population relating to protocol non-adherence and any statistical methods to handle missing data (eg, multiple imputation).

PRO Elaboration

State how missing data will be described and outline the methods for handling missing items or entire assessments (eg, approach to imputation and sensitivity analyses).

Explanation:

2 levels of missing PRO data:

1) Some items in a questionnaire are missed - whether/how these are imputed is specified in the instrument's scoring algorithm.

2) Entire PRO assessment missed - analysis requires assumptions about why those data were missing (ie, the missing data mechanism).

- The protocol should acknowledge and summarize these issues, with full details provided in the statistical analysis plan.

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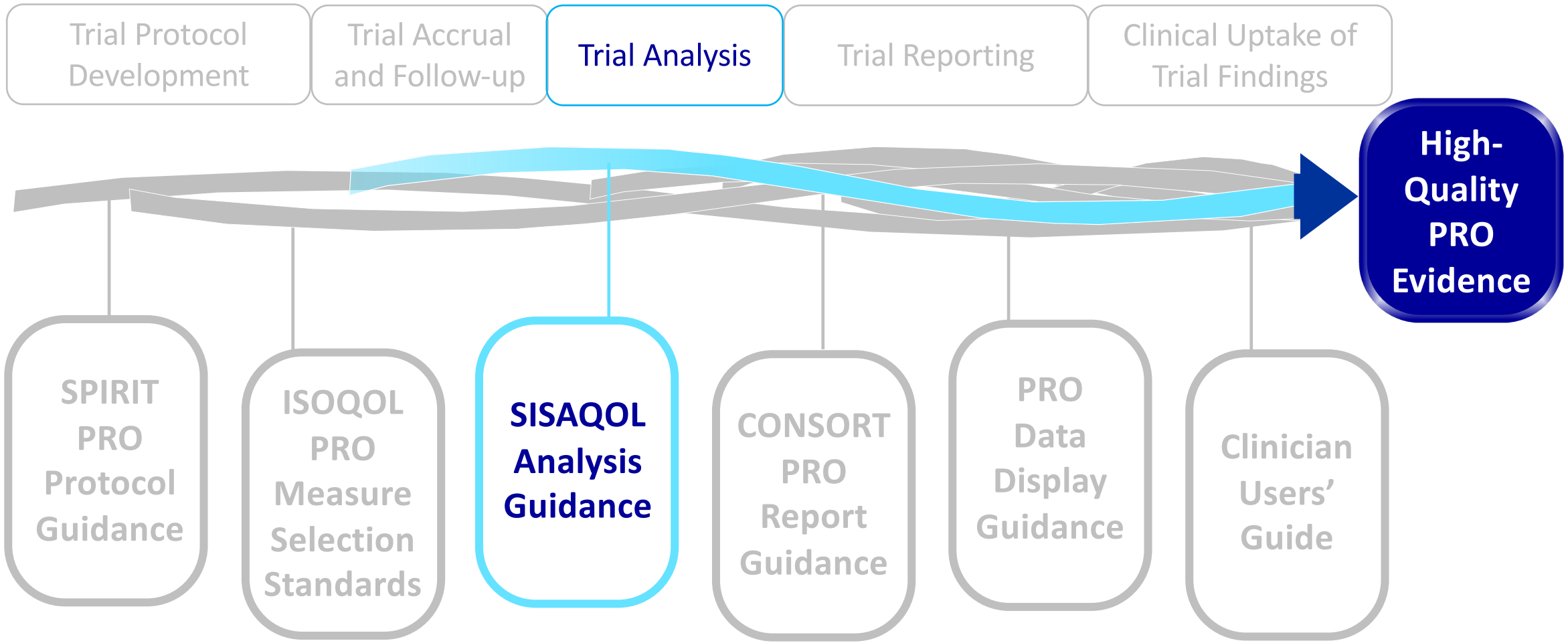
Analyzing PRO Data Properly



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What is SISAQOL?

- **S**etting **I**nternational **S**tandards in **A**nalyzing Patient-Reported Outcomes and **Q**uality **o**f **L**ife Endpoints Data
- SISAQOL guidance aims to improve the standards for the statistical analysis of PROs
- International multi-stakeholder consortium
- Current Focus: randomized clinical trials (RCT) in oncology

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SISAQOL

SISAQOL 2020 Guidance

International standards for the analysis of quality-of-life and patient-reported outcome endpoints in cancer randomised controlled trials: recommendations of the SISAQOL Consortium

Corneel Coens, Madeline Pe*, Amylou C Dueck, Jeff Sloan, Ethan Basch, Melanie Calvert, Alicyn Campbell, Charles Cleeland, Kim Cocks, Laurence Collette, Nancy Devlin, Lien Dorme, Hans-Henning Flechtner, Carolyn Gotay, Ingolf Griebsch, Mogens Groenvold, Madeleine King, Paul G Kluetz, Michael Koller, Daniel C Malone, Francesca Martinelli, Sandra A Mitchell, Jammbe Z Musoro, Daniel O'Connor, Kathy Oliver, Elisabeth Piault-Louis, Martine Piccart, Chantal Quinten, Jaap C Reijneveld, Christoph Schürmann, Ashley Wilder Smith, Katherine M Soltys, Martin J B Taphoorn, Galina Velikova, Andrew Bottomley; for the Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data Consortium*

Patient-reported outcomes (PROs), such as symptoms, function, and other health-related quality-of-life aspects, are increasingly evaluated in cancer randomised controlled trials (RCTs) to provide information about treatment risks, benefits, and tolerability. However, expert opinion and critical review of the literature showed no consensus on optimal methods of PRO analysis in cancer RCTs, hindering interpretation of results. The Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data Consortium was formed to

Lancet Oncol 2020; 21: e83-96

*Joint first authors

European Organisation for Research and Treatment of Cancer, Brussels, Belgium

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Coens, et al Lancet Oncol 2020, 21, e83-96

SISAQOL

SISAQOL 2020 Guidance

All components are relevant to biostatisticians

- A taxonomy of research objectives is provided to ensure PRO objectives are well defined.
- Best-practice statistical methods are recommended for time to event, intensity of event at time t, proportion of patients with event at time t, and overall PRO score over time.
- A standardized definition for available data rate and completion rate is given.
- Missing data is acknowledged as problematic and should be prevented. Reasons for missing data need to be collected to better understand the underlying missing data mechanism.

