Disclosures

- The PROTEUS Consortium has received funding from the Patient-Centered Outcomes Research Institute and unrestricted grants from Genentech and Pfizer

- Dr. Snyder has received consulting fees from Janssen via Health Outcomes Solutions

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Optimizing the Use of Patient-Reported Outcomes in Clinical Trials to Inform Decision Making:

The PROTEUS Consortium

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

Claire Snyder, PhD

Professor of Medicine, Oncology, and Health Policy & Management

Johns Hopkins Schools of Medicine and Public Health

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

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Organizations with PROTEUS Participants*

AcademyHealth	Industry (GlaxoSmithKline)
American Cancer Society	International Society for Quality of Life Research
American Society for Radiation Oncology	ISPOR
American Society of Clinical 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)

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

Trials Steering Committee

Principal Investigator
Claire Snyder, PhD
Johns Hopkins School of Medicine

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Norah Crossnohere, PhD
Ohio State University

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

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

Elissa Thorner, MHS
Patient Advocate

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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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The PROTEUS Consortium's Rationale

- Clinical trial protocols are often sub-optimal with regard to their PRO components
- Clinical trial reporting of the PRO components is often sub-optimal or doesn't happen at all
  - *Tools are available to improve trial protocol design, execution, reporting and uptake with regard to PRO endpoints*

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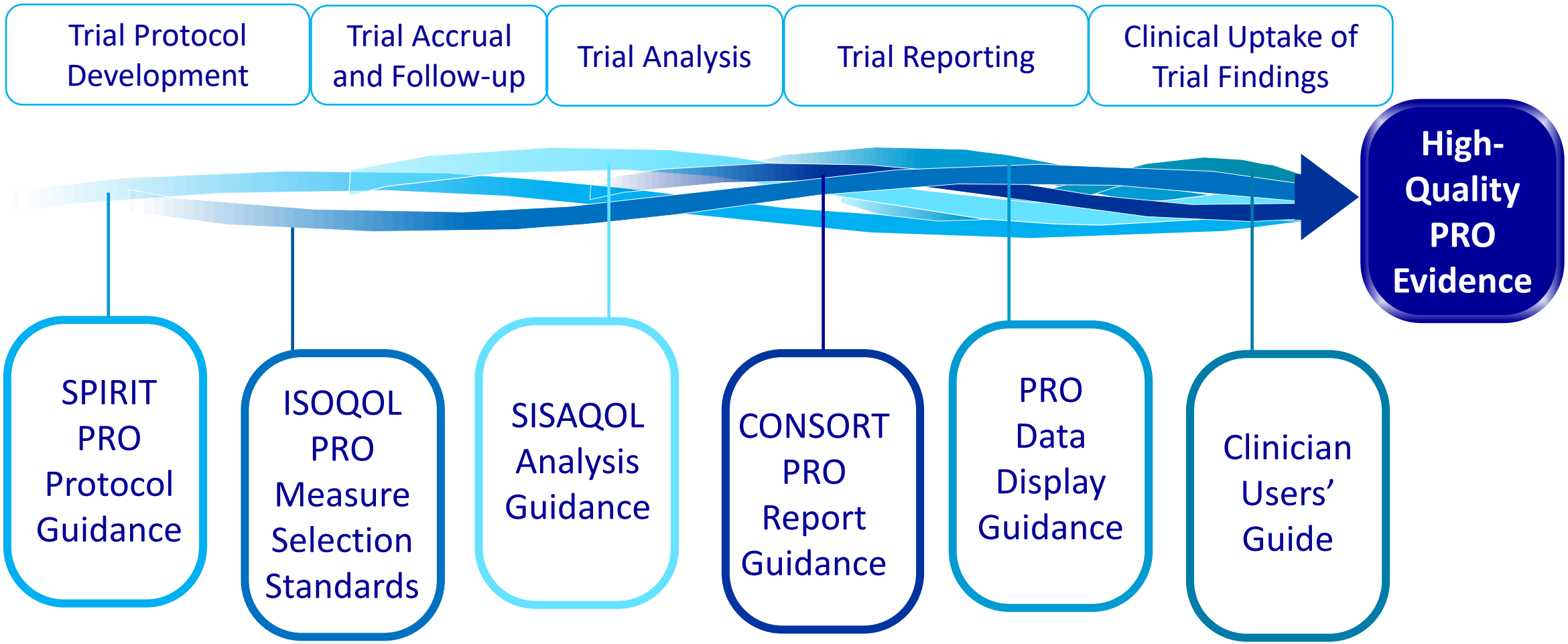
PROTEUS Roadmap



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“6 Tools-1 Paper Paper”

Short Communication

CLINICAL TRIALS

Clinical Trials
1–8

DOI: 10.1177/17407745221077691
journals.sagepub.com/home/ctj
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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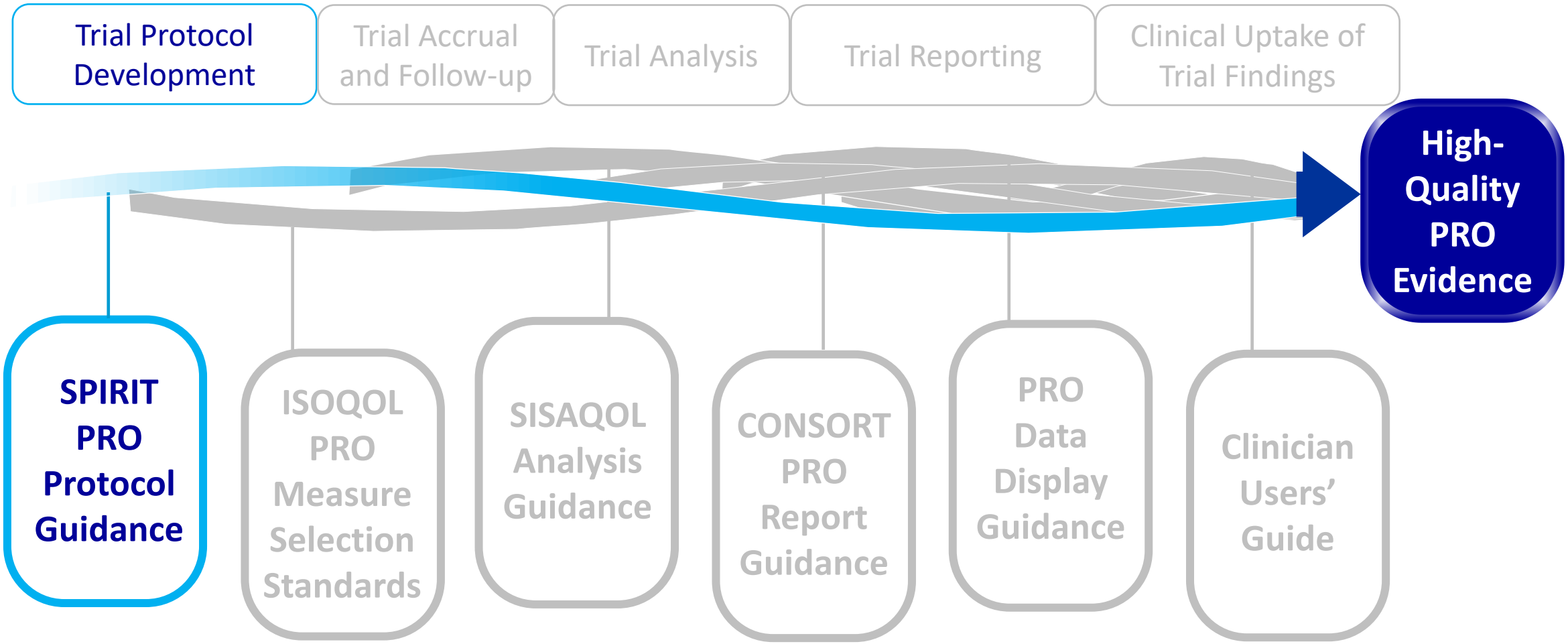
Specifying PRO Methods Appropriately



