Disclosures

– Linda Nelsen is an employee of GlaxoSmithKline and holds stock in GlaxoSmithKline

PROTEUS

An industry perspective

Linda Nelsen
Senior Director and Head, Oncology Patient Centered Outcomes
Value Evidence and Outcomes, Global Medical
GlaxoSmithKline

Value of PROs in Clinical Trials

PROs represent the **patient's voice embedded into clinical trials** in a way that allows us to **quantify** important concepts of patient experience of treatment benefit [and risk]

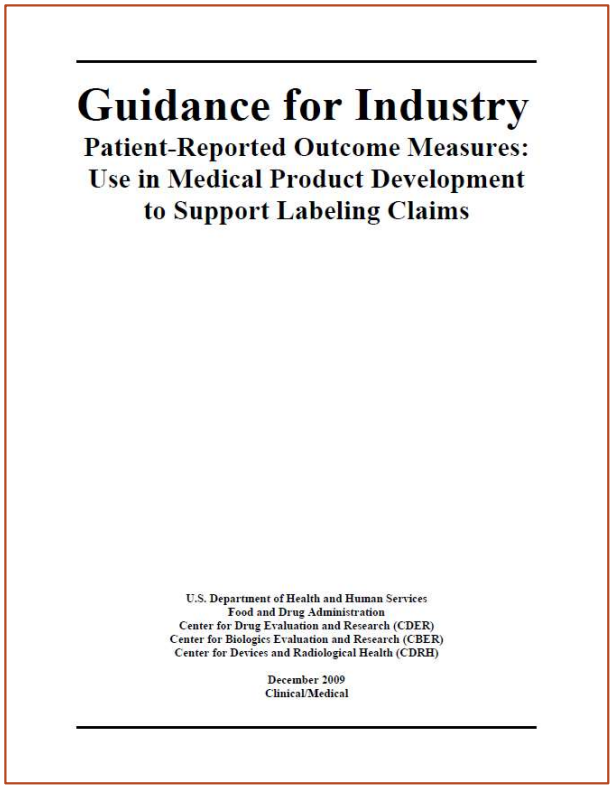
– Supports **patient focused drug development** (PFDD)

– Captures **patient perspective** on the treatment benefits (efficacy) and risks/harms (tolerability) of treatment to provide crucial understanding of the value of a therapy

– Successful PRO data collection supports **labeling claims** and is **informative to clinicians** for prescribing

– Physicians and patients can more fully **understand what it is like to live and function on a treatment** and make **better informed treatment decisions**

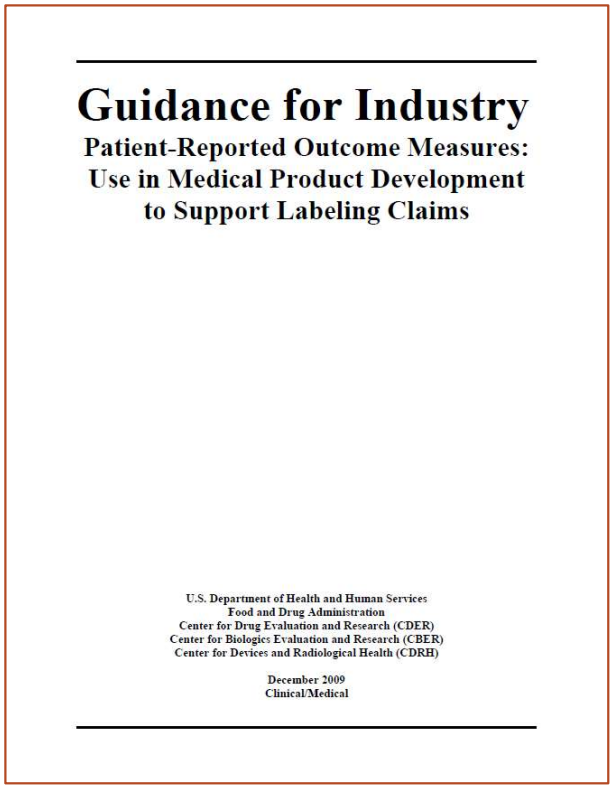
Current Evidence Standards for COA Assessments: *FDA PRO Guidance (c. 2009)*



