Patient-Reported Outcomes in Clinical Trials and Clinical Practice: The PROTEUS Consortium

Claire Snyder, PhD
PROTEUS Consortium Principal Investigator
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The PROTEUS Consortium:

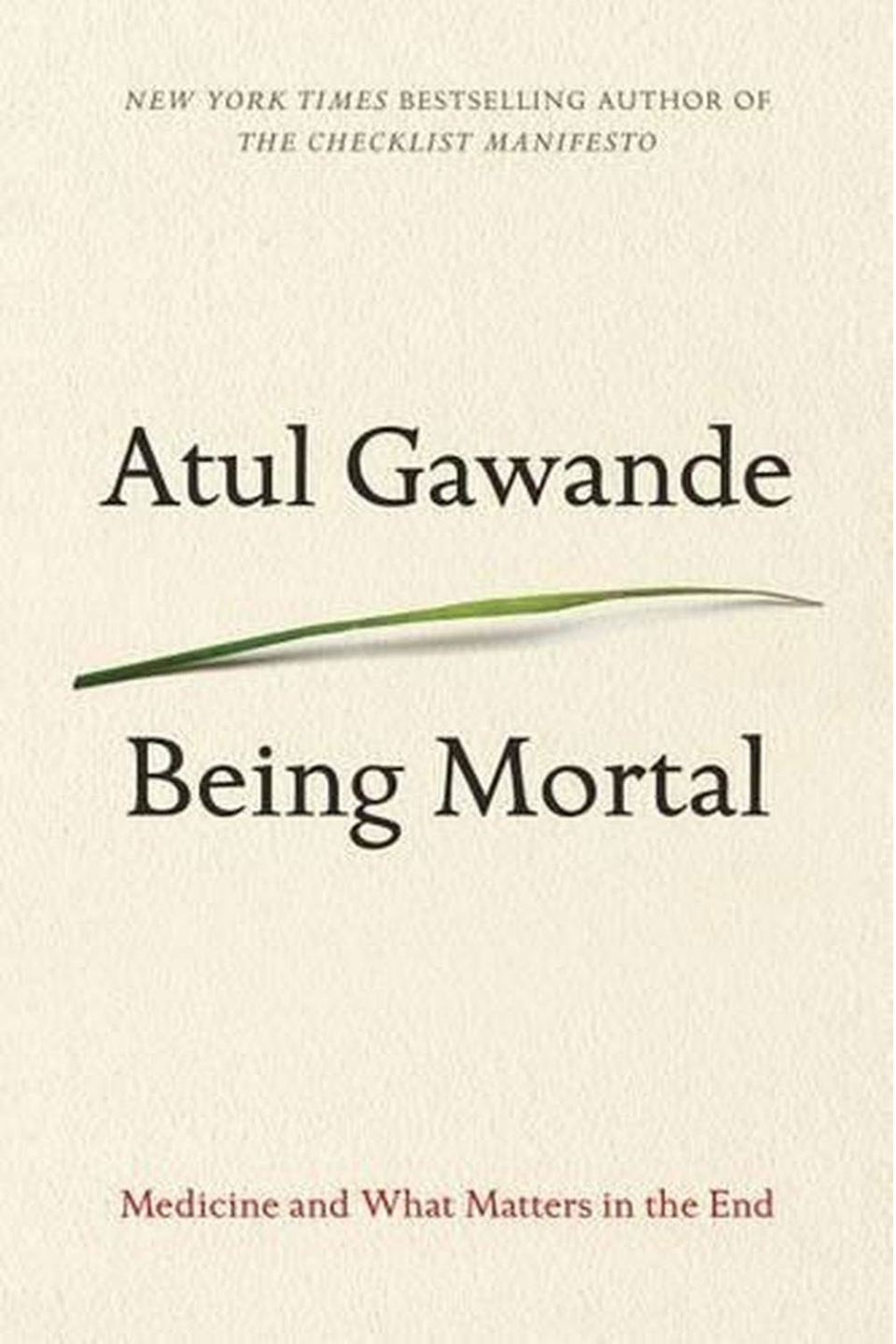
- Originally funded by the Patient-Centered Outcomes Research Institute and unrestricted funding from Genentech
- Ongoing unrestricted support from Pfizer

PROTEUS-Pfizer Collaborations:

- PRO Implementation Grants Project
- Advisory Group for PRO Implementation in Vulnerable and Underserved Populations
- Grants Project on the Value of PROs

Other Disclosures:

- Personal consulting fees from Shionogi



"As time passed, my father noticed no change in his symptoms…It was ultimately a year before he returned to see [the doctor]. A repeat MRI showed the tumor had enlarged. Yet physical examination found no diminishment in my dad's strength, sensation, or mobility. ***So, they decided to go primarily by how he felt, not by what the pictures looked like.*** *The MRI reports would say haunting things, like the imaging 'demonstrates significant increase in size of the cervical mass at the level of the medulla and midbrain.' But for months at a stretch, nothing occurred to change anything relevant for how he lived."*

p199

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

How are Patient Perceptions 'Measured'? i.e., Turned Into Valid and Reliable Data

- Standardization is the key
- 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

➢ 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')

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Example: Physical Function Measure

	Not at all	A little bit	Quite a bit	Very much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or 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 the house?	1	(2)	3	4
4. Do you need to stay in bed or a 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

Scale Score = [1- (Raw Score-1)/Range]*100

Raw Score (Mean of Component Items): (3+3+2+2+1)/5 = 2.2
Convert to 0-100 Range: [1-(2.2-1)/3]*100 = **60**

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CONSORTIUM

Patient-Reported Outcomes Tools: Engaging Users & Stakeholders

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

TheProteusConsortium.org

The PROTEUS Consortium

- **OBJECTIVE**

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

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Organizations with PROTEUS Participants

Clinician & Patient Advocates

1. American Cancer Society
2. American Society for Radiation Oncology
3. American Society of Clinical Oncology
4. Canadian Association of Radiation Oncology
5. National Coalition for Cancer Survivorship
6. Oncology Nursing Society
7. Patient perspective

Research & Methods Organizations

8. AcademyHealth
9. Consolidated Standards for Reporting of Trials (CONSORT)
10. International Society for Quality of Life Research
11. ISPOR
12. Society for Clinical Trials
13. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)
14. International Consortium for Health Outcomes Measurement (ICHOM)
15. medical journal editor perspective

Clinical Trials Groups

16. Australian Clinical Trials Alliance
17. Critical Path Institute PRO Consortium
18. European Organization for the Research and Treatment of Cancer
19. Industry (GSK)
20. National Clinical Trials Network PRO representatives

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

Organizations with PROTEUS Participants

Funding & Govt. Agencies

21. European Medicines Agency-Scientific Advice Working Party / Dutch Medicines Evaluation Board
22. Food & Drug Administration - Oncology Center of Excellence
23. HealthCanada
24. Medicines and Healthcare Products Regulatory Agency
25. National Cancer Institute
26. National Institute for Health and Care Excellence
27. Patient-Centered Outcomes Research Institute

Universities & Health Systems

28. AmbuFlex Center for Patient Reported Outcomes (Denmark)
29. Amsterdam University Medical Center and the KLIK PROM Portal
30. CancerAustralia
31. Cancer Care Alberta
32. Centre for Patient Reported Outcomes Research, University of Birmingham (UK)
33. Children's Hospital of Philadelphia
34. Dartmouth Health and The Dartmouth Institute for Health Policy and Clinical Practice
35. Emory University
36. George Washington University
37. Kettering Health
38. MD Anderson
39. Memorial Sloan Kettering Cancer Center
40. Moffitt Cancer Center
41. Northwestern University
42. PROMPT-Care (Australia)
43. PROVE Center at Brigham Health
44. Thomas Jefferson University
45. University of California-Los Angeles
46. University of California-San Francisco
47. University of Michigan
48. University of North Carolina-Chapel Hill
49. University of Rochester
50. University of Utah Health
51. Washington University in St. Louis
52. West Virginia University

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

Use of Patient-Reported Outcomes in Clinical Trials

Mr. Q (1)

- Diagnosed with a new, early-stage non-small cell lung cancer in 2003
- Treated with thoracotomy that accomplished an apparent complete resection
- Data show that chemotherapy is associated with a 3-year survival benefit, but at the cost of side effects and toxicities

What information does Mr. Q need to make his decision regarding chemotherapy?