Taxonomy of Research Objectives

Aspect of objective	Options
High-level	confirmatory, exploratory/descriptive
Between-arm comparison	superiority, equivalence/non-inferiority
Expectation within-arm	improvement, worsening, overall effect
Endpoint	- mean PRO scores, at specified times or overall - time to improvement/worsening - proportion of responders at time t

- A research objective should be stated for each PRO domain of interest
- A priori hypotheses are required for confirmatory objectives, but not for exploratory/descriptive objectives

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Endpoints Link to Statistical Methods

PRO Endpoint	Statistical Method
Mean PRO scores - at specified times, overall (over all times)	Linear mixed models (time as discrete)
Time to improvement/worsening	Cox proportional hazards
% improved/stable/worsened	Logistic mixed model

- Correction for multiple testing needed, i.e. if there are multiple PRO domains of interest (e.g., specific symptoms, aspects of functioning)
- Adjustment for covariates should include baseline PRO values

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Missing Data: Standardizing Terminology

- PRO data is missing if data would be meaningful for the analysis of a given research objective but were not available for any reason

- Therefore: PRO study population ≠ PRO analysis population
  - PRO study population: all patients who consented to and were eligible to participate in the PRO data collection
    (ITC: intention-to collect population)
  - PRO analysis population: all patients who will be included in the primary PRO analysis

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Missing Data: Standardizing Terminology

Missing data rates:

- The available data rate (a fixed denominator rate):

$$\frac{Nbr\ of\ patients\ submitting\ valid\ PRO\ assessment\ at\ time\ t}{Number\ of\ patients\ in\ PRO\ study\ population}$$

- The completion rate (a variable denominator rate):

$$\frac{Nbr\ of\ patients\ submitting\ valid\ PRO\ assessment\ at\ time\ t}{Nbr\ of\ patients\ on\ PRO\ assessment\ at\ time\ t}$$

Note: the denominator of the completion rate depends on the research question

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Missing Data: Standardizing Terminology

- PRO data is missing if data would be meaningful for the analysis of a given research objective but were not available for any reason

- Consequence:
  - Not all unobserved assessments are considered as missing data
  - Missingness depends on the objective, i.e., within a trial several missing data rates are possible
  - Data is meaningful for analysis if it reduces the sample size (non-informative missing data), distorts the treatment estimate (informative missing data) or both

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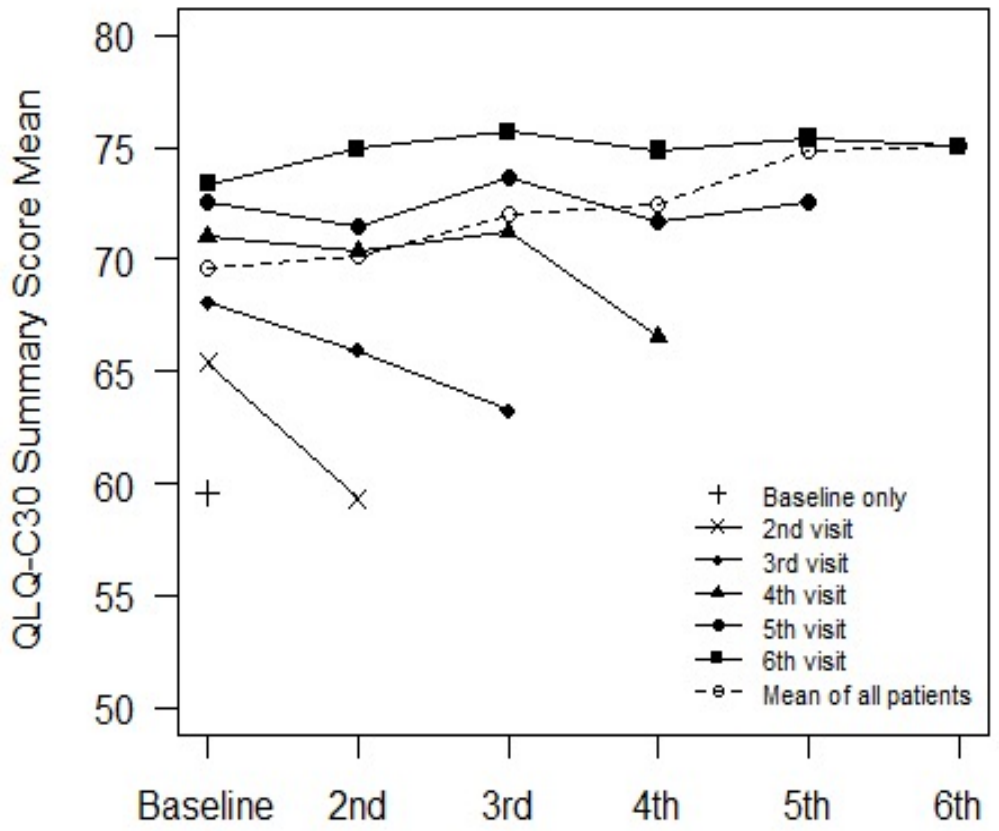
Informative Missing Data

Example: Palliative chemotherapy for recurrent ovarian cancer

- Health-related quality of life (HRQL, QLQ-C30) grouped by last PRO assessment
- Patients with lowest HRQL at baseline drop off first
- HRQL is falling at the last assessment in the early drop-out groups
- Most missing data is probably from sicker/dying patients
- Mean of available HRQL data suggests improvement over time: misleading



No. patients:

	Baseline	2nd	3rd	4th	5th	6th
Baseline only	98					
2nd visit	98	98				
3rd visit	135	121	135			
4th visit	122	108	115	122		
5th visit	80	71	67	71	80	
6th visit	332	313	312	311	303	332
Total	865	711	629	504	383	332

Lee YC, et al. Int J Gynecol Cancer, 2022

Missing Data - Reasons

- Missing data should be minimized prospectively – see **SPIRIT-PRO Item 18b**
- Capturing the **reasons** for missing PRO assessments is important
  - Impact of missing data depends on the reasons for missing data, which can be linked to mechanisms for missing data
  - Reasons for missing data should be collected during trial conduct in a standardized way - this should be planned in the protocol, see **SPIRIT-PRO Items 18b and 20c**
- Primary statistical analysis approach:
  - Critical assessment of missing data rates and reasons (by arm and time point)
  - Use all available data
  - Simple imputation is not recommended unless justified within the context of the clinical trial

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Missing Data – Sensitivity Analysis