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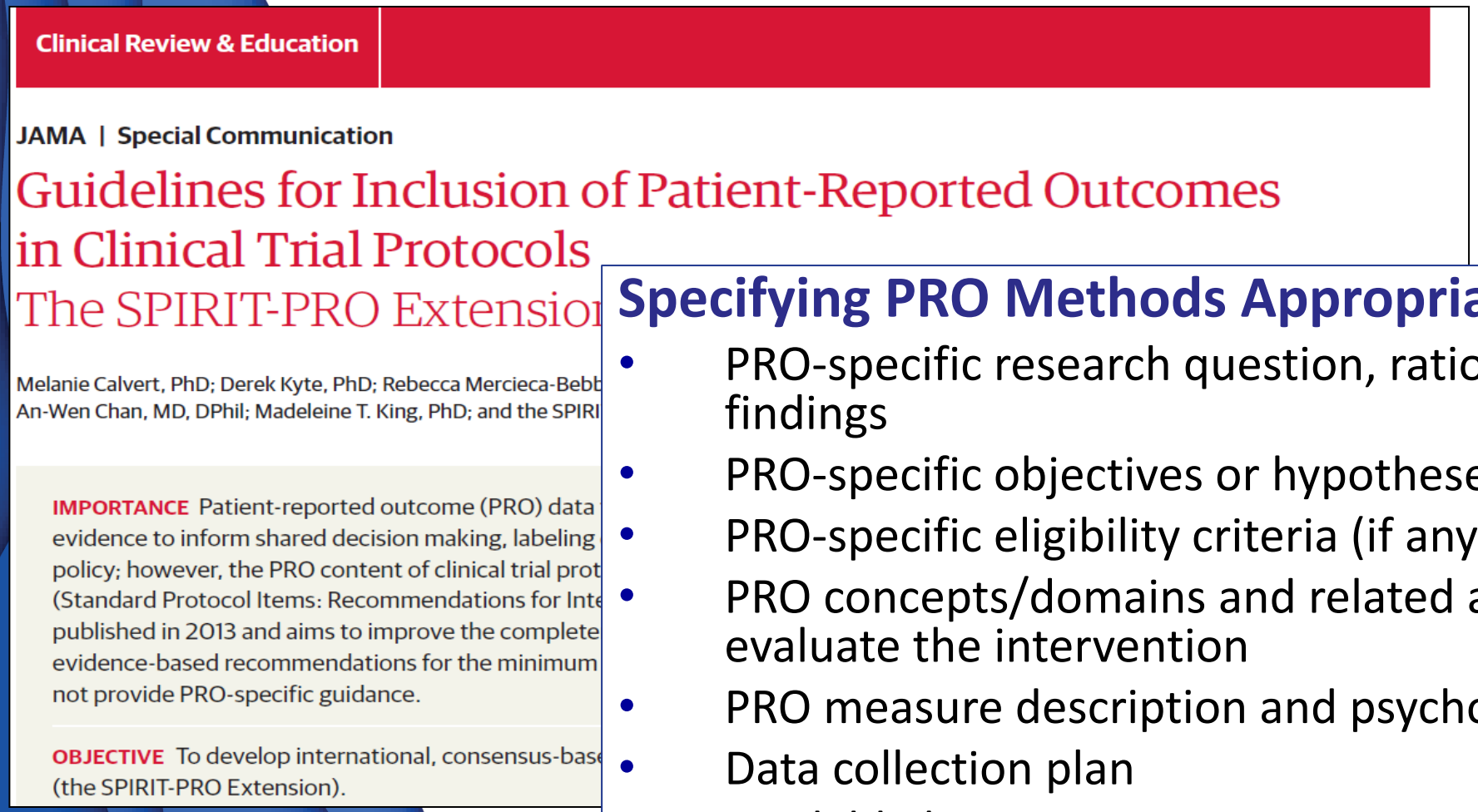

Clinical Review & Education

JAMA | Special Communication

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

Melanie Calvert, PhD; Derek Kyte, PhD; Rebecca Mercieca-Bebb
An-Wen Chan, MD, DPhil; Madeleine T. King, PhD; and the SPIRI

IMPORTANCE Patient-reported outcome (PRO) data
evidence to inform shared decision making, labeling
policy; however, the PRO content of clinical trial prot
(Standard Protocol Items: Recommendations for Inte
published in 2013 and aims to improve the complete
evidence-based recommendations for the minimum
not provide PRO-specific guidance.

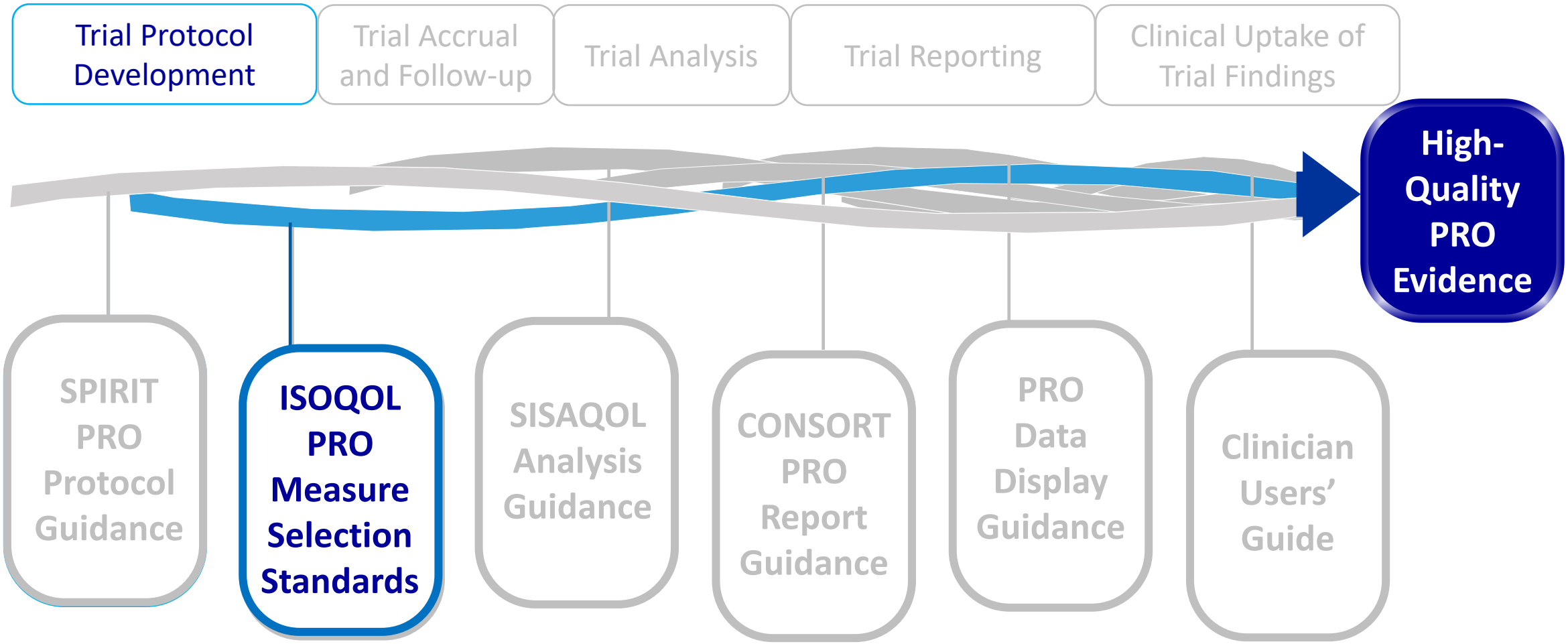
OBJECTIVE To develop international, consensus-base
(the SPIRIT-PRO Extension).