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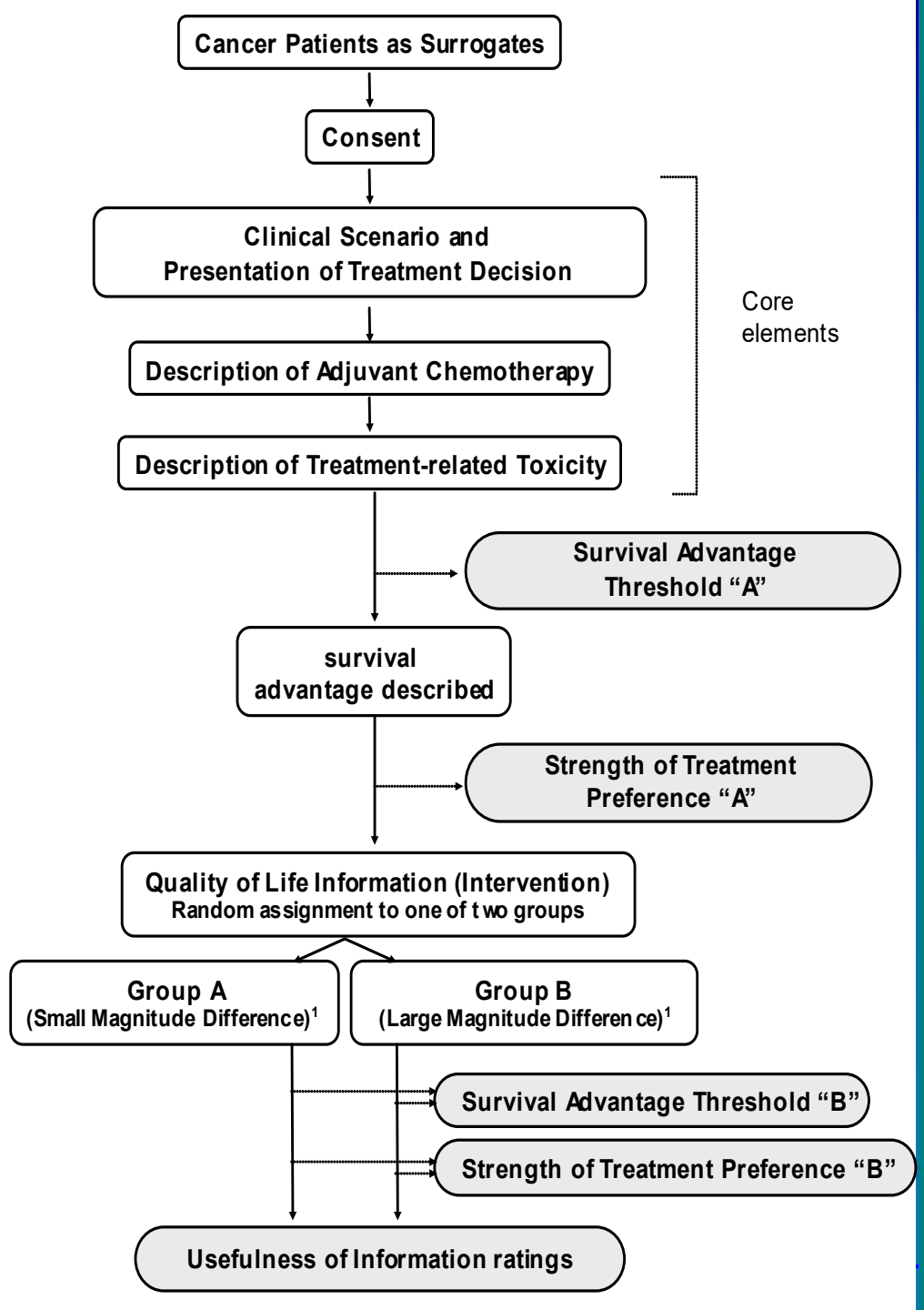
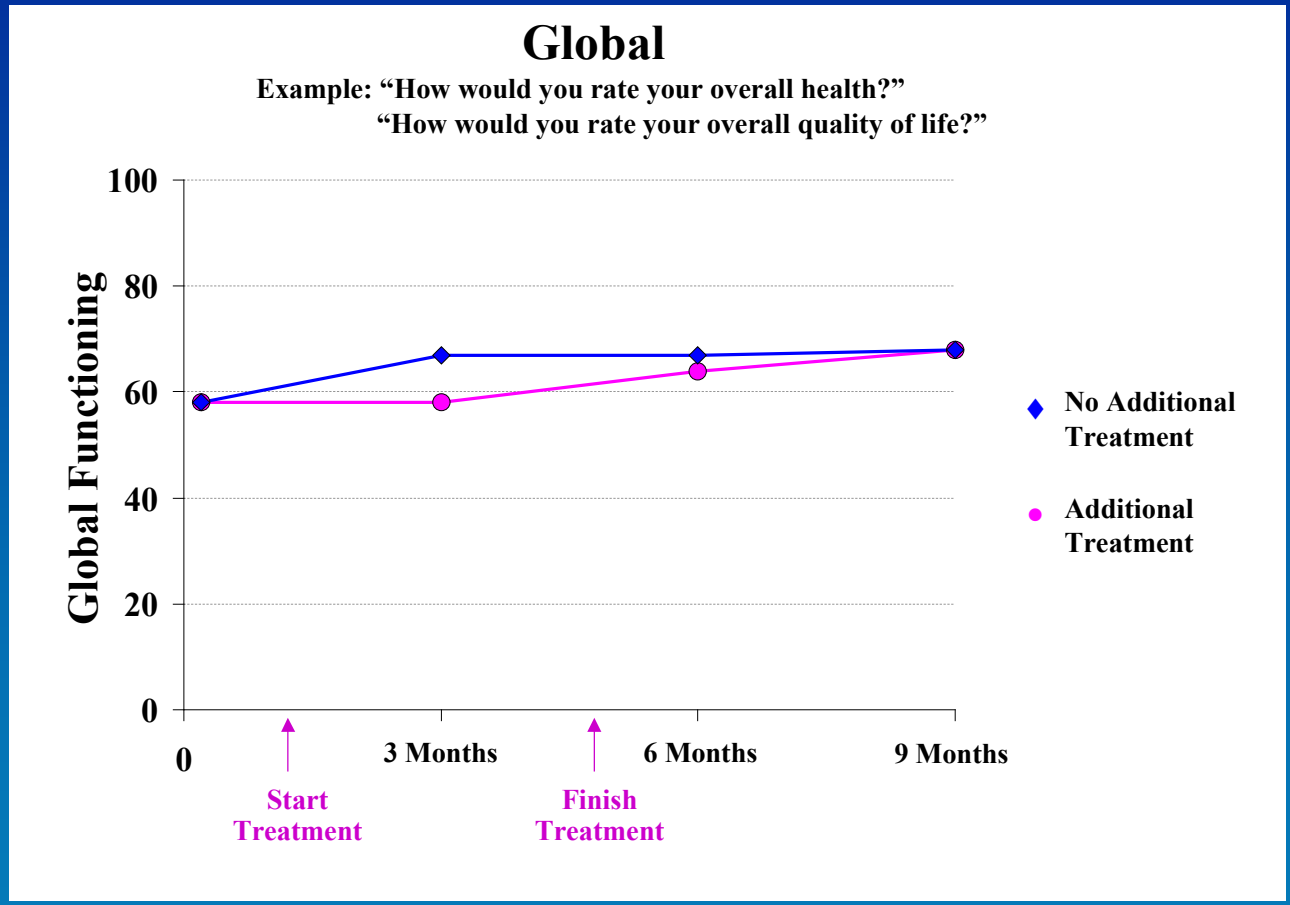
Slide courtesy of Michael Brundage, MD, MSc
Queen's Cancer Research Institute