- Sensitivity analysis should be specified *a priori* within the protocol/statistical analysis plan
- At least two different approaches to handle missing data are recommended to assess the impact of missing data across various assumptions
  - If the results are consistent with the primary analysis, this provides some assurance that the missing data did not have an important effect on the study conclusions
  - If they produce inconsistent results, their implications for the conclusions of the trial must be discussed

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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 health policy
- More standardized PRO analysis will lead to easier and better cross-trial comparison of PRO results improving the value of such outcomes
- Necessity of clear pre-specified PRO objectives requires implementation at study design stage, as per SPIRIT-PRO
- Foster better collaboration and understanding between clinicians, patients and methodologists on statistical analysis and the interpretation
- Better PRO analysis will facilitate high-quality reporting, including clear and comprehensible description of the analysis methods used
  - Consider reporting in relation to CONSORT (http://www.consort-statement.org)

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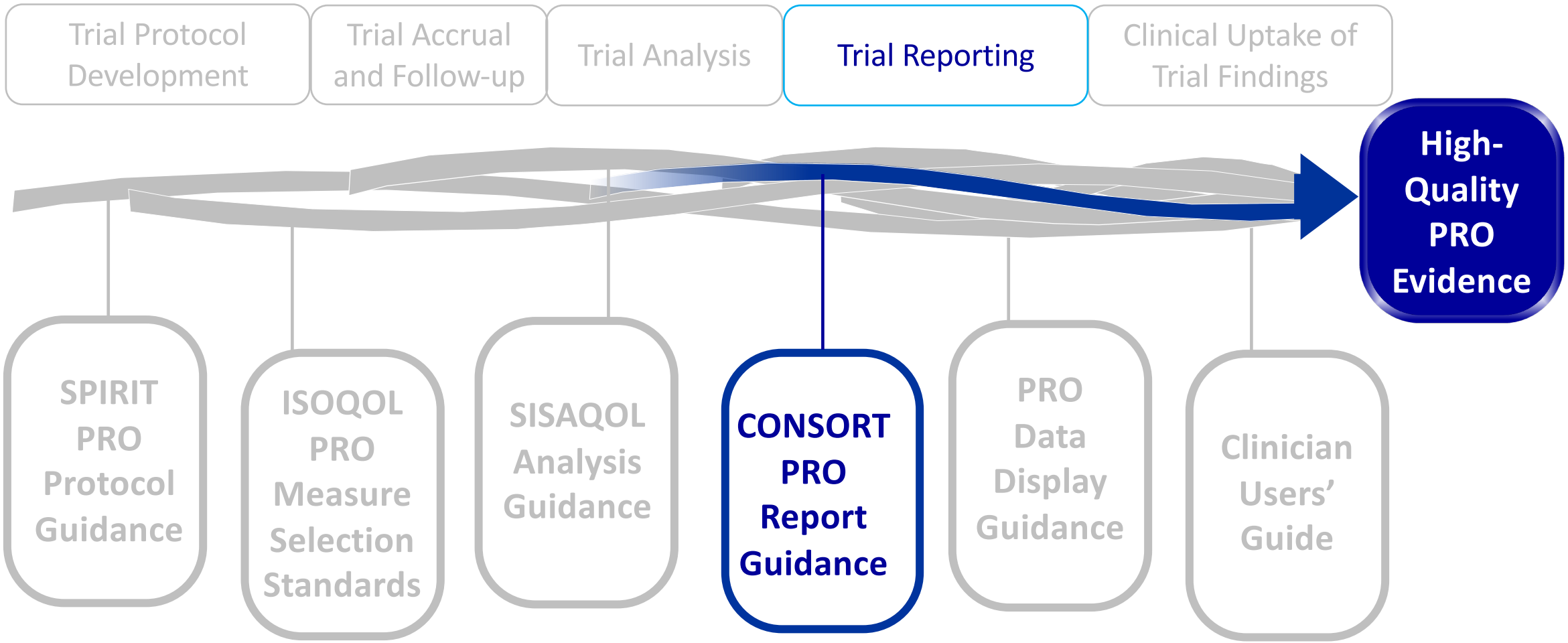
Reporting the PRO Results Clearly (1)



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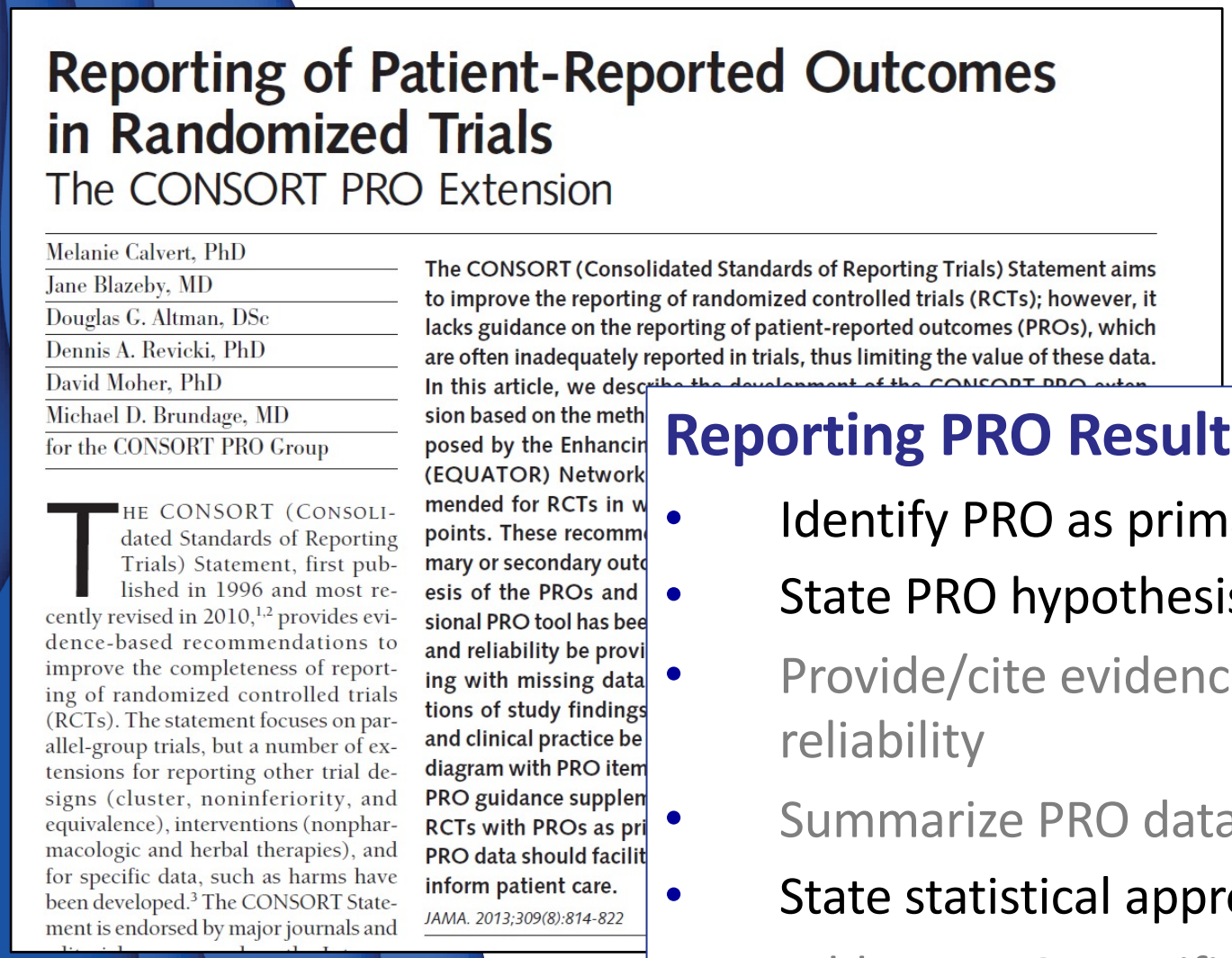