Specifying PRO Methods Appropriately

- 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)
- Strategies to minimize and address missing data
- Whether PRO data will be monitored to inform care

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

Measuring PROs Effectively



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ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research

Bryce B. Reeve · Kathleen W. Wyrwich · Albert W. Wu · Galina Velikova · Caroline B. Terwee · Claire F. Snyder · Carolyn Schwartz · Dennis A. Revicki · Carol M. Moinpour · Lori D. McLeod · Jessica C. Lyons · William R. Lenderking · Pamela S. Hinds · Ron D. Hays · J
David Feeny · Peter M. Fayers · Da
Sara Ahmed · Neil K. Aaronson · Z

Accepted: 17 December 2012 / Published on

Measuring PROs Effectively

- Conceptual and measurement model, including intended population
- Reliability
- Validity (content, construct, responsiveness)
- Interpretability of scores
- Translations
- Patient and Investigator Burden

Reeve et al, Qual Life Res 2013, 22, 1889-1905

Quality of Life Research
https://doi.org/10.1007/s11136-020-02625-z

REVIEW

International guida
measures in clinica

Norah L. Crossnohere[1] · Mi
Elissa Thorner[6] · Albert W. Wu

Domain	ISOQOL minimum standards	COSMIN Initiative	EMA appendix 2	FDA PRO	FDA PFDD[a]	MOT review criteria	Red-IRYSS EMPRO[b]
Conceptual & measurement model	√	√	√	√	√	√	√
Reliability	√	√	√	√	√	√	√
Content validity	√	√	√	√	√	√	√
Construct validity	√	√	X	√	√	√	√
Responsiveness	√	√	√	√	√	√	√
Interpretability of scores	√	±	√	√	√	√	√
Translation	√	√	√	√	√	√	√
Burden	√	±	√	√	√	√	√
Additional domains		• Structural validity • Quality assessment	• Alternative mode of admin • COAs • Special patient populations	• Alternative mode of admin • Special patient populations • Context of use	• COAs • Context of use, fit-for-purpose • Special patient populations • Alternate modes of admin	• Alternative mode of admin	• Alternative mode of admin • Global assessment of instrument by rater

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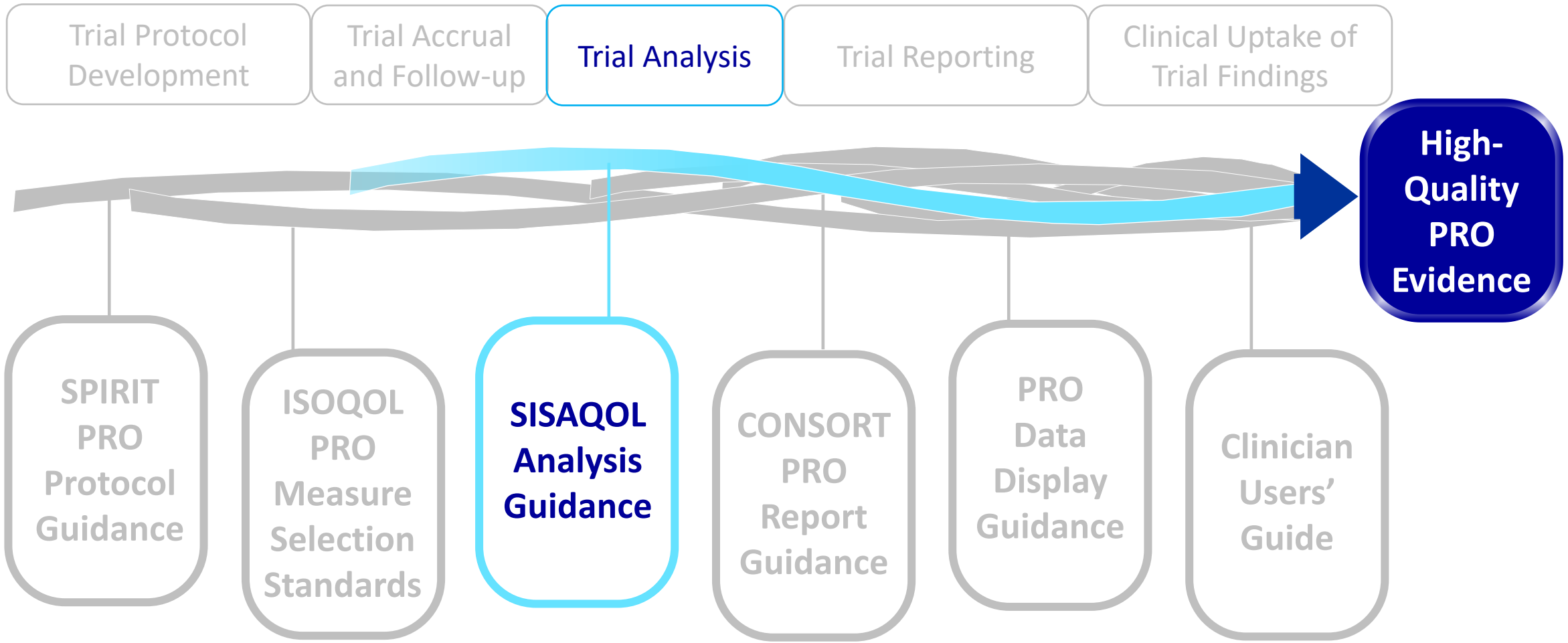
Crossnohere et al, Qual Life Res 2021;30:21-40