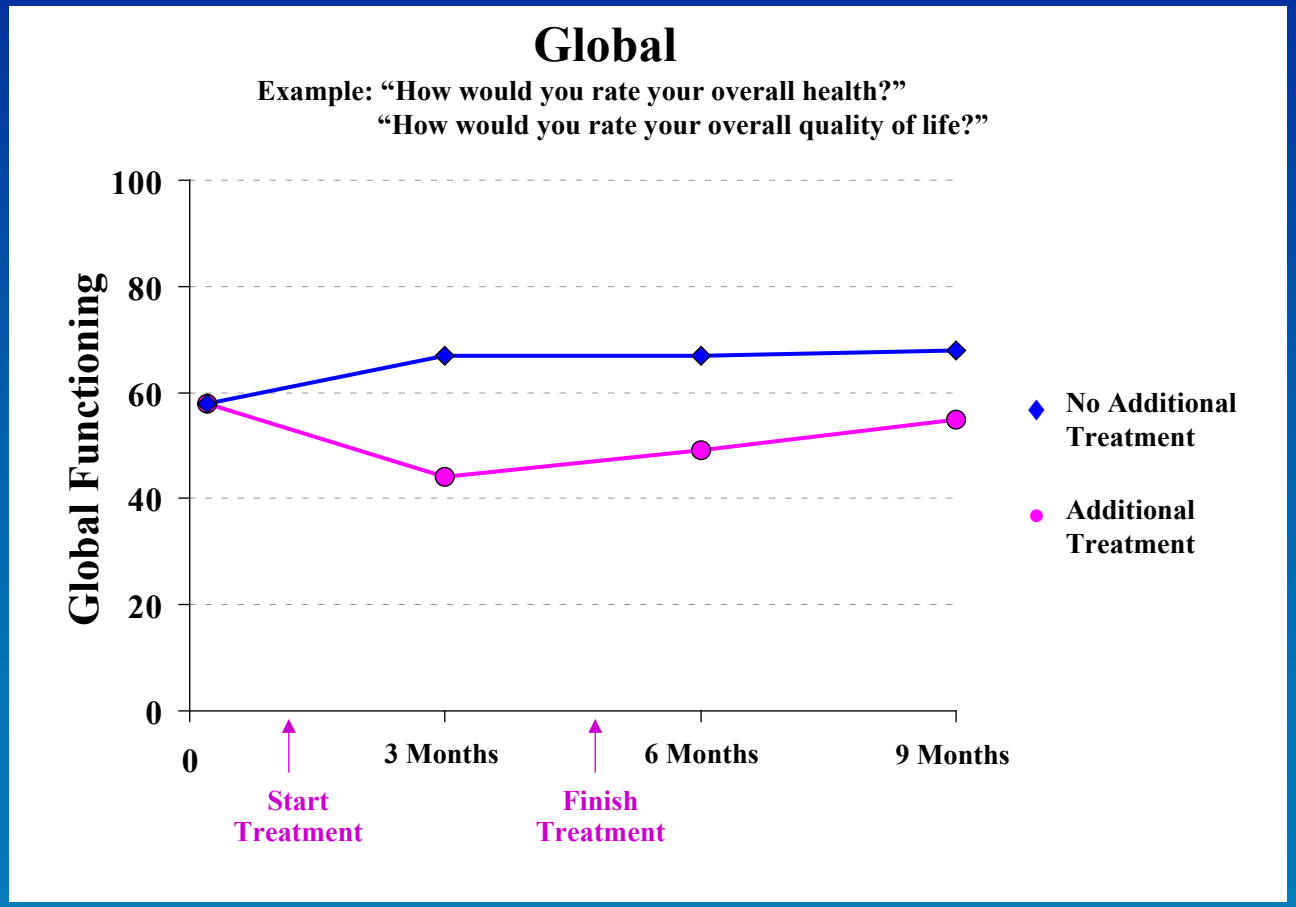


Global Quality of Life Results



Slide courtesy of Michael Brundage, MD, MSc Queen's Cancer Research Institute

Global Quality of Life Results



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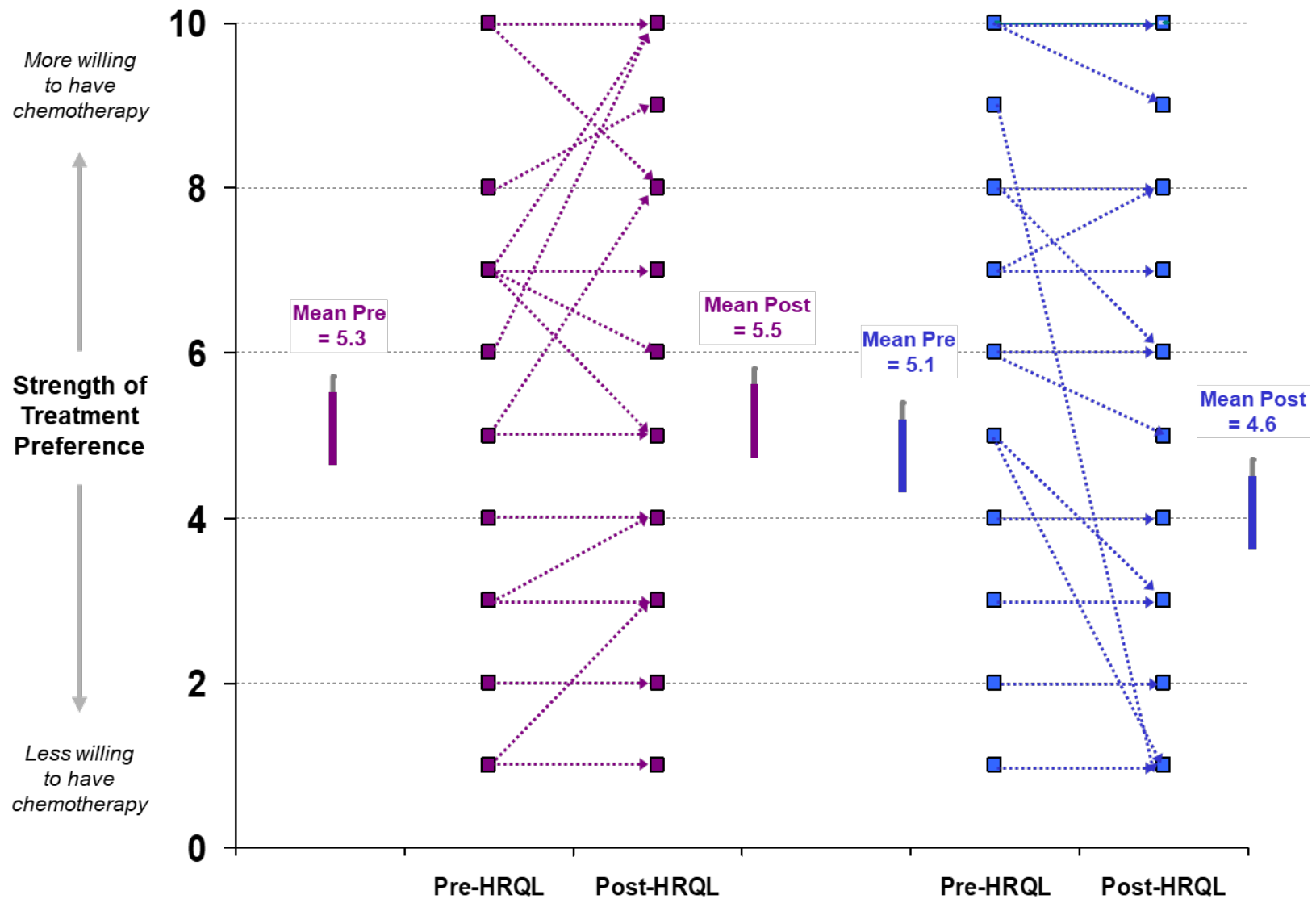
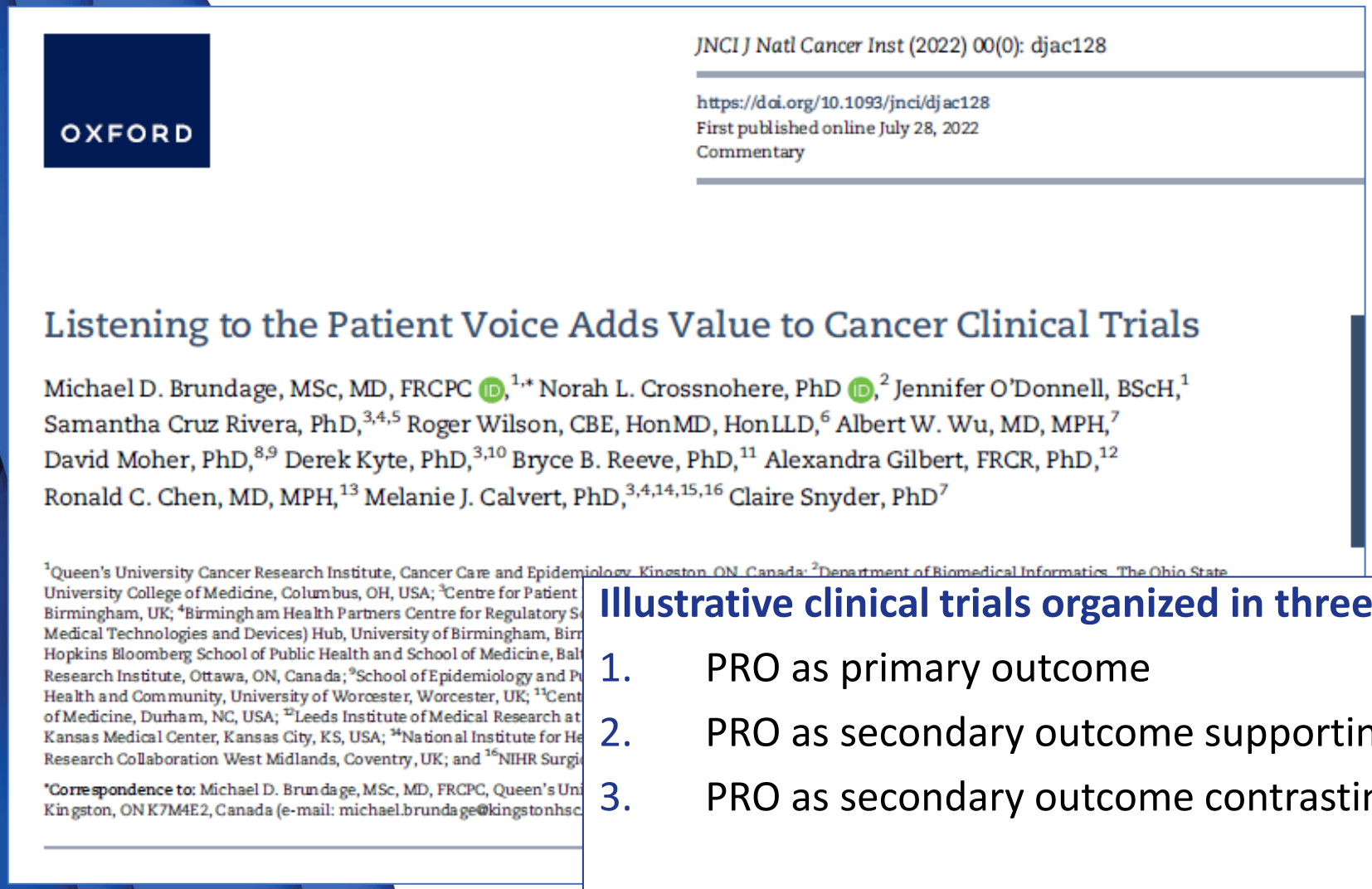


Small-magnitude HRQL difference **Large-magnitude HRQL difference**

Slide courtesy of Michael Brundage, MD, MSc Queen's Cancer Research Institute



JNCI J Natl Cancer Inst (2022) 00(0): djac128

https://doi.org/10.1093/jnci/djac128
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Commentary

Listening to the Patient Voice Adds Value to Cancer Clinical Trials

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Illustrative clinical trials organized in three categories:

1. PRO as primary outcome
2. PRO as secondary outcome supporting primary outcome findings
3. PRO as secondary outcome contrasting primary outcome findings

➢ Impact on clinical decision making, clinical guidelines, drug labeling claims, cost-effectiveness, or health policy, etc.