Reporting of Patient-Reported Outcomes in Randomized Trials

The CONSORT PRO Extension

Melanie Calvert, PhD
Jane Blazeby, MD
Douglas G. Altman, DSc
Dennis A. Revicki, PhD
David Moher, PhD
Michael D. Brundage, MD
for the CONSORT PRO Group

The CONSORT (Consolidated Standards of Reporting Trials) Statement aims to improve the reporting of randomized controlled trials (RCTs); however, it lacks guidance on the reporting of patient-reported outcomes (PROs), which are often inadequately reported in trials, thus limiting the value of these data. In this article, we desc
sion based on the meth
posed by the Enhancin
(EQUATOR) Network
mended for RCTs in w
points. These recomm
mary or secondary outc
esis of the PROs and
sional PRO tool has bee
and reliability be provi
ing with missing data
tions of study findings
and clinical practice be
diagram with PRO item
PRO guidance supplen
RCTs with PROs as pri
PRO data should facilit
inform patient care.

JAMA. 2013;309(8):814-822

THE CONSORT (CONSOLIdated Standards of Reporting Trials) Statement, first published in 1996 and most recently revised in 2010,[1,2] provides evidence-based recommendations to improve the completeness of reporting of randomized controlled trials (RCTs). The statement focuses on parallel-group trials, but a number of extensions for reporting other trial designs (cluster, noninferiority, and equivalence), interventions (nonpharmacologic and herbal therapies), and for specific data, such as harms have been developed.[3] The CONSORT Statement is endorsed by major journals and

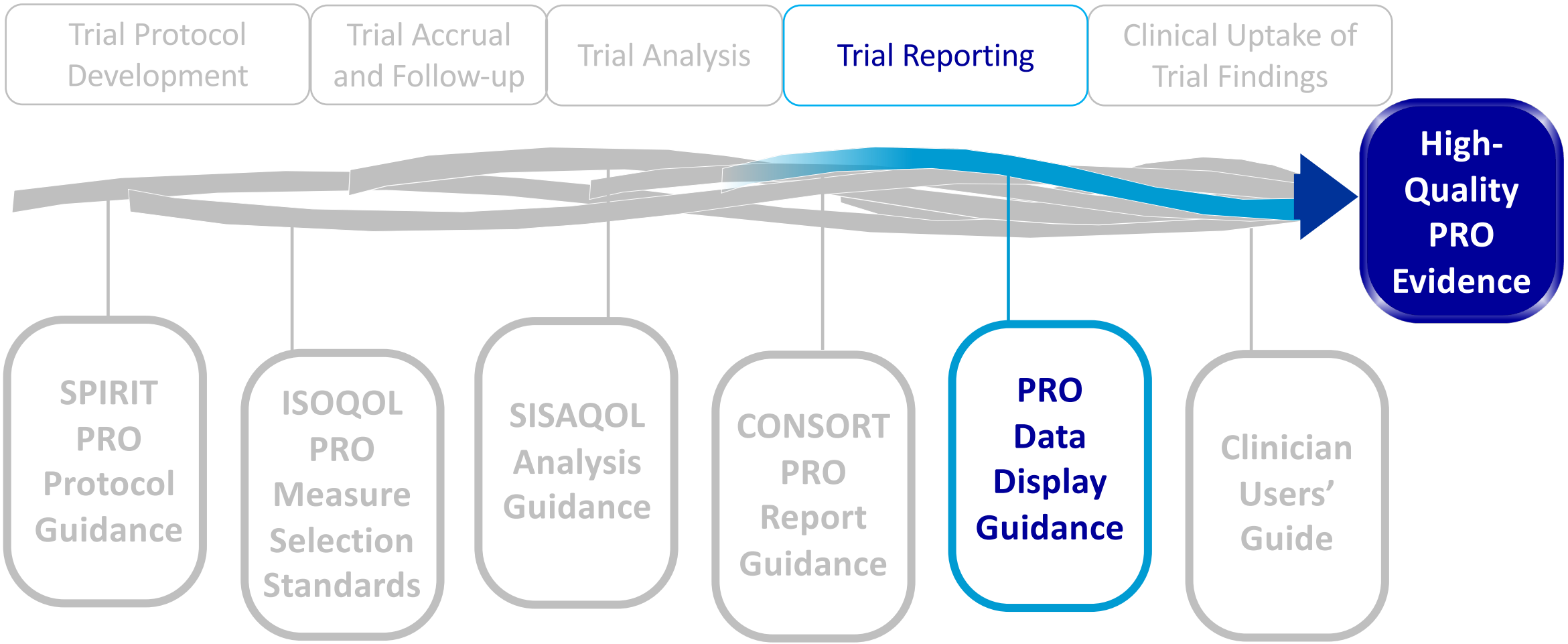
Components in black are relevant to biostatisticians

Reporting PRO Results Clearly (1)

- Identify PRO as primary or secondary endpoint
- State PRO hypothesis, specifying domains if applicable
- Provide/cite evidence of PRO instrument validity and reliability
- Summarize PRO data collection procedures
- State statistical approaches for dealing with missing data
- Address PRO-specific limitations and implications for generalizability