Analyzing PRO Data Properly



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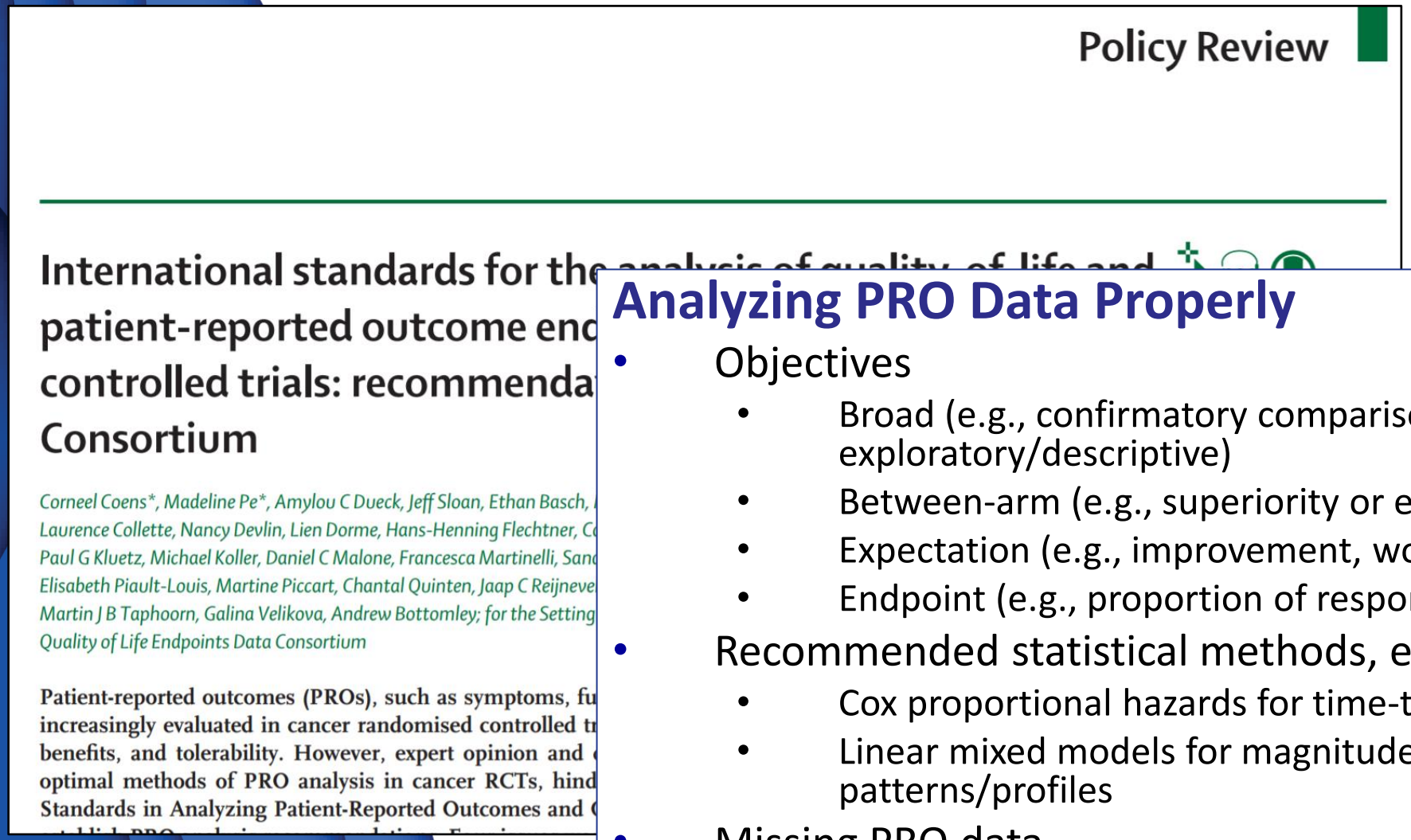

Policy Review

International standards for the
patient-reported outcome enc
controlled trials: recommenda
Consortium

Corneel Coens*, Madeline Pe*, Amylou C Dueck, Jeff Sloan, Ethan Basch,
Laurence Collette, Nancy Devlin, Lien Dorme, Hans-Henning Flechtner, C
Paul G Kluetz, Michael Koller, Daniel C Malone, Francesca Martinelli, San
Elisabeth Piault-Louis, Martine Piccart, Chantal Quinten, Jaap C Reijneve
Martin J B Taphoorn, Galina Velikova, Andrew Bottomley; for the Setting
Quality of Life Endpoints Data Consortium

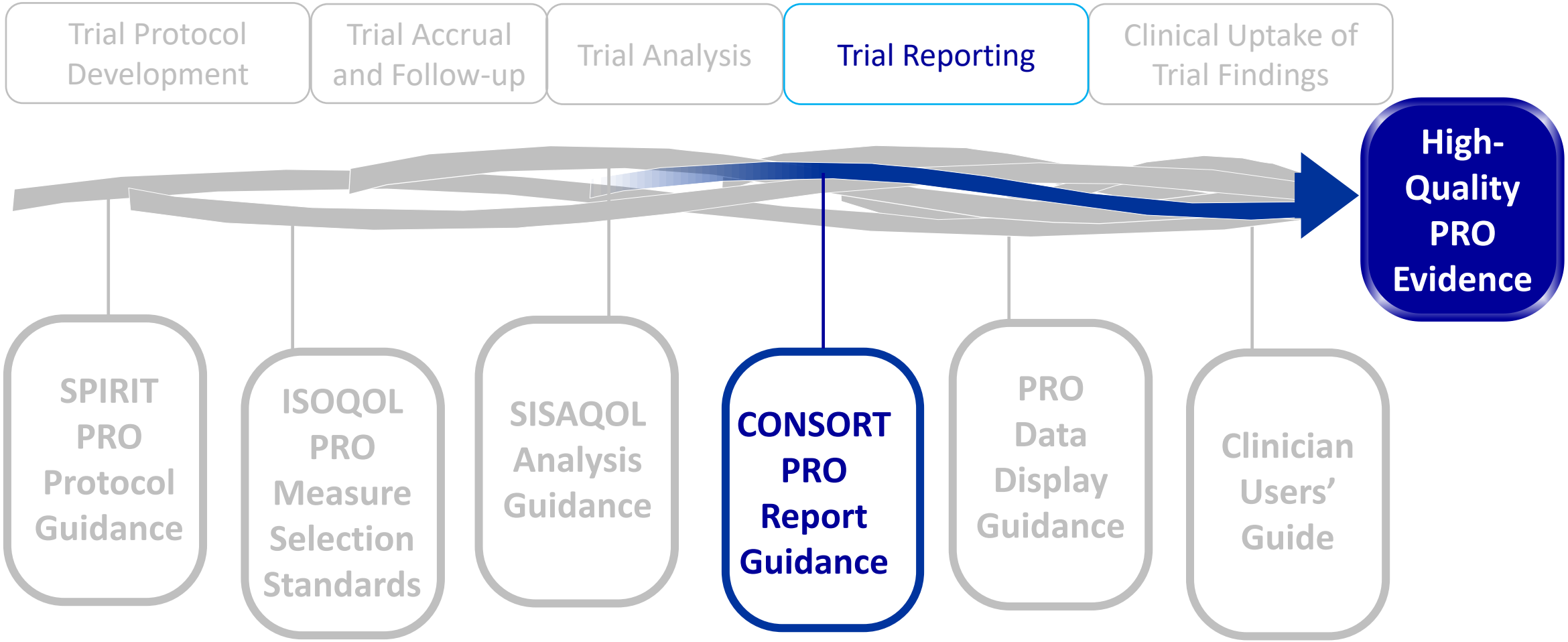
Patient-reported outcomes (PROs), such as symptoms, fu
increasingly evaluated in cancer randomised controlled t
benefits, and tolerability. However, expert opinion and
optimal methods of PRO analysis in cancer RCTs, hind
Standards in Analyzing Patient-Reported Outcomes and