Brundage et al, JNCI 2022;djac128

Qual Life Res (2011) 20:979–985
DOI 10.1007/s11136-011-9848-0

A knowledge translation challenge: clinical use of quality of life data from cancer clinical trials

Michael Brundage · Brenda Bass · Ringash Jolie · Kimberley Foley

42% Feel comfortable interpreting quality of life data from the clinical trial literature

67% Feel need to improve/increase use of clinical trial quality of life data in clinical practice

PROTEUS Trials 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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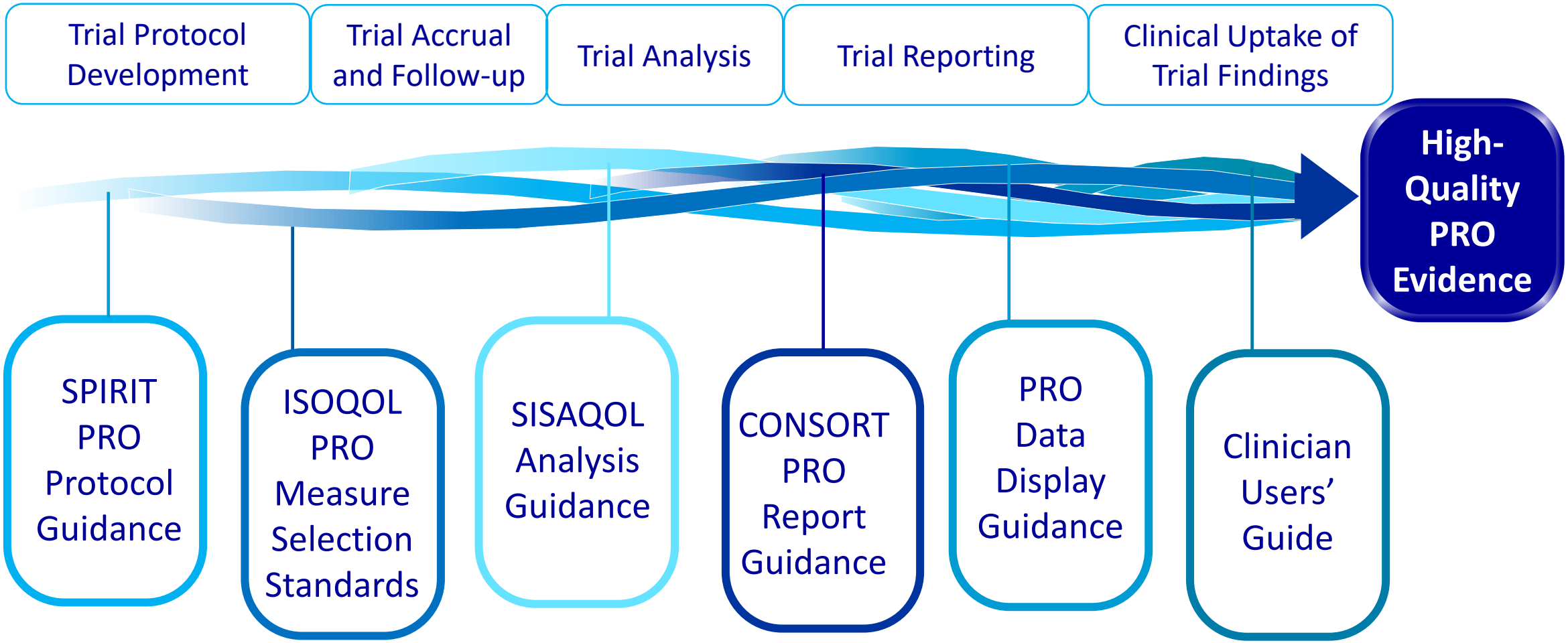
PROTEUS Trials Roadmap



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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 ow
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

“6 Tools-1 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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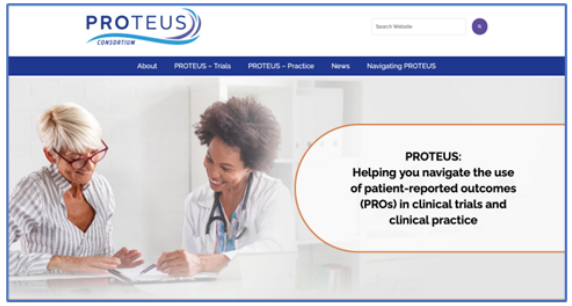
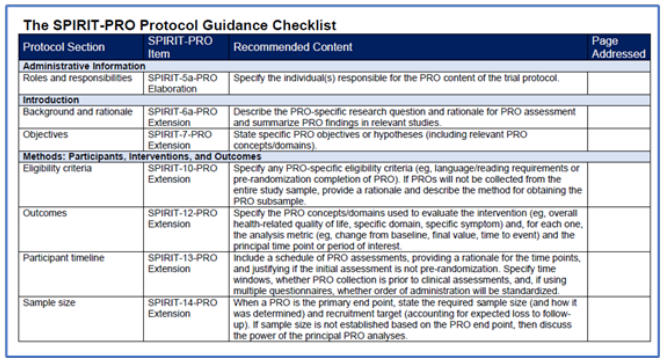
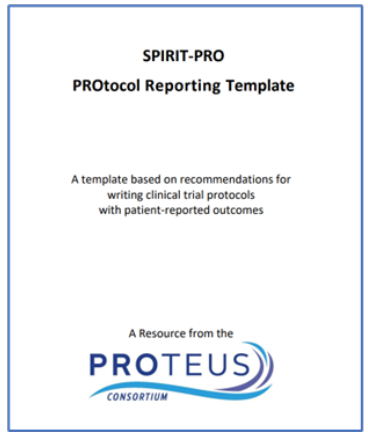
Resources to Support the Use of PROs in Clinical Trials

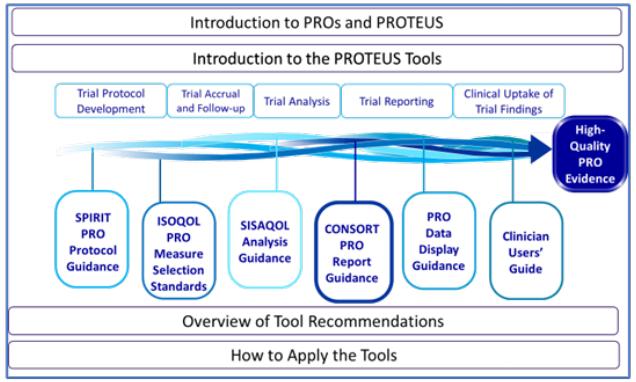


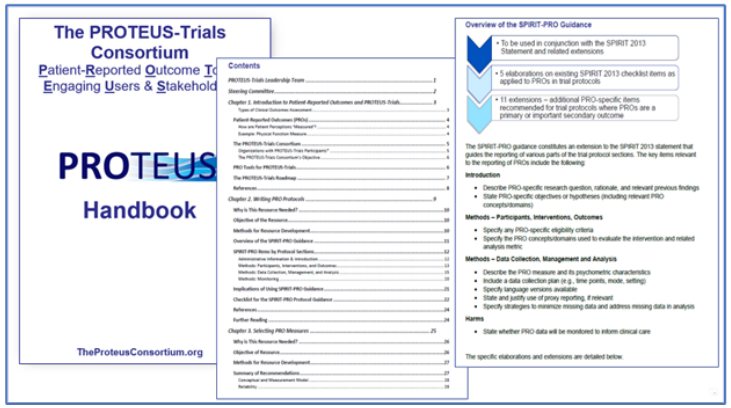


The SPIRIT-PRO Protocol Guidance Checklist

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.	







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Use of Patient-Reported Outcomes in Clinical Practice

Mr. Q (2)

- Decides to undergo chemotherapy
- Advised he may experience hair loss, fatigue, anorexia, gastrointestinal symptoms, respiratory symptoms, infections, and neurologic symptoms

What role can PROs play in caring for Mr. Q during treatment?

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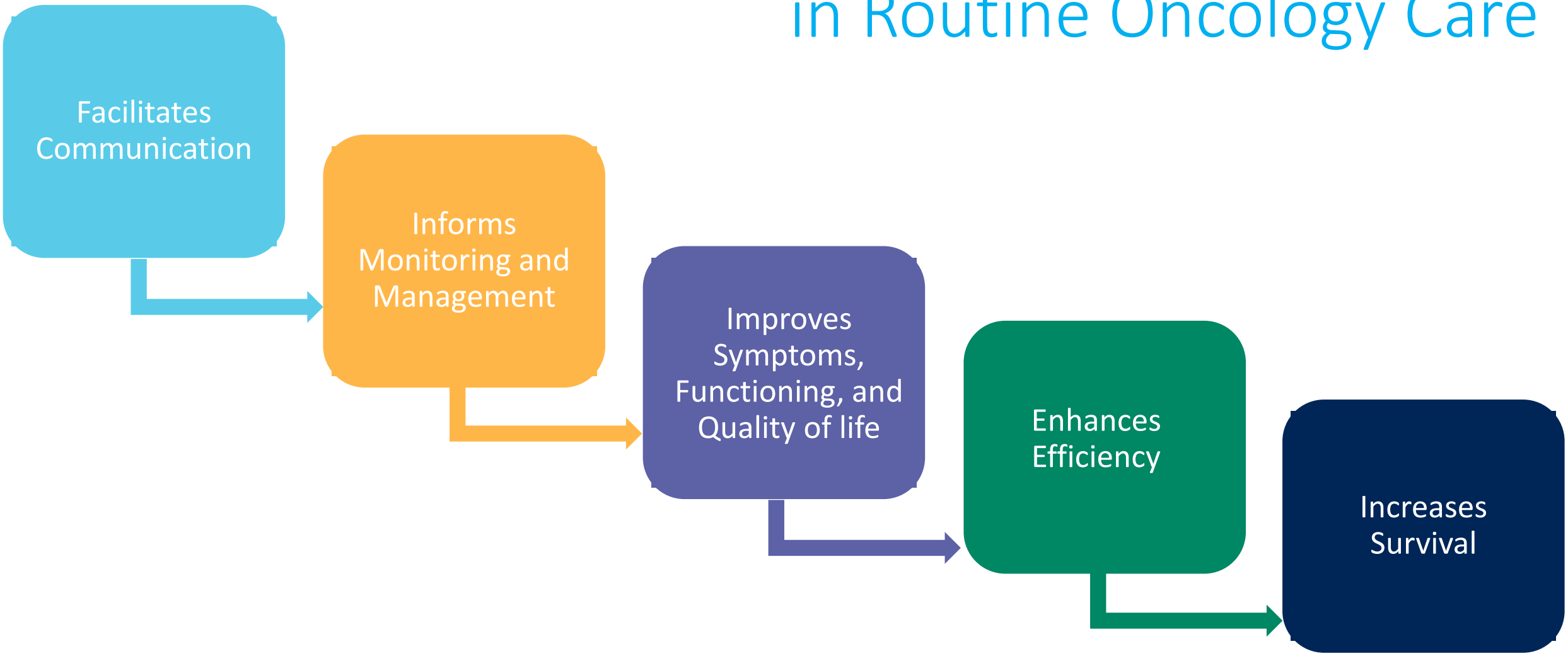
“When the doctor asks, ‘How are you?’ and you say, ‘Fine,’ the doctor thinks he has gathered clinical facts, while you think you have been polite.”