- ✓ **Defines how the Agency interprets "well-defined and reliable**" (21 CFR 314.126) for PRO measures intended to provide evidence of treatment benefit
- ✓ **Defines good measurement principles for PRO measures which can be applied to all COA**
- ✓ **Content validity:** Evidence, **with patients,** that instrument measures the claimed concept
- ✓ **Context of use:** Use endpoint model to define role of PRO in context of ALL non-exploratory endpoints
- ✓ **Clinical trial data interpretation:** responder definition and Cumulative Distribution Function analysis emphasized; what is meaningful change?
- ✓ **PRO Evidence Package**: Submitted to FDA with NDA/ BLA

FDA PRO Guidance (c. 2009) Provides Evidentiary Standards

… but does not provide "how-to"



Guidance for Industry

Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

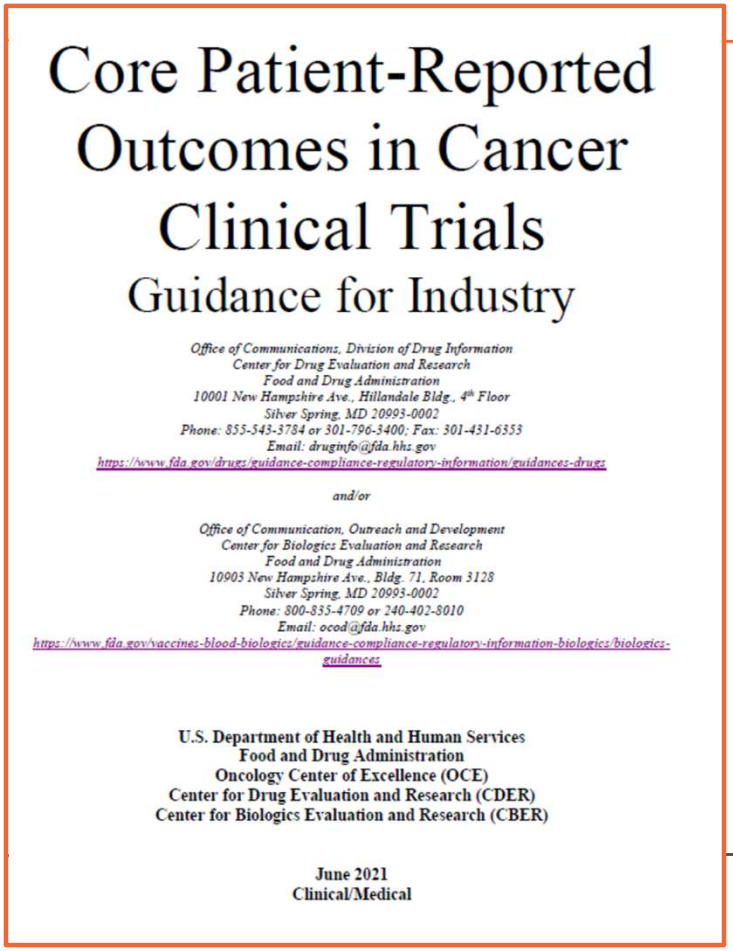
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2009
Clinical/Medical

- ✓ Standards to define fit-for-purpose PROs
- χ Key elements of a protocol with respect to PRO inclusion (SPIRIT-PRO)
- χ Optimal statistical analytic methods (SISAQOL)
- χ Reporting standards (CONSORT-PRO)
- χ Guidance for Graphical displays (PRO Data Display Guidance)
- χ Support for colleagues requiring an understanding of PRO data in publications and studies

Current Evidence Standards for COA Assessments: *Core Patient-Reported Outcomes in Cancer Clinical Trials (2021)*

WHC3



Core Patient-Reported Outcomes in Cancer Clinical Trials

Guidance for Industry

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

and/or

Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov
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U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2021
Clinical/Medical

Clarifies PFD and core PRO concepts

- Disease symptoms, treatment tolerability, physical function and role function
- Endorses approaches to reduce patient burden through flexible administration and use of pre-defined item subsets and subscales
- Links to PRO Guidance (2009) and upcoming PFDD Guidances 3 and 4