Analyzing PRO Data Properly

- Objectives
  - Broad (e.g., confirmatory comparisons vs. exploratory/descriptive)
  - Between-arm (e.g., superiority or equivalence/non-inferiority)
  - Expectation (e.g., improvement, worsening, overall effect)
  - Endpoint (e.g., proportion of responders at time *t*)
- Recommended statistical methods, e.g.:
  - Cox proportional hazards for time-to-even
  - Linear mixed models for magnitude-of-event, describe response patterns/profiles
- Missing PRO data
  - Handling analytically
  - Collecting reasons

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

Reporting the PRO Results Clearly (1)



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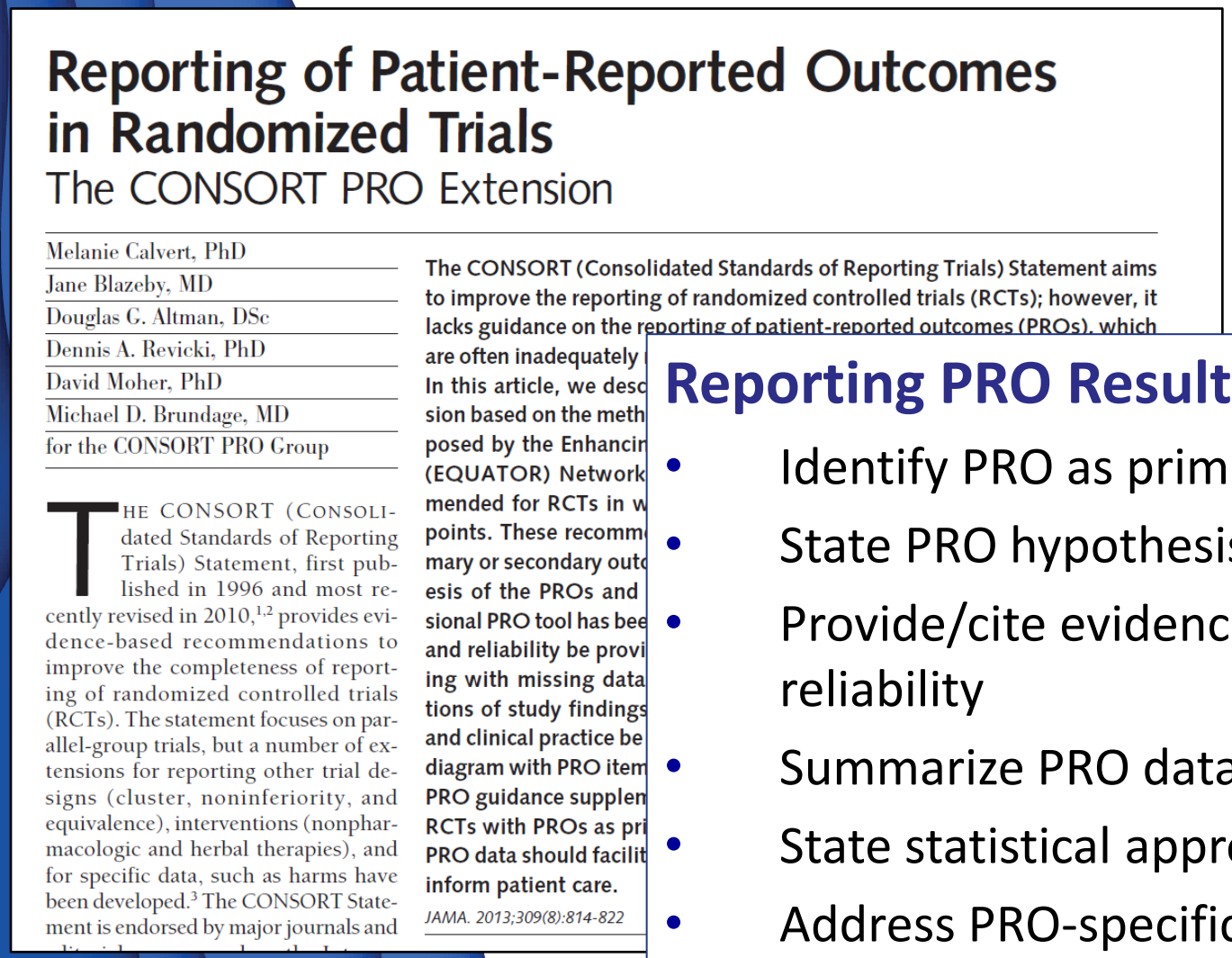


Reporting of Patient-Reported Outcomes in Randomized Trials

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
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

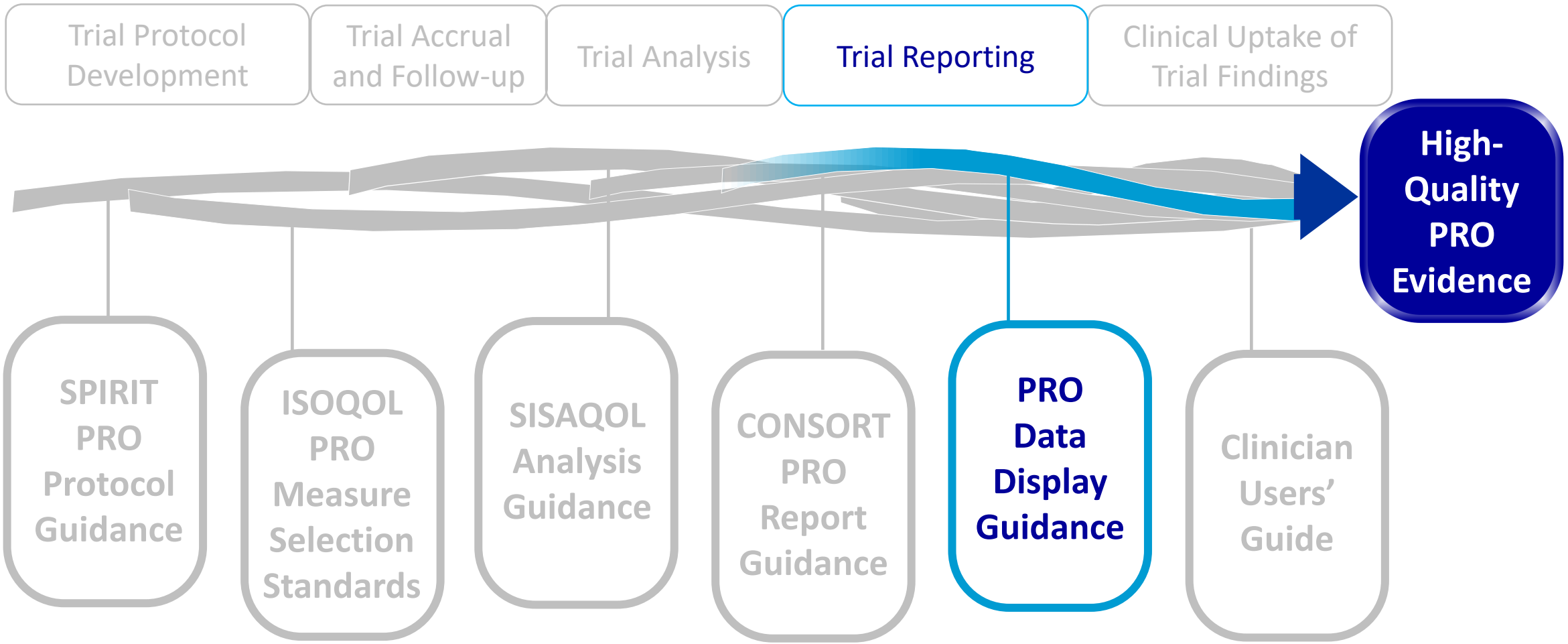
THE CONSORT (CONSOLIdated Standards of Reporting Trials) Statement, first published in 1996 and most recently revised in 2010,[1,2] provides evidence-based recommendations to improve the completeness of reporting of randomized controlled trials (RCTs). The statement focuses on parallel-group trials, 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