Mother of a Child with Cancer

Lynn et al, Handbook for Mortals, p69

Possible Benefits of Using PROs in Routine Oncology Care



Better Communication

"I think this is a good idea especially for people who tend to forget in between appointments what was going on and what they want to tell the doctor when they see him…"

"I had never thought to bring up the body image issues with my doctor because I didn't really think that they were "medical" things…If he hadn't asked about it, we would never have talked about it. I am glad we did though. It was reassuring."

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Snyder et al. Psycho-Oncology 2013;22:895-901

Better Communication

"…it showed me that she was having more symptoms of depression than she had been reporting to me during her visits."

"I felt that he was more engaged in the treatment by taking the surveys."

"…we adjusted her treatment schedule and dosing to address the issues that she raised."

"It was less painful than I thought it would be."

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Snyder et al. Psycho-Oncology 2013;22:895-901

Better Symptom Control

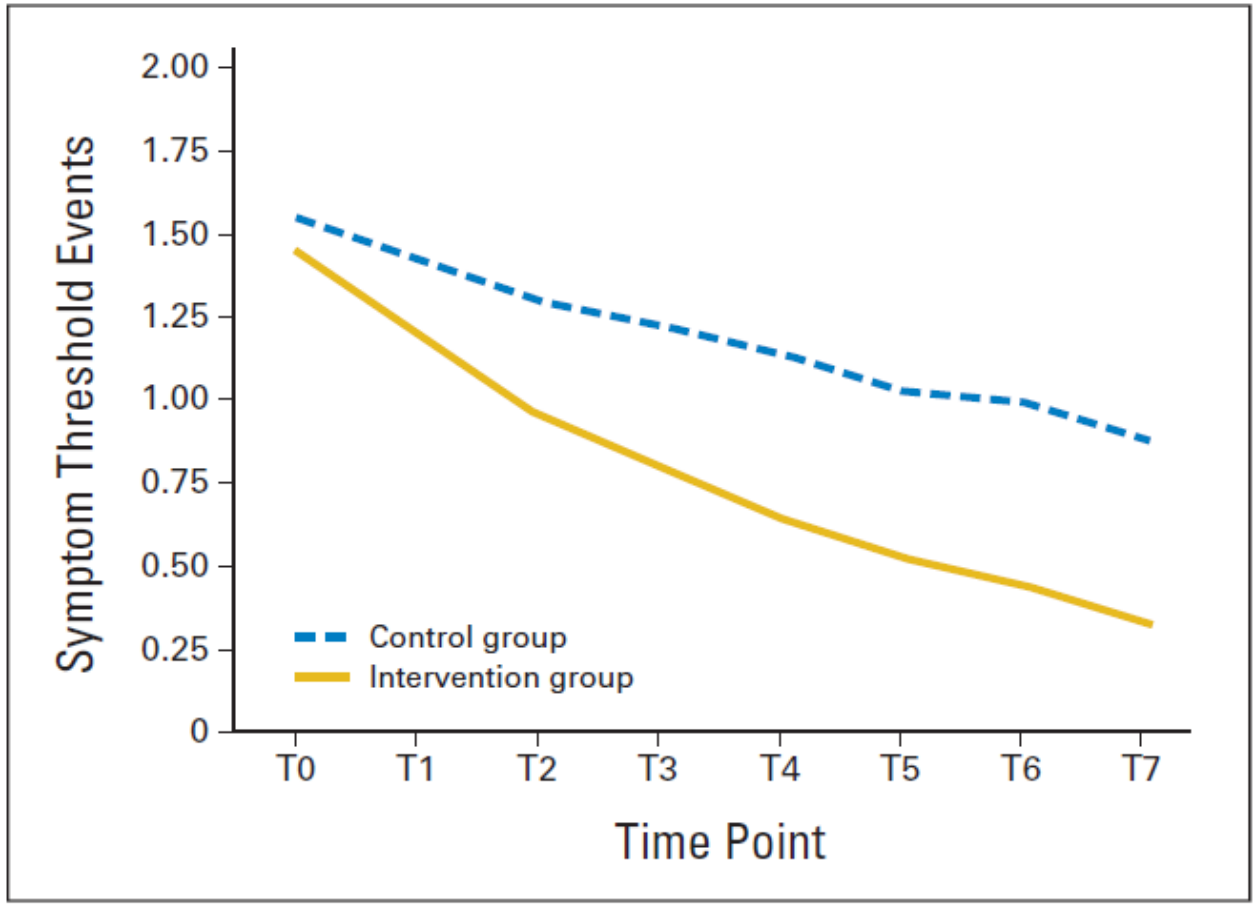

Fig 3. Mean symptom threshold events per patient.

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Cleeland et al. JCO 2011;29:994-1000

Improved Quality of Life

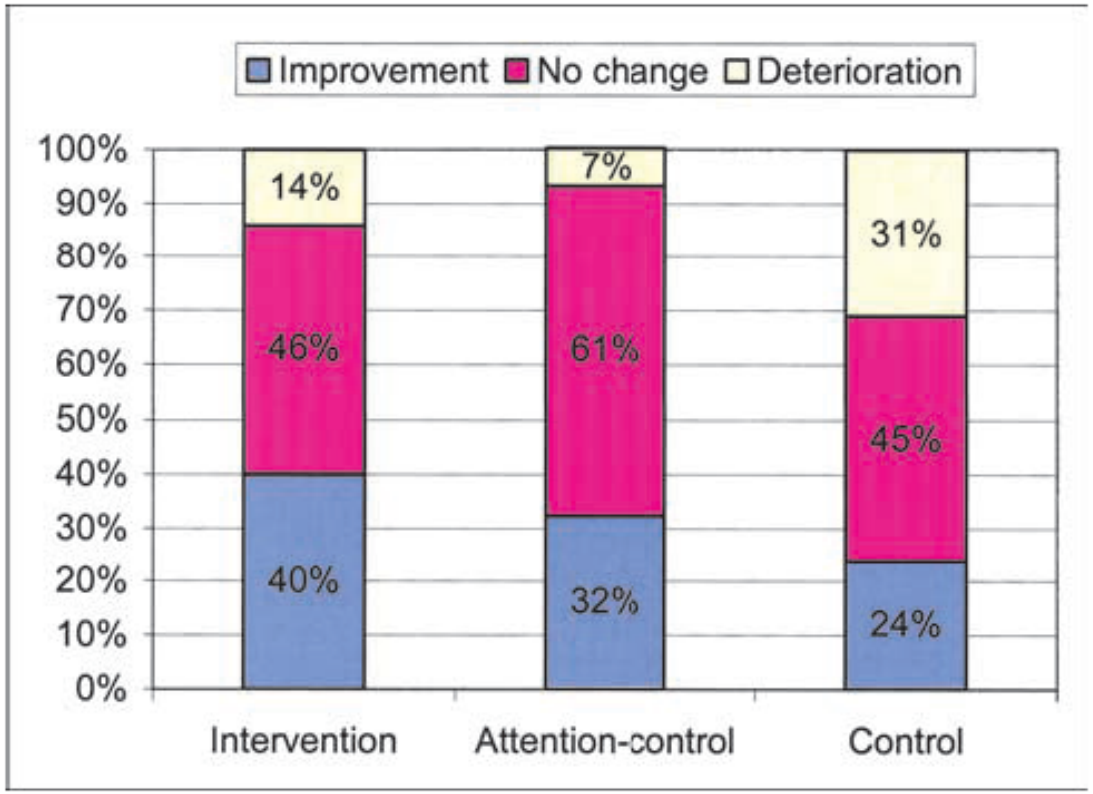

Fig 4. Proportions of patients showing clinically meaningful improvement, no change, or deterioration in Functional Assessment of Cancer–General (FACT-G) score after three encounters, by study arm. Intervention versus attention-control and control groups, $P = .001$; intervention and attention-control versus control, $P = .003$, using ordinal regression, controlling for baseline FACT-G, performance status, and time on study.

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Velikova et al. JCO 2004;22:714-724