Calvert et al, JAMA 2013, 309(8), 814-822

Reporting the PRO Results Clearly (2)



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Quality of Life Research
https://doi.org/10.1007/s11136-018-2020-3

Making a picture worth a thousand numbers: recommendations for graphically displaying patient-reported outcomes data

Claire Snyder[1,2,3] · Katherine Smith[2,3] · Bernhard Holzner[4] · Yonaira M. Rivera[2] · Elissa Bantug[3] · Michael Br
PRO Data Presentation Delphi Panel

Accepted: 29 September 2018

All components are relevant to biostatisticians

Reporting PRO Results Clearly (2)

- Directionality (whether higher scores are better or worse)
- Conveying score meaning
- Conveying statistically significant differences
- Illustrating clinically important differences

Snyder et al, Qual Life Res 2019, 28(2), 345-356

Illustrative Example for Presentation to Clinicians/Researchers

Labels for directionality

Reinforce directionality

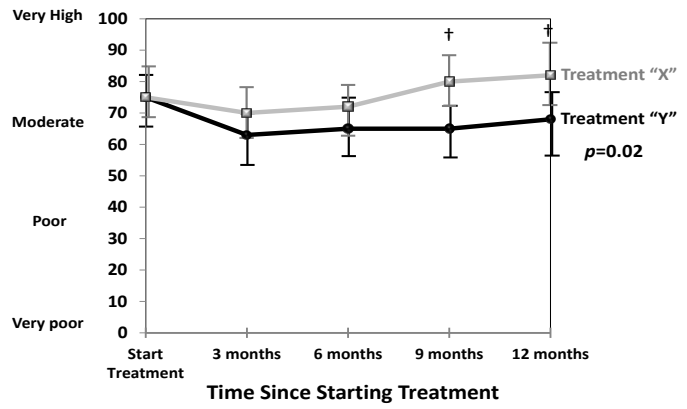
Descriptive anchor labels

Visually separate domains with different directionality

Patients' Functioning

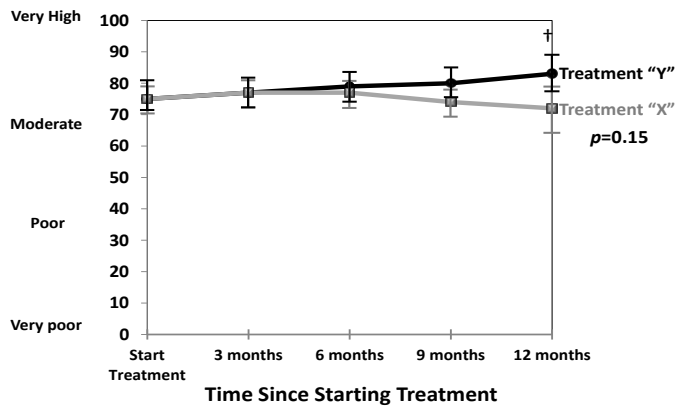
Physical

(line going up means better able to do physical activities)



Emotional

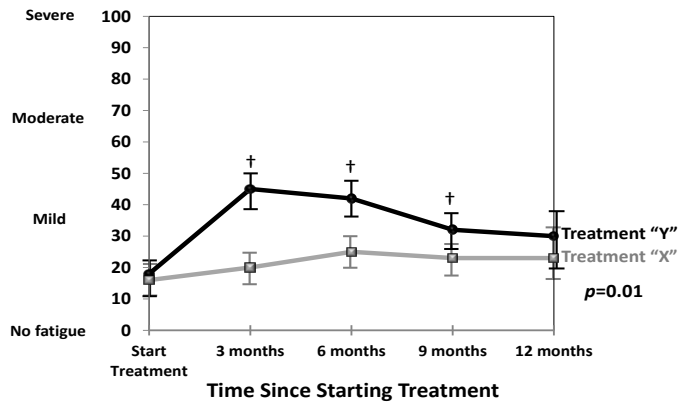
(line going up means better emotional well-being)



Patients' Symptoms

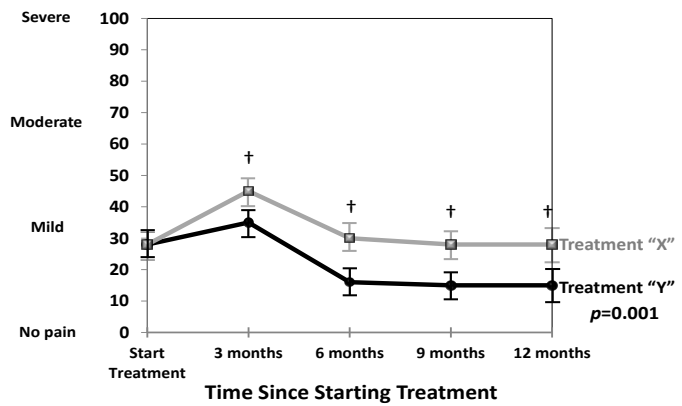
Fatigue

(line going up means worse fatigue)



Pain

(line going up means worse pain)



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.