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)



PROTEUS

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 Brundage[5] · PRO Data Presentation Delphi Panel

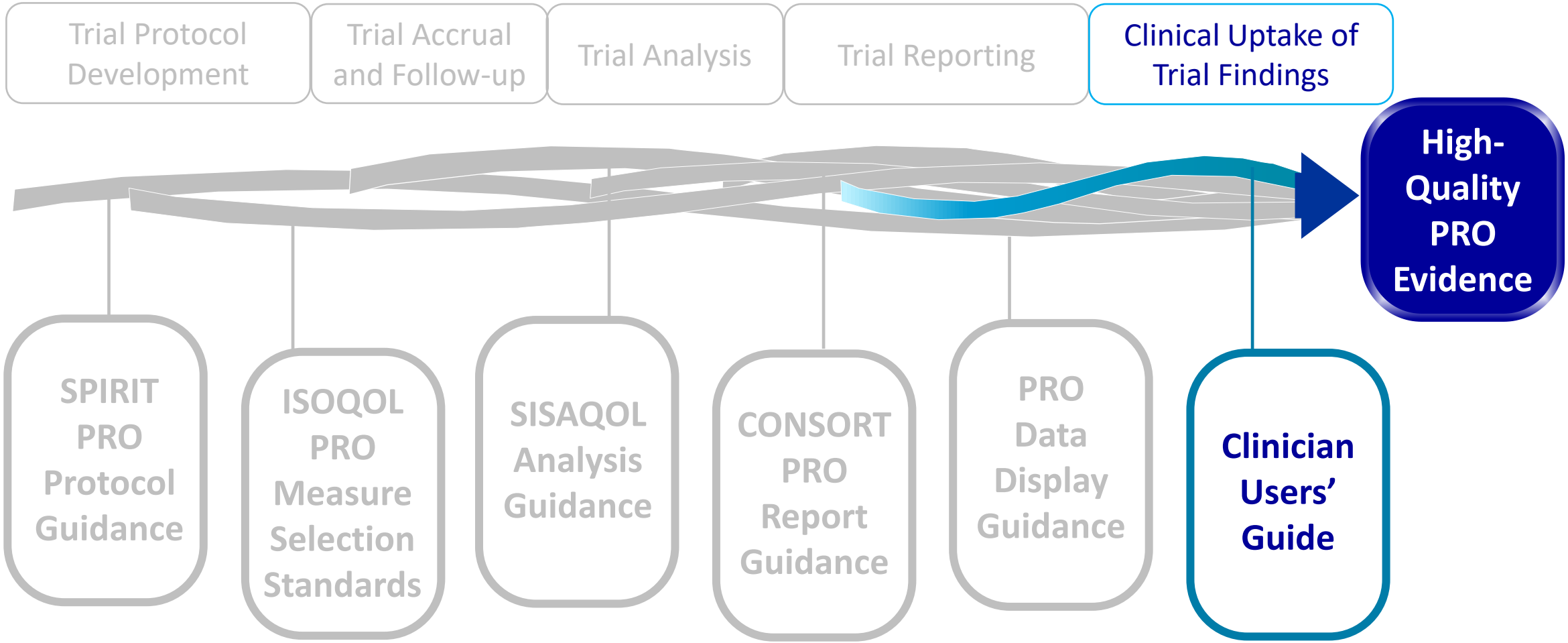
Accepted: 29 September 2018

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

Applying PRO Findings in Practice



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Clinician's Checklist for Reading and Using an Article About Patient-Reported Outcomes

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

Abstract

Clinicians need evidence-based medicine to help them make clinical decisions with their patients. For many health problems, the goal of treatment is to help the patient to function and feel better. To measure patient functioning, well-being, and symptoms, questionnaires referred to as patient-reported outcome (PRO) measures are often used. Clinicians are generally not trained in survey design, scale development, and questionnaire administration, making it difficult for them to interpret and effectively use PROs as clinical evidence. It is increasingly important that clinicians be able to understand and use outcomes measured from both the clinical and patient perspectives to inform thei
to help practicing clinicians understand clinical researc
can be used for decision making. This checklist provid
consider in evaluating research articles. We propose tha
using PROs: study design and PRO assessment strat
context of the findings, and generalizability to their own
an increasingly prominent role in clinical research and
the patient-centeredness of care. Clinicians will need to
and help them function and feel better. The proposed C
evaluate PRO studies by determining whether the st
surement approach was adequate and properly execu
application of the results to a specific patient populati

Applying PRO Findings in Practice

1. Was the PRO assessment strategy appropriate?
2. Did they measure PROs effectively?
3. Should I believe the results?
4. Were the results placed in clinical context?
5. Do the results apply to my patients?

Wu et al, Mayo Clin Proc 2014, 89(5), 653-661

RESEARCH METHODS AND REPORTING

Recommendations for including or reviewing patient reported outcome endpoints in grant applications

Claire Snyder,[1] Alexandra Gilbert,[2] David Moher,[3] Derek Kyte,[4] Ellie Daniels,[5] Madeleine King,[6] Melanie Calvert,[4,7] Ronald C Chen,[8] Michael Brundage,[9] on behalf of the PROTEUS consortium

Patient reported outcomes are increasingly included in research studies to provide the patient perspective. Grant applicants and grant reviewers require guidance on the key information that should be included in funding applications to demonstrate rigorous methods for patient reported outcomes. This paper provides prioritised practical recommendations from an international consortium of experts on patient reported outcomes to inform grant applicants in preparing their research strategies and grant reviewers in evaluating applications.