Improved Quality of Life

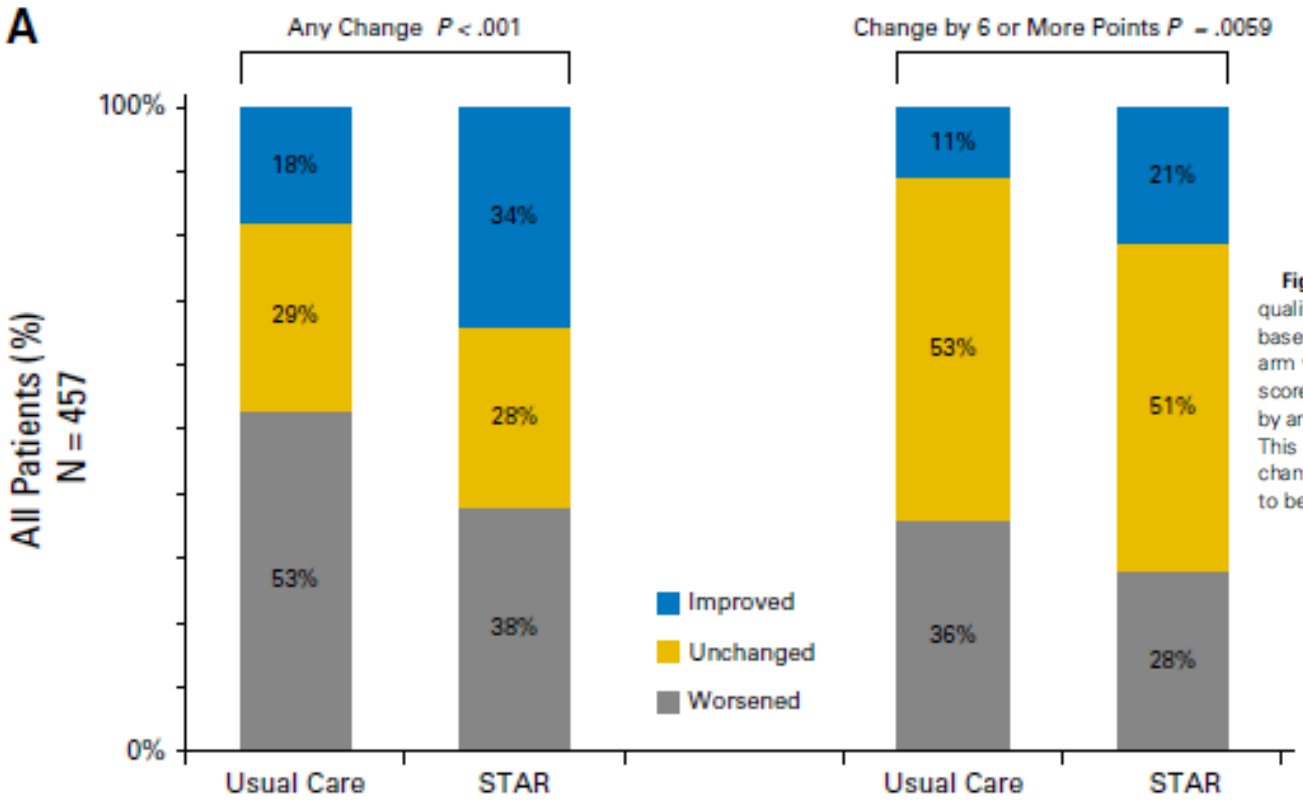

Fig 2. Proportion of patients with health-related quality-of-life changes at 6 months compared with baseline. The proportion of patients in each study arm was tabulated for which EuroQol EQ-5D Index scores improved, remained unchanged, or worsened by any amount at 6 months compared with baseline. This analysis was repeated using a threshold for change of six or more points, an amount considered to be clinically meaningful in US cancer populations.

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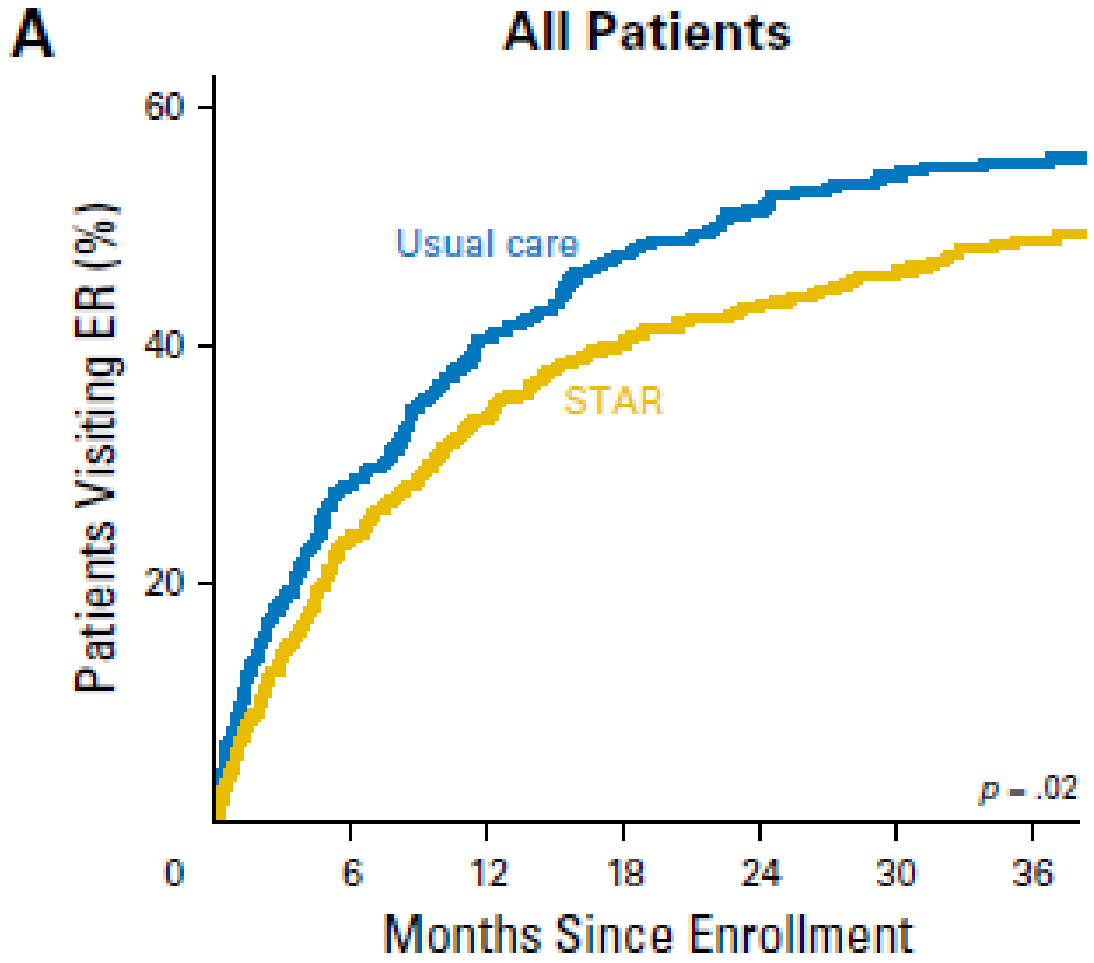
Basch et al. JCO 2015;34:557-565

More Efficient Resource Use



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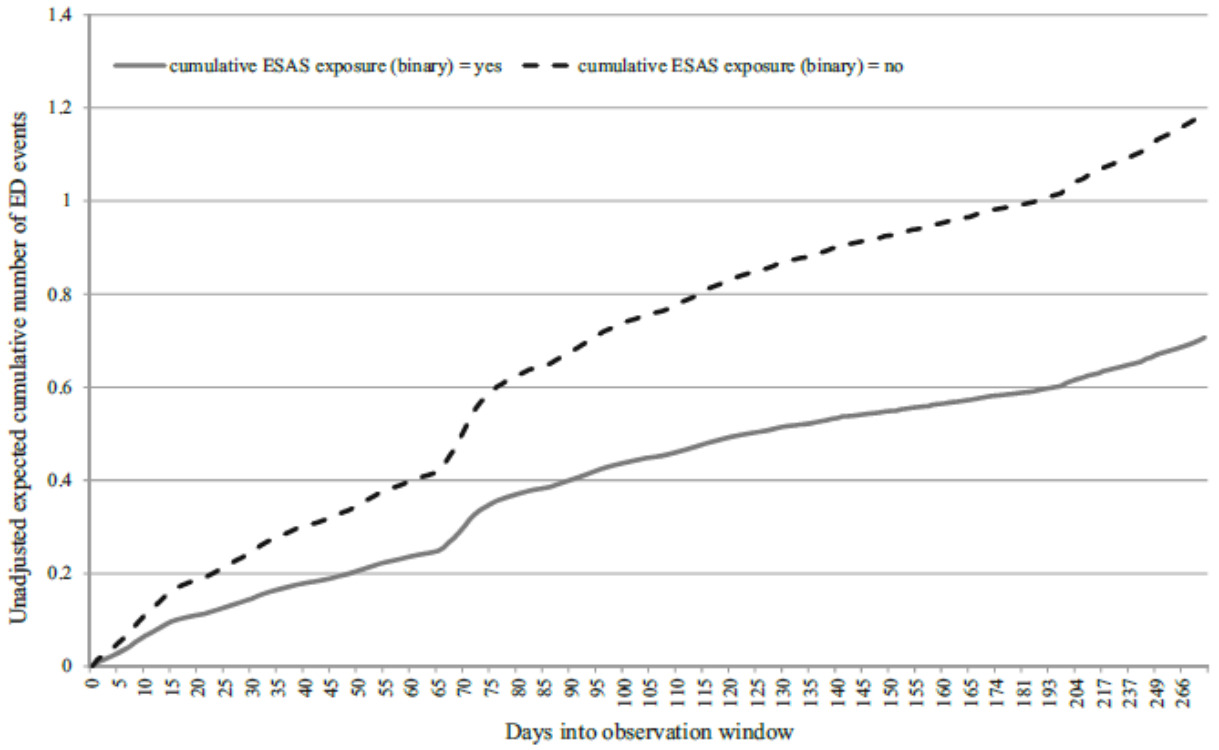
Basch et al. JCO 2015;34:557-565

More Efficient Resource Use

Fig. 1 Mean cumulative unadjusted ED rate by ESAS exposure



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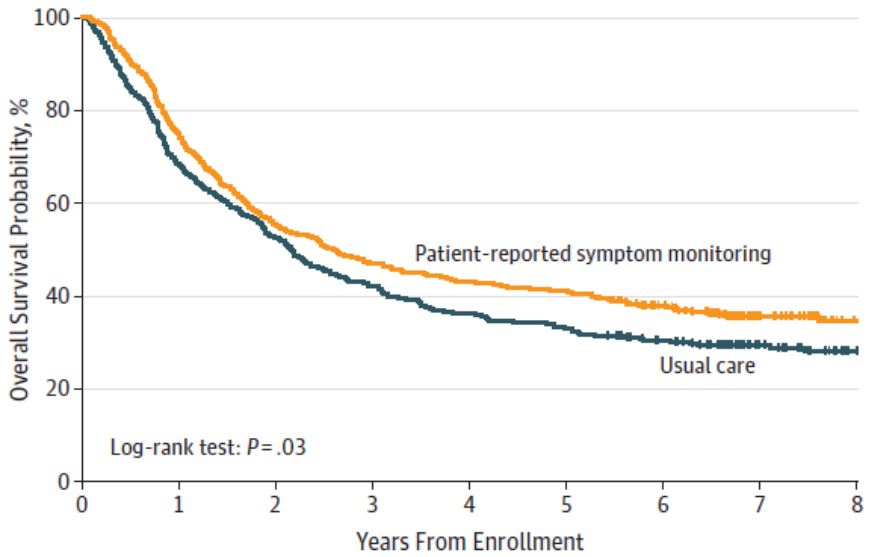
Barbera et al. Support Care Cancer 2015;23:3025-32