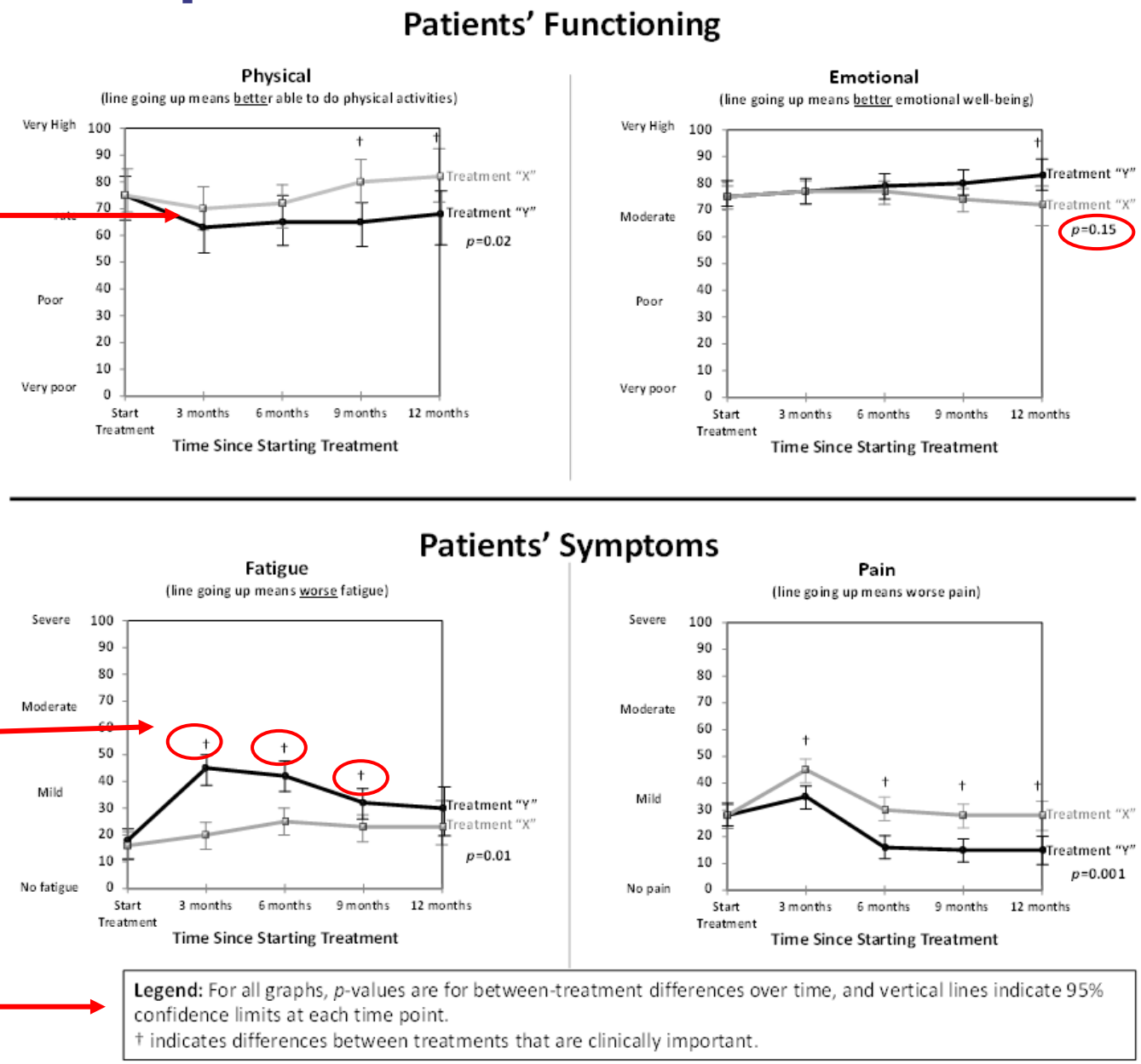
Illustrative Example for Presentation to Clinicians/Researchers

Confidence limits

p-values

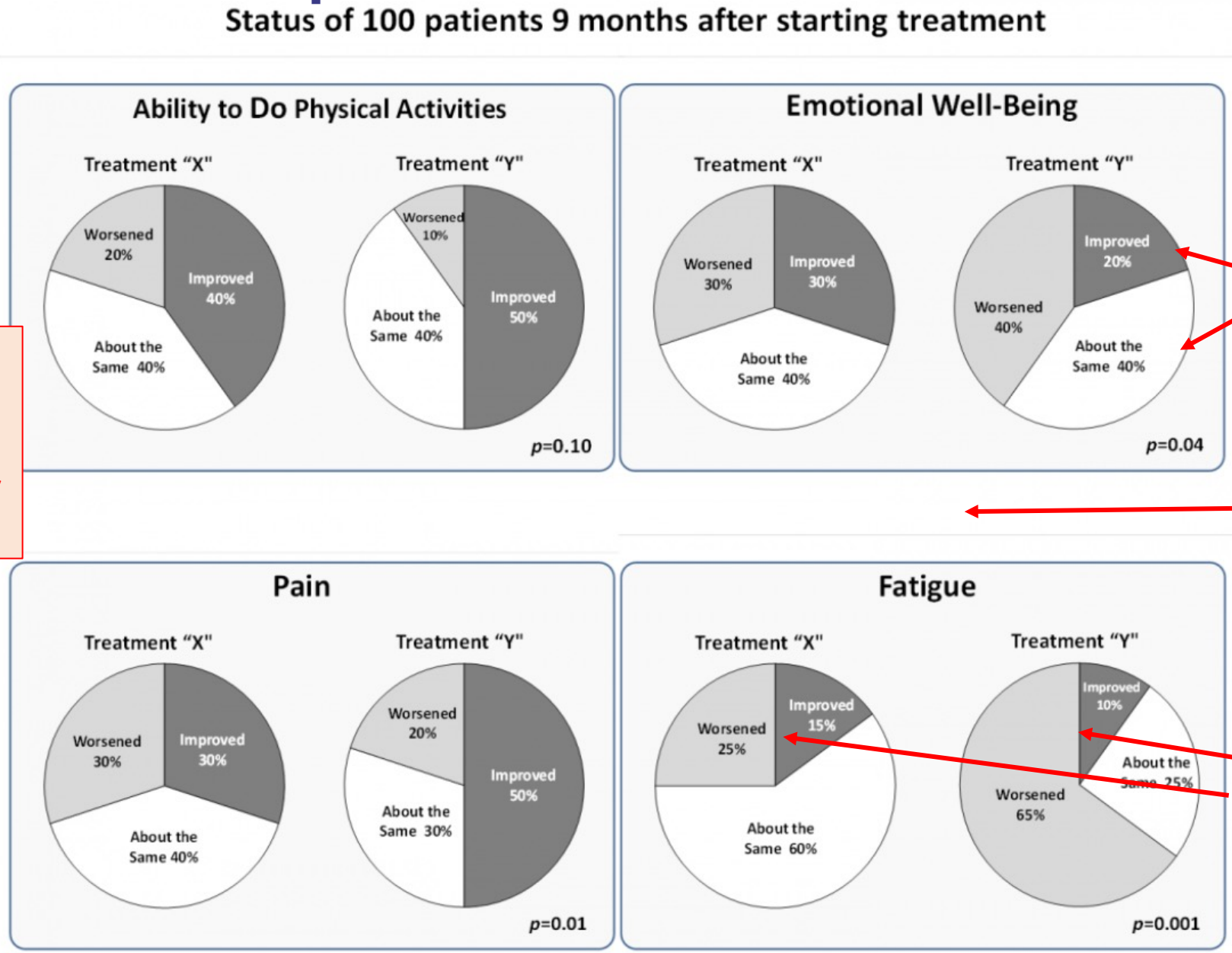
Symbols illustrating clinically important differences between group scores

Legend explanations



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.