Recommendations organized in three categories:

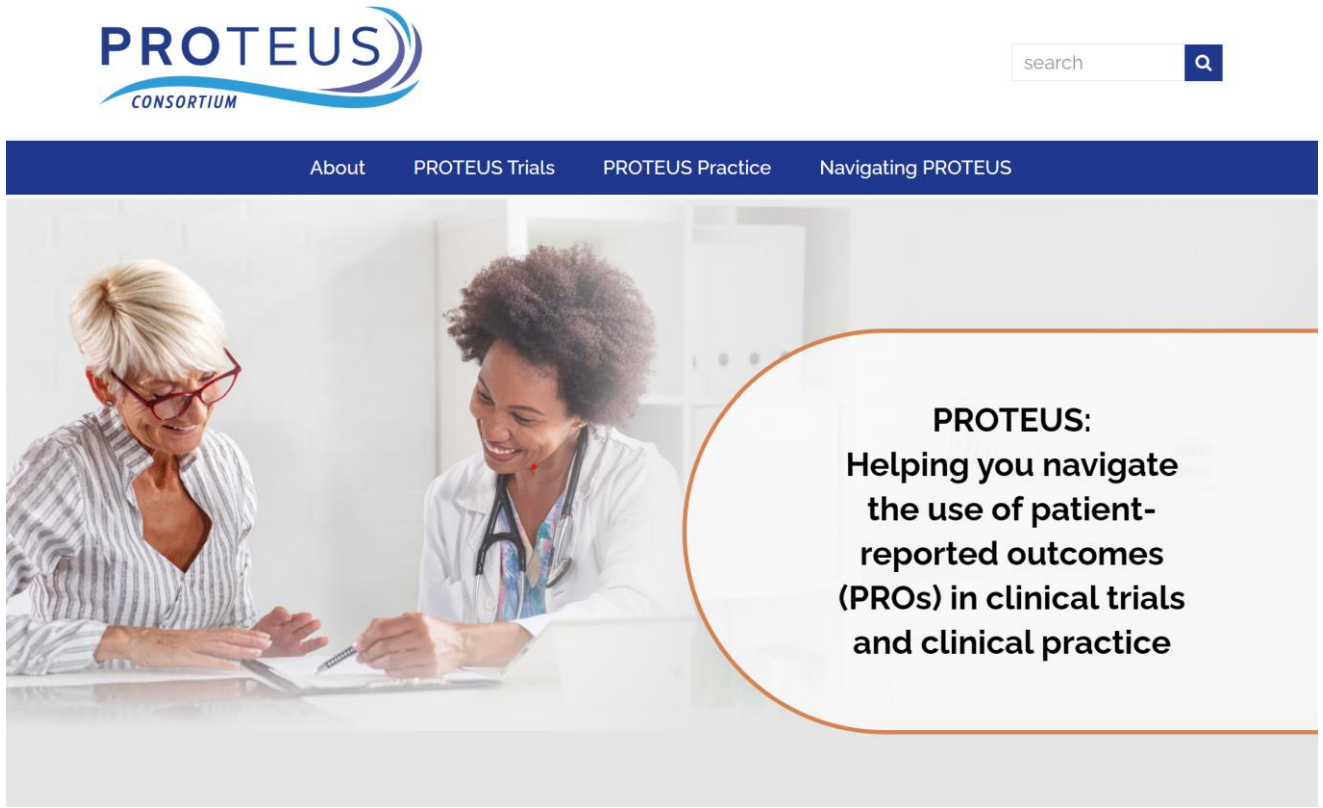
1. Always cover*
   Assumes 1 paragraph of space is available
2. Cover if PRO is a primary endpoint, or if a second paragraph of space is available*
3. Cover if space allows

**example text provided*

Snyder et al, BMJ 2021;373:n1367

The PROTEUS Website

ThePROTEUSConsortium.org



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- Study Reporting

- Developing Protocols
- Selecting Measures
- Analyzing Data

PROTEUS:
Helping you navigate the use of patient-reported outcomes (PROs) in clinical trials and clinical practice

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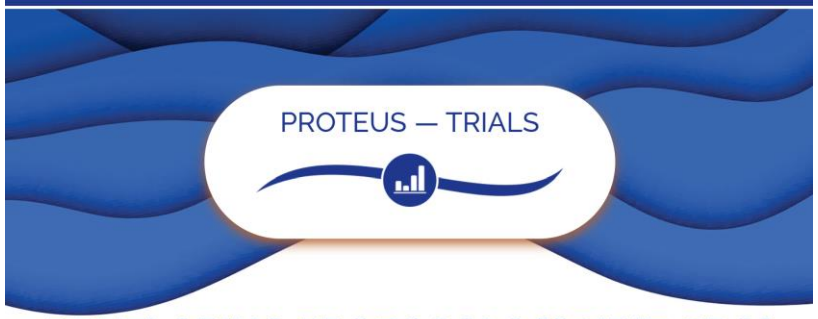

DEVELOPING PROTOCOLS [SPIRIT-PRO]

Patient-reported outcome (PRO) data from clinical trials can provide valuable evidence to inform shared decision making, labeling claims, clinical guidelines, and health policy.

The paper **Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols: The SPIRIT-PRO Extension** recommends best practices for writing the PRO aspects of randomized controlled trial protocols by specifying the items that are critical to address when PROs are primary or key secondary outcomes.

The SPIRIT-PRO Extension builds on the general 2013 SPIRIT clinical trial protocols guidance by addressing the minimum elements related to PROs that should be included.

SPIRIT-PRO BENEFITS

Using SPIRIT-PRO guidance provides benefits to stakeholders by:

- Helping protocol writers improve PRO trial design by encouraging and facilitating careful planning of PRO components.
- Helping protocol reviewers, research ethics committees, and patient partners assess PRO elements.
- Helping trial staff and patient participants understand the rationale for PRO assessment and improve PRO data completeness and quality.

CORE RESOURCES

Article

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

Learn more →

Checklist

The Spirit PRO Protocol Guidance Checklist

Learn more →

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The SPIRIT-PRO Protocol Guidance Checklist

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 (eg, language/reading requirements or pre-randomization 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 (eg, overall health-related quality of life, specific domain, specific symptom) and, for each one, the analysis metric (eg, change from baseline, final value, time to event) and the principal time point or period of interest.	
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 pre-randomization. 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 Extension	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.	