Improved Survival

Figure. Overall Survival Among Patients With Metastatic Cancer Assigned to Electronic Patient-Reported Symptom Monitoring During Routine Chemotherapy vs Usual Care



No. at risk									
Patient-reported symptom monitoring	441	331	244	207	190	181	148	65	33
Usual care	325	223	171	137	118	107	89	50	27

Crosses indicate censored observations. Enrollment in the patient-reported symptom monitoring group was enriched for a preplanned subgroup with low baseline computer experience as part of a feasibility substudy with a 2:1 randomization ratio in that subgroup (N = 227) and a 1:1 ratio in the computer-experienced subgroup (N = 539), yielding 441 participants in the patient-reported symptom monitoring group, and 325 in the usual care group. With a minimum follow-up of 5.4 years, median follow-up was 6.9 years (interquartile range, 6.5-7.7) for the electronic patient-reported symptom monitoring group and 7 years (interquartile range, 6.6-8.1) for the usual care group.

jama.com

JAMA Published online June 4, 2017

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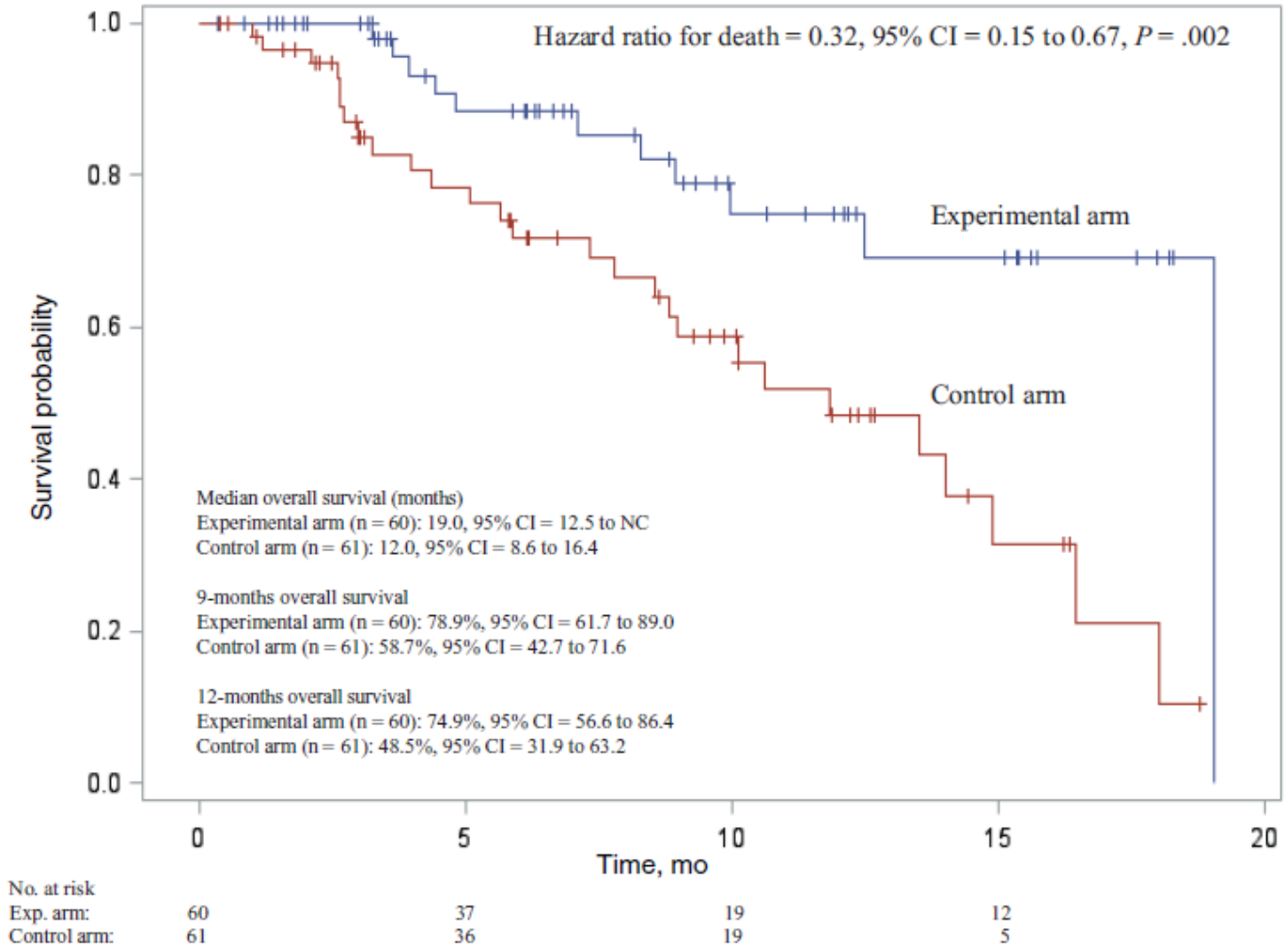
Basch et al. JAMA 2017 [Epub June 4]

Improved Survival



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Denis et al. JNCI 2017;109:djx029

PROTEUS-Practice

- **OBJECTIVE**

  Advance the use of patient-reported outcomes in clinical practice

- **REQUIRES**
  - Collecting the PRO data efficiently
  - Communicating the PRO results usefully
  - Interpreting the PRO scores meaningfully
  - Acting on the PRO findings effectively

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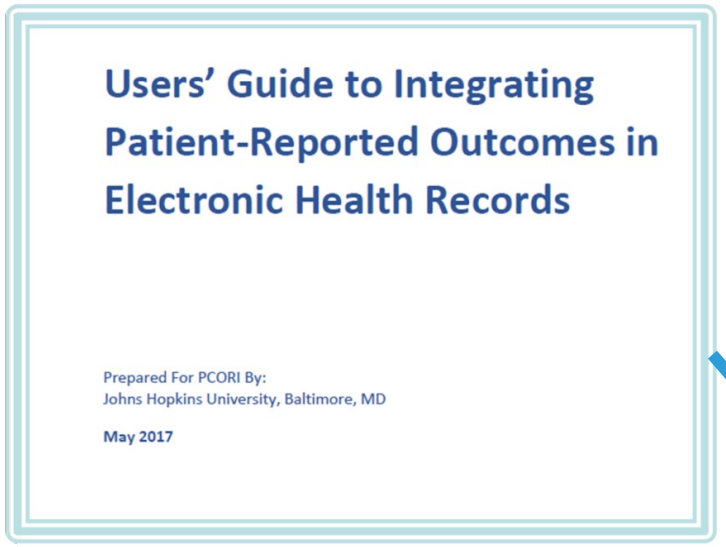
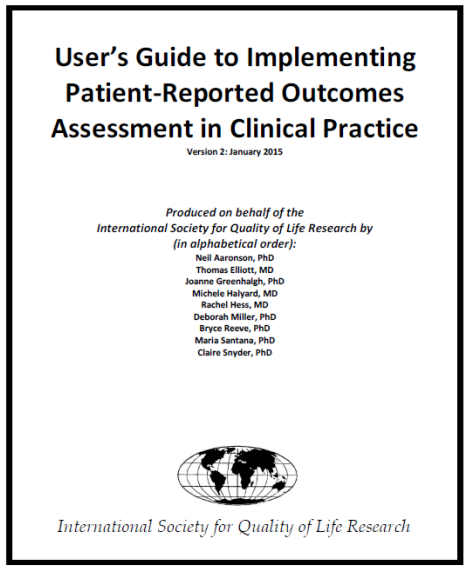


Making a picture worth a thousand numbers: recommendations for graphically displaying patient-reported outcomes data