Emphasizes good trial design with respect to PROs with respect to

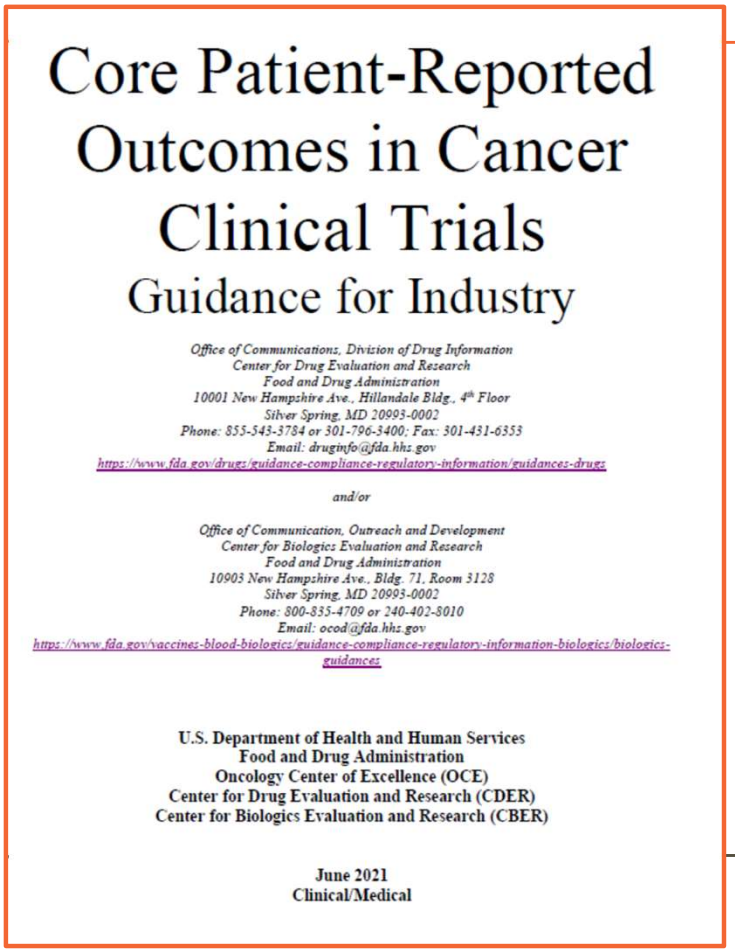
- Flexibility in frequency and timing of assessments related to treatment and PRO concept
- Minimization of missing data
- Rigorous endpoint definition
- Clearly defined analysis plans
- Rigorous protocol and analysis plan definition

Slide 6

WHC3 Does this oncology guidance provides what is lacking in the 2009 PRO guidance? I see that it does not per the next slide. In this case, is it necessary to show both guidance?

Wen-Hung Chen, 4/27/2022

Current Evidence Standards for COA Assessments: Provides Core Patient-Reported Outcomes *but not "how-to"*



Core Patient-Reported Outcomes in Cancer Clinical Trials

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U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2021
Clinical/Medical

- ✓ Standards to select fit-for-purpose PROs
- ✓ Key elements of a protocol with respect to PRO inclusion (SPIRIT-PRO)
- χ Optimal statistical analytic methods (SISAQOL)
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FDA Core Outcomes in Oncology

Framework of PRO Concepts for Oncology Clinical Trials

Overall Survival
Progression Free Survival
Overall Response Rate
Serum Biomarkers

CTCAE Safety Data
Dose Modifications

Hospitalizations
ED Visits
Morbid Procedures
Supportive Care Use

Clinician Reported and Biomarker Data

Disease Symptoms

Symptomatic Adverse Events

Overall Side Effect Impact

Physical Function:

Ability to carry out activities that require physical effort

Role Function:

Ability to work and perform leisure activities

Patient Generated Data

FDA. Core Patient Reported Outcomes in Cancer Clinical Trials. Guidance for Industry. *Draft Guidance*. June 2021

Final PRO Strategy for a Clinical Trial

Considerations beyond Proposed Core Concepts

Disease Symptoms

Symptomatic Adverse Events

Overall Side Effect Impact

Physical Function:

Ability to carry out activities that require physical effort

Role Function:

Ability to work and perform leisure activities

+

- Other agency preferences for alternate PROs
- Requirements from HTA for specific PROs or version
- PRO concepts in competitor labels
- PRO completion burden
- Data management and analytic constraints
- Licensing and translation within timelines

Patient Generated Data

FDA. Core Patient Reported Outcomes in Cancer Clinical Trials. Guidance for Industry. *Draft Guidance*. June 2021

Characterizing the Patient Experience:
PRO Concept Measurement to Support Clinical Endpoints