Illustrative Example for Presentation to Clinicians/Researchers



Color pie charts recom-mended for patients

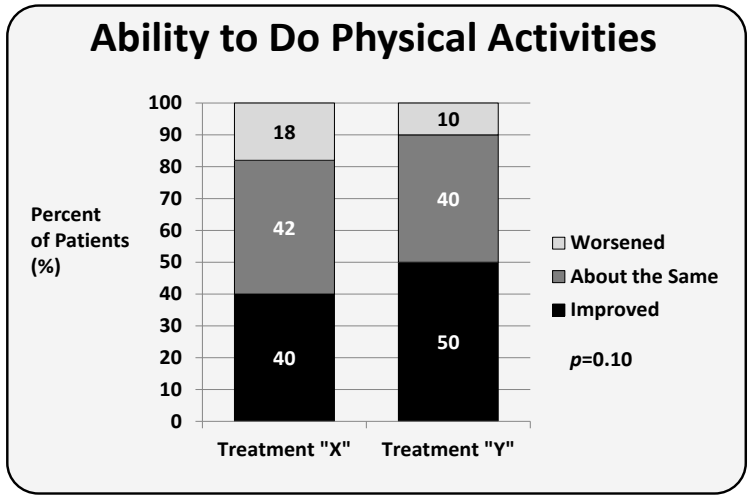
Data labels annotated on each slice

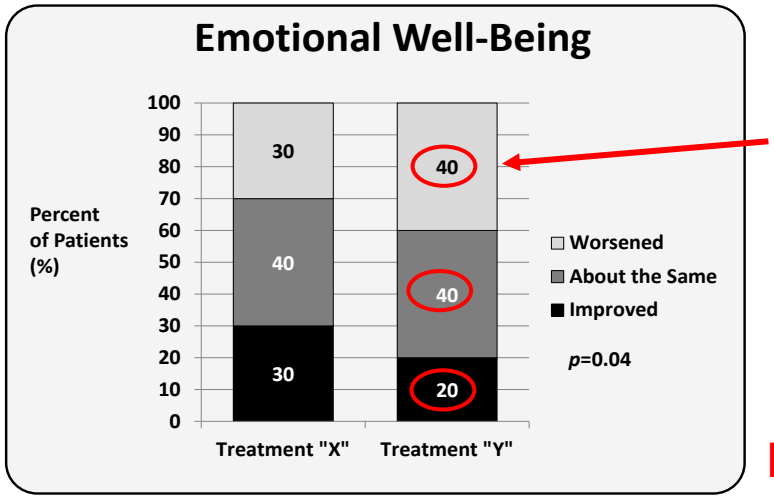
No horizontal line separating domains since directionality not relevant with proportions

"Improved" slice consistently starts at 12:00 position

Illustrative Example for Presentation to Clinicians/Researchers

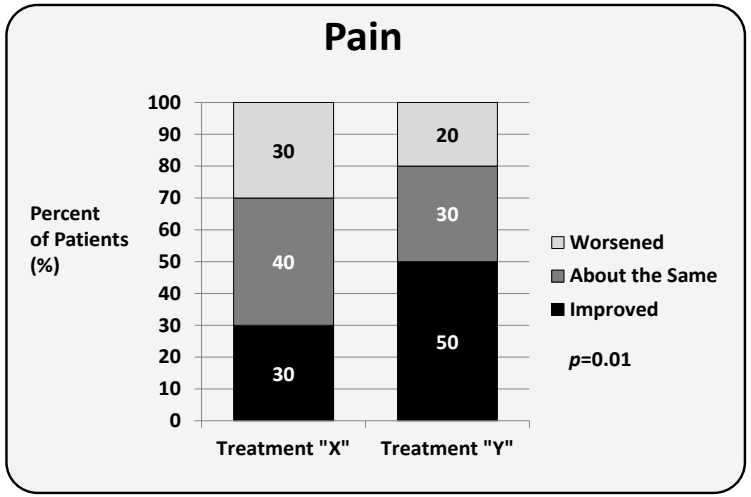
Status of 100 patients 9 months after starting treatment

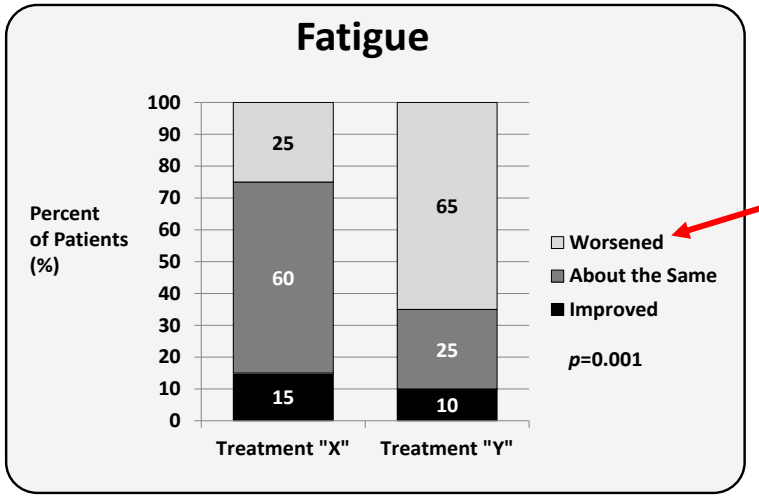




Data labels annotated on each slice so stacked proportions can be read directly

No horizontal line separating domains since directionality not relevant with proportions