Specifying PRO Methods Appropriately: The SPIRIT-PRO Extension Protocol Guidance

Melanie Calvert, PhD and Madeleine King, PhD

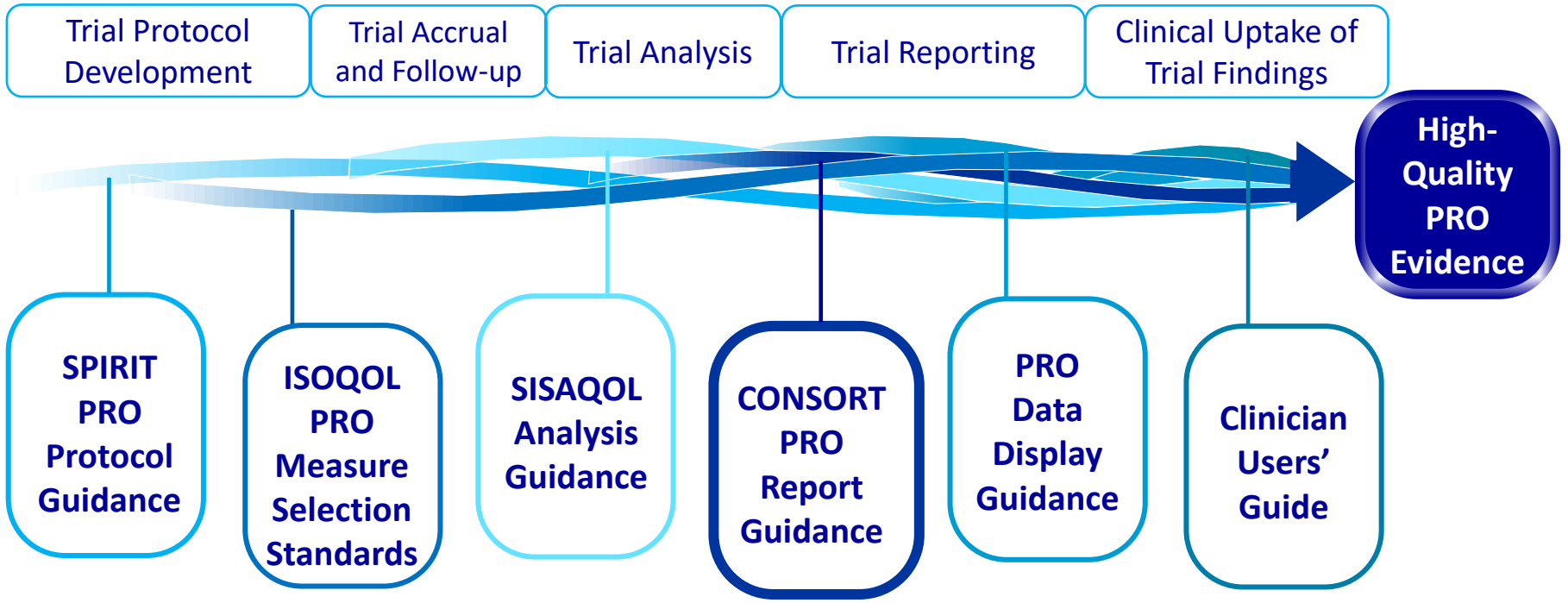
Funded by the Patient-Centered Outcomes Research Institute and Genentech

PROTEUS
Patient-Reported Outcomes Tools: Engaging Users and Stakeholders

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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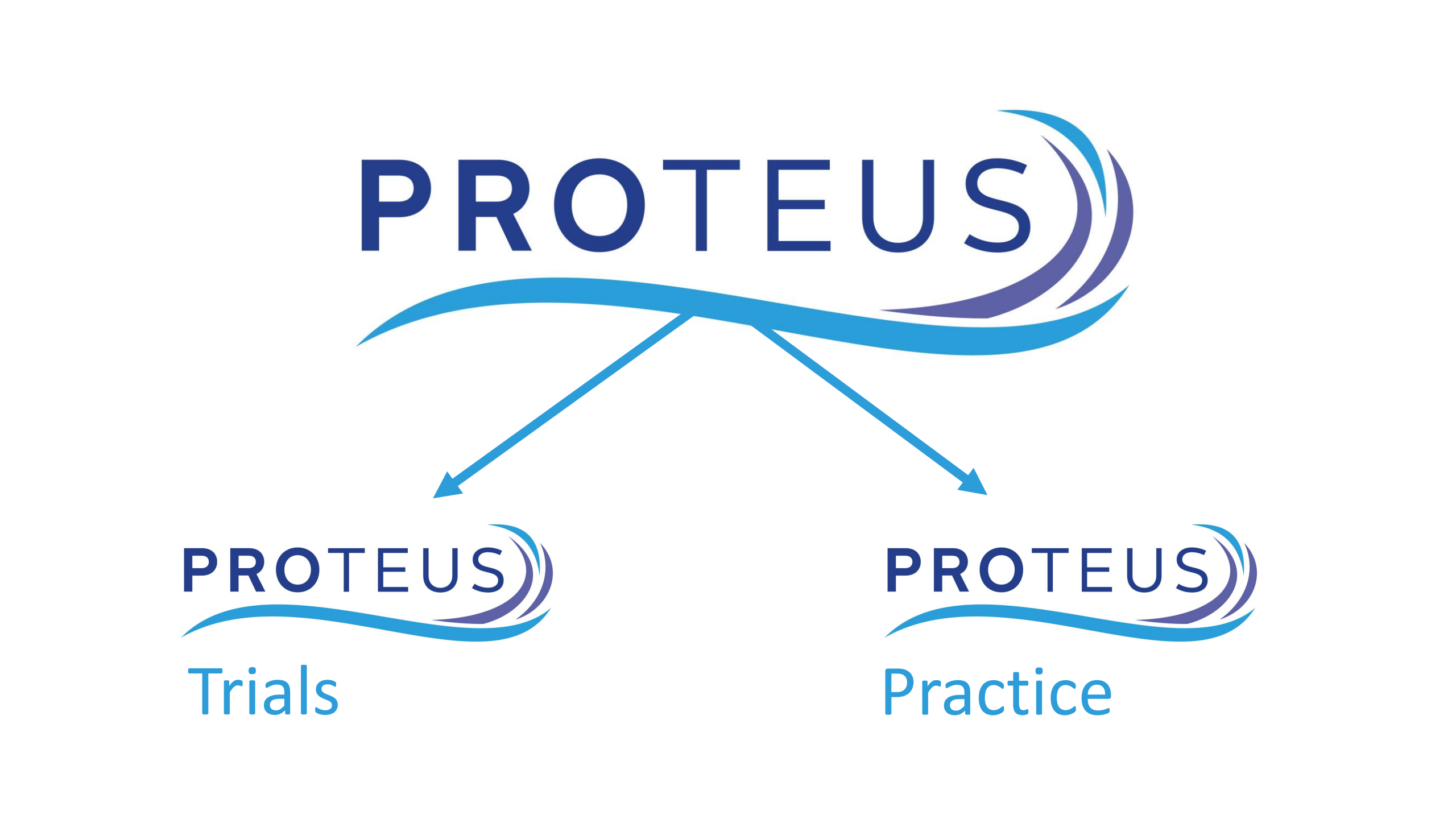
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Practice

Today's Presenters

Linda Nelsen, MHS

Sr Director and Head, Value Evidence and Outcomes - Patient Centered Outcomes
GlaxoSmithKline

Vishal Bhatnagar, MD

Associate Director for Patient Outcomes Oncology Center of Excellence, U.S. Food and Drug Administration

Pall Jonsson, BSc, PhD

Programme Director Data, Data and Analytics
National Institute for Health and Care Excellence (NICE)

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