PRO Concepts	PRO Measures	Endpoint Hierarchy	Endpoint
▪ Specific XXX Symptoms	▪ EORTC XXX Cancer Module	Secondary	▪ Time to deterioration in XXX cancer symptoms
▪ Physical Function	▪ EORTC QLQC30 Physical Function domain + supplemental items	Secondary	▪ Time to deterioration in physical function
• Symptomatic Side Effect	▪ PRO CTCAE	Exploratory	• Frequency and severity of pre-specified AEs and impacts as measured by the PRO-CTCAE
▪ Overall Side Effect Impact	▪ FACT GP5	Exploratory	• Level of overall bother/tolerability as measured by the single item FACT-GP5
▪ HRQOL	▪ EORTC QLQ-C30	Exploratory	• Time to deterioration in other cancer symptoms, functioning and HRQOL as measured by EORTC QLQ-C30 and EORTC XXX
▪ HRQOL and Utilities	▪ EQ-5D-3L	Exploratory	• Change from baseline and overall HRQOL and for health state utilities

Consideration of Patient PRO Completion Burden

PRO Completion Timing

PRO	C1	C2	C3	C4-C17	EOT	Follow-up
PRO CTCAE	X	X	X	Every 2nd cycle	X	--
EORTC QLQC30 EORTC XXX PROMIS-PF-8C PGI-S	X	X	X		X	Q180D
PGI-C		X	X		X	
EQ-5D-3L	X	X	X		X	--

Some Considerations

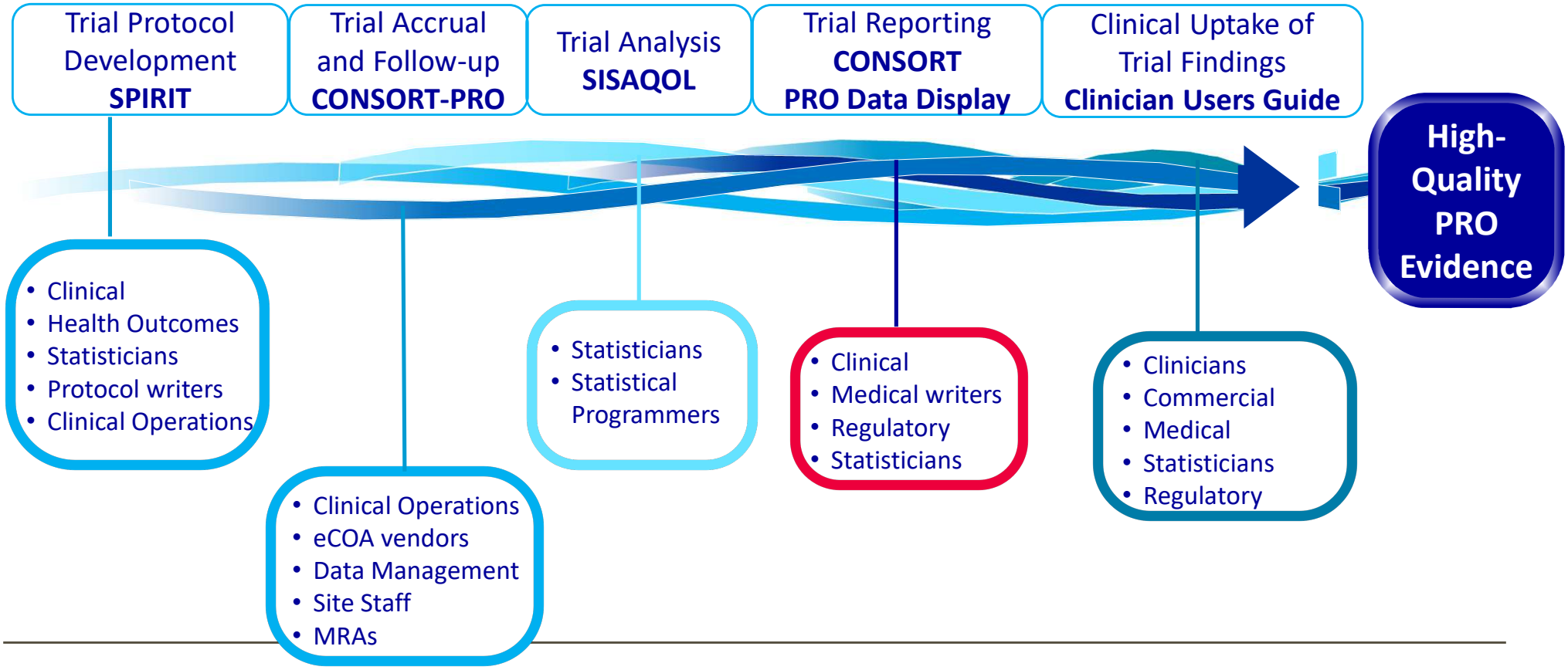
- Symptom trajectory
- Symptomatic tolerability trajectory
- Home or site completion
- Site burden
- Patient burden