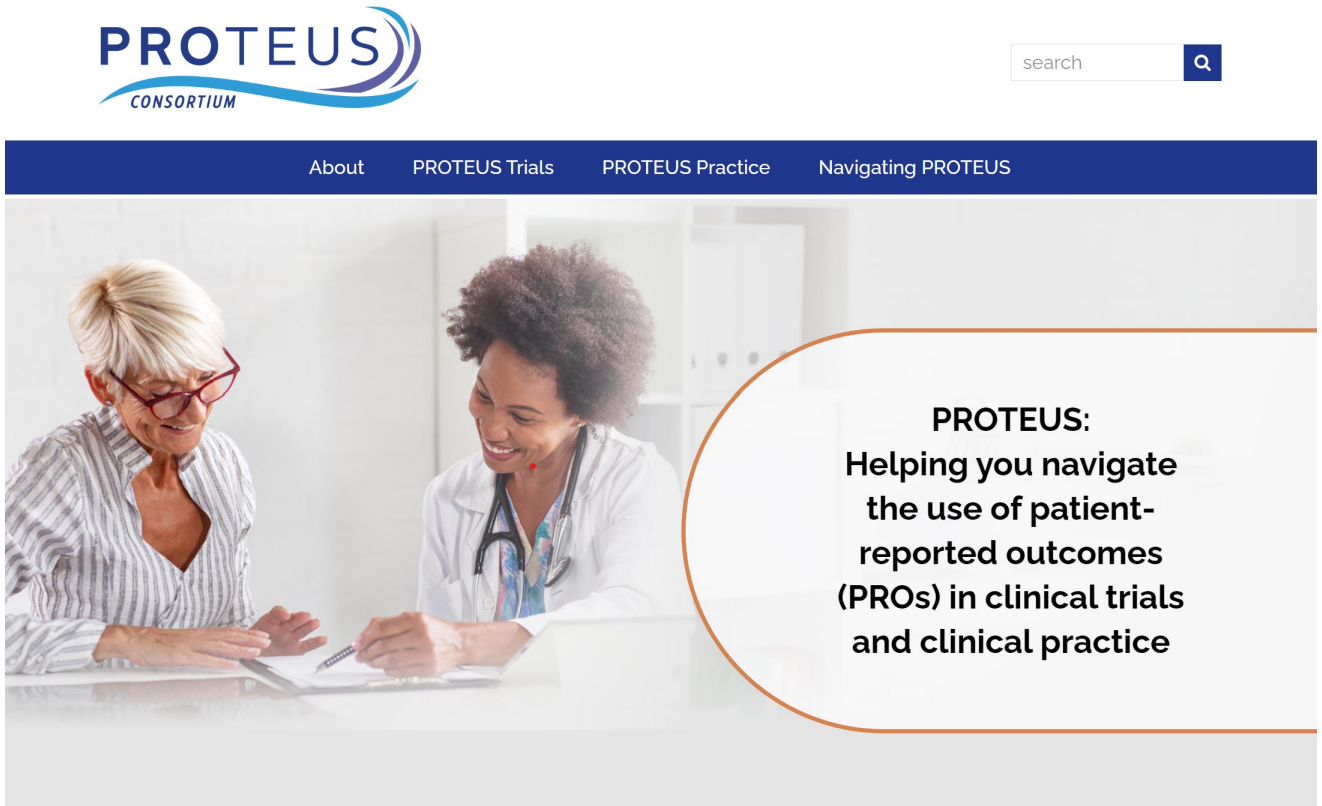


Legend replicated for easy access and order is the same as stacked bar sections

The PROTEUS Website

TheProteusConsortium.org

Contains information and resources including web tutorials and checklists for each tool, and a handbook that pulls it all together.

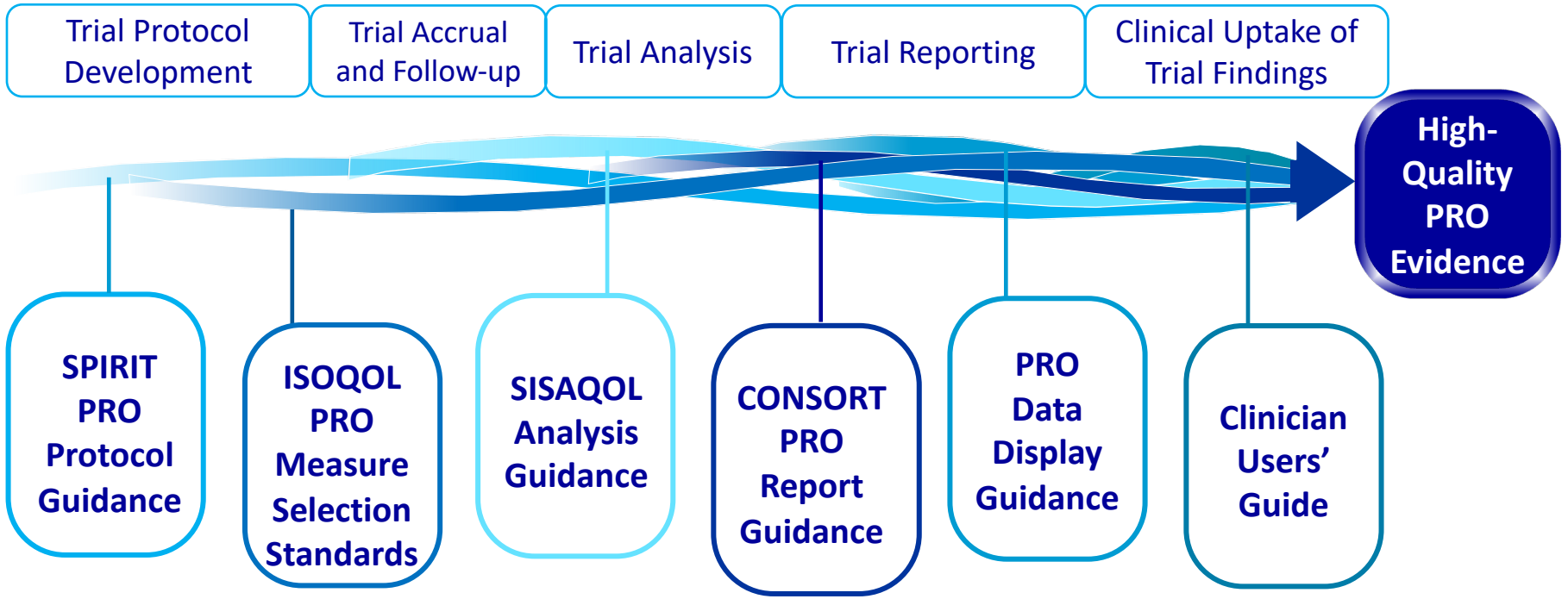


PROTEUS

Overview of Web Tutorials

Introduction to PROs and PROTEUS

Introduction to the PROTEUS Tools



Overview of Tool Recommendations

How to Apply the Tools

The PROTEUS-Trials Consortium

Patient-Reported Outcome To
Engaging Users & Stakehold

PROTEUS

Handbook

ThePROTEUSConsortium.org

Contents

Overview of the SPIRIT-PRO Guidance

- To be used in conjunction with the SPIRIT 2013 Statement and related extensions
- 5 elaborations on existing SPIRIT 2013 checklist items as applied to PROs in trial protocols
- 11 extensions – additional PRO-specific items recommended for trial protocols where PROs are a primary or important secondary outcome

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.

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THANK YOU

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