Analysis of PRO Endpoints

Ongoing training for Statisticians on Challenges unique to PRO data

- **Treat PRO endpoints within the endpoint hierarchy with the same rigor as clinical endpoints**
  - Define hypothesis and estimands
  - Test with pre-specified plan for analysis including thresholds for meaningful change
- **Non-inferiority or equivalence claims** (i.e. maintenance therapies) require evidence that the measure is sensitive and trial adequately designed with a justified non-inferiority margin
- Definition and use of clinically meaningful change thresholds
- Scoring of PROs
- Handling informatively and randomly missing data

PROTEUS Roadmap
It takes a village in Pharma …



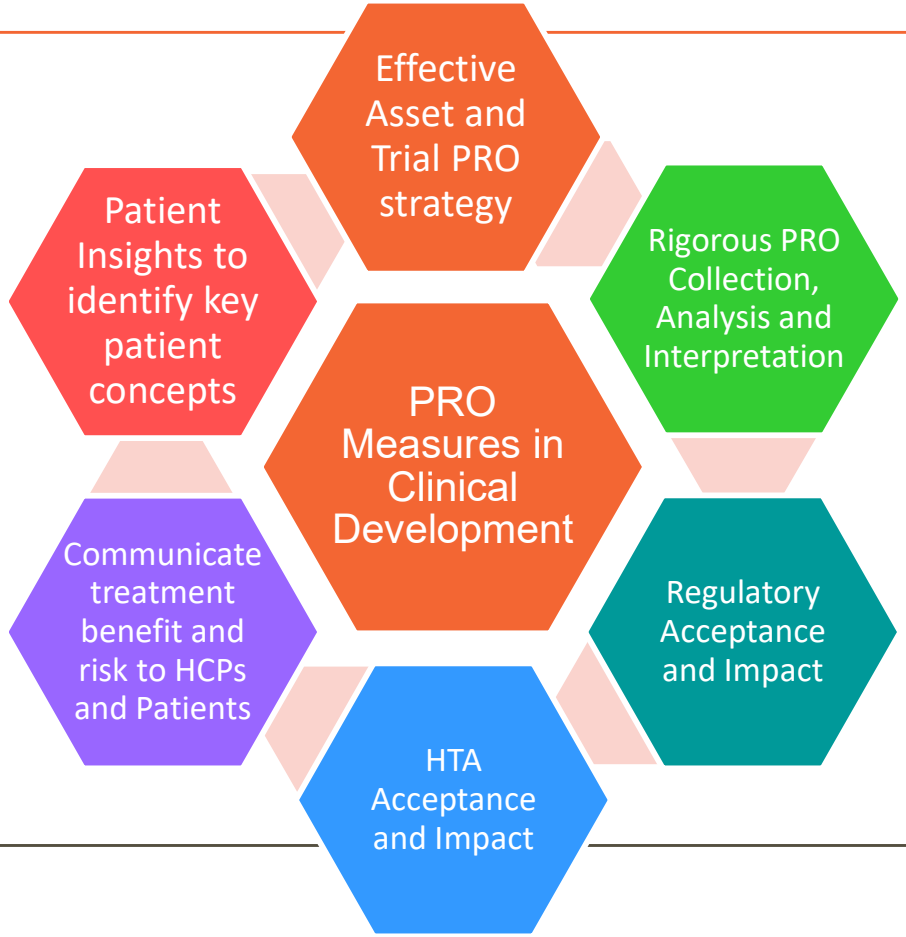
PROTEUS

How can Industry use PROTEUS tools efficiently

- Training
  - “Just in time” targeted training specific to function
- Working Checklists
  - Provide to protocol and medical writers
- Quality Control reviews
  - Support informed review of documents
- Support internal standards development
- Support communication between PRO team and internal stakeholders

Challenges in Demonstrating PRO Value

Go beyond the Clinical Trial



Conclusions

Pharmaceutical Perspective on PROTEUS

- PROTEUS helps to develop internal confidence and understanding of PRO implementation, analysis and interpretation in clinical trials
- Supports awareness of current published best practices for PRO identification, implementation, analysis, reporting and dissemination
- Supports efficient targeted training
- Provides accessible tools for study teams

- Supports rigorous implementation, analysis and reporting of PRO data from clinical trials to optimize patient focused drug development

Contact Information

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