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

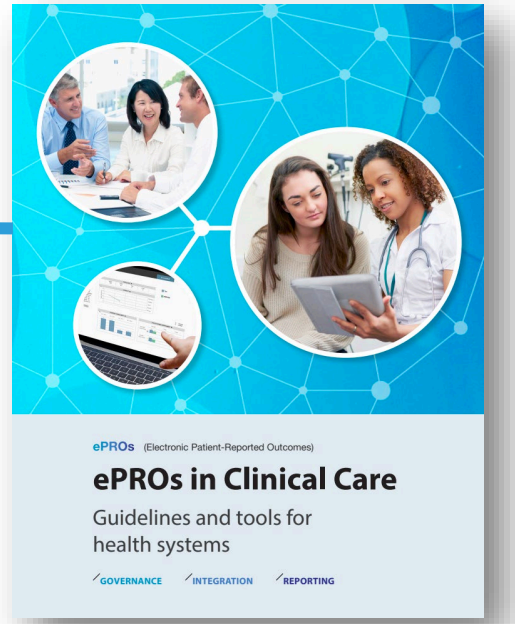
Accepted: 29 September 2018



The PROTEUS Guide to Implementing Patient-Reported Outcomes in Clinical Practice

A Synthesis of Resources

A Resource from the PROTEUS CONSORTIUM



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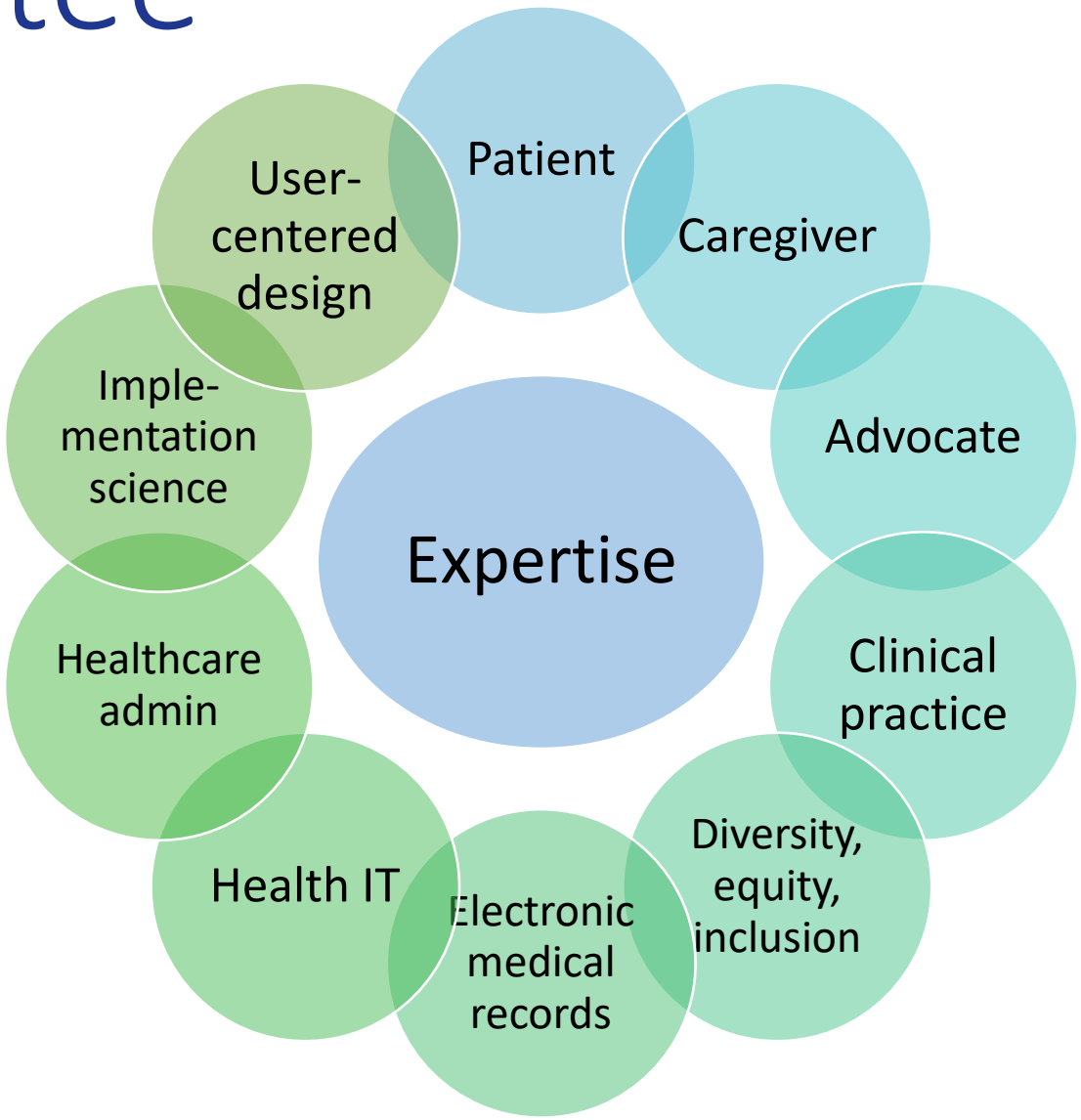
- Garrett Ursin
- Galina Velikova, MD



PROTEUS

IMPLEMENTING PROS IN CLINICAL PRACTICE:

A RESOURCE CHART

DESIGN

Goals
Barriers & Facilitators
Training & Engagement
Identifying Patients
Outcomes & Measures
Frequency & Timing

IMPLEMENTATION

Administering & Scoring
Workflow
Results Presentation
Interpretation
Responding to Issues

MANAGEMENT

Evaluation
EHR Integration
Governance
Data Pooling/Exchanging
Ethical/Legal Issues

No “One-Size-Fits-All” Approach

- Provides a range of options rather than one “right” way
- Options not mutually exclusive – pick more than one
- Applicable to a broad range of health systems
  - Solo practices to large group practices
  - Outpatient to inpatient settings
  - Small clinics to large, integrated health systems

PROTEUS

DESIGN

Goals
Barriers & Facilitators
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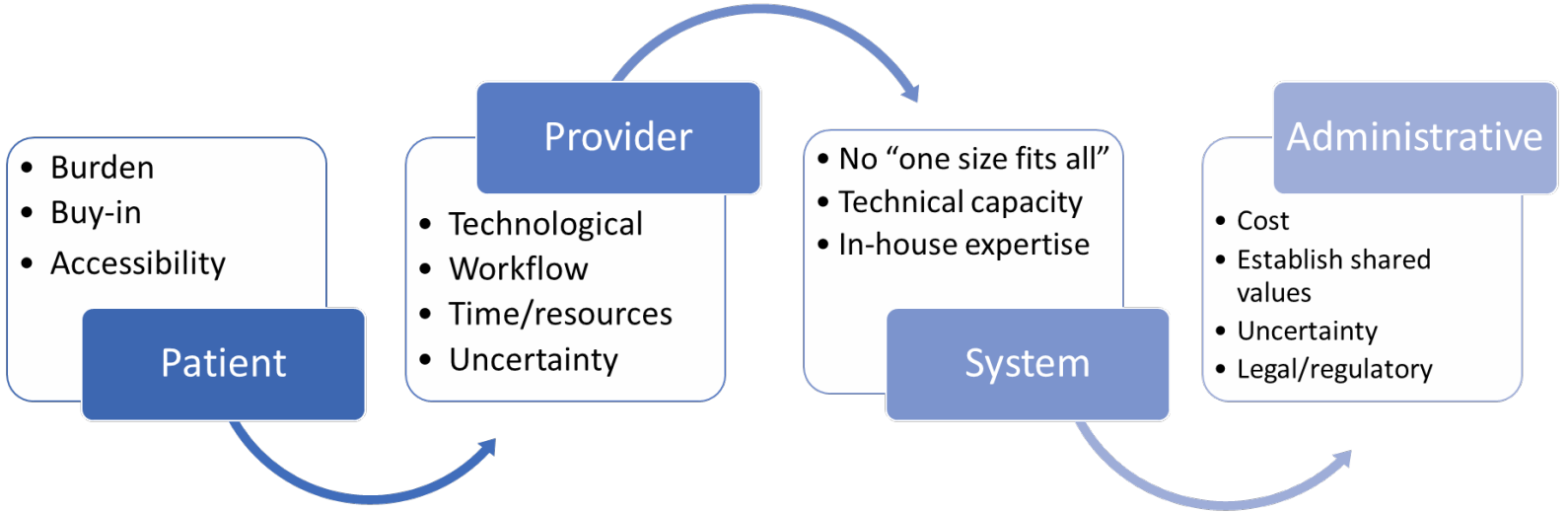
Identifying Patients
Outcomes & Measures
Frequency & Timing



SELECTING GOALS

- To enhance individual patient care
- To improve population health
- To facilitate research
- To improve quality (beyond using individuals' PRO data to aid in their management)
- To inform billing, reporting, and value-based purchasing

SELECTING OUTCOMES

- To enhance individual patient care
- Ensure that the outcomes are relevant to stakeholders
- Ensure that information on the outcomes will advance the goals of the PRO system
- Ensure content relevance
- Consider the use of core outcome sets

SELECTING PROMs

- Generic vs. disease-specific measures
- Profile vs. preference based
- Single item vs. multi-item
- Static vs. computer adaptive test (CAT) measure

PROTEUS

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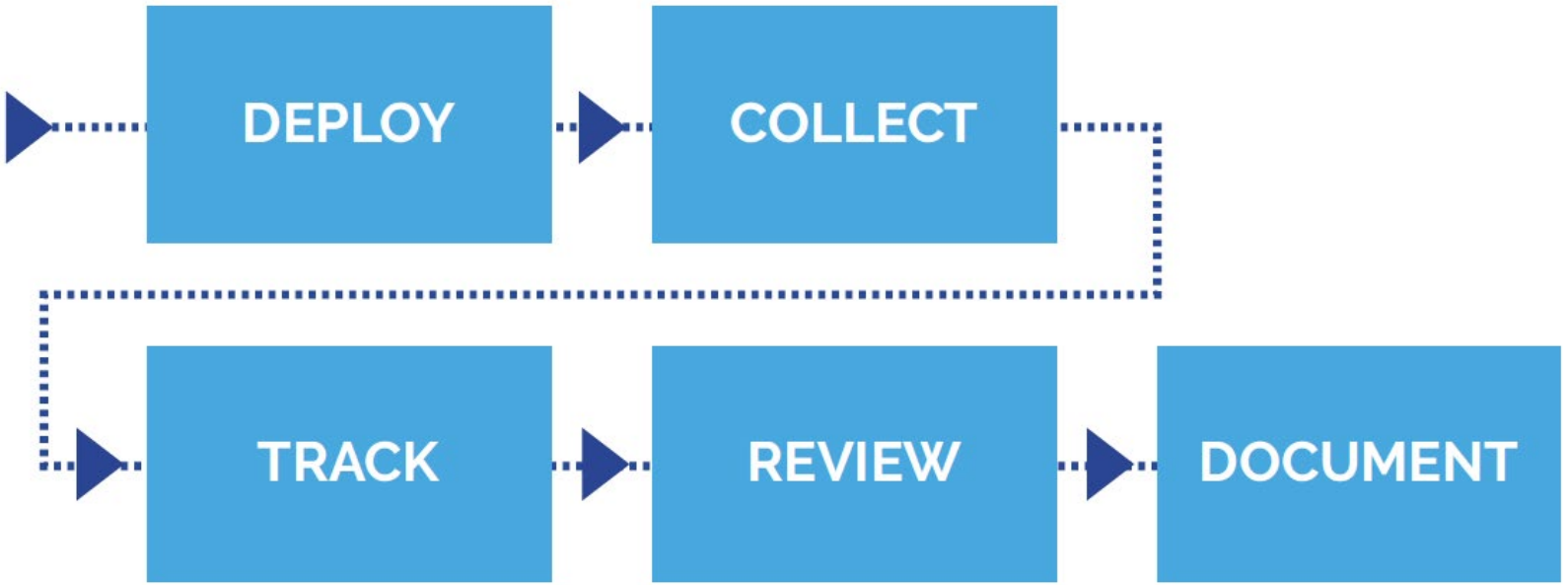

PROTEUS

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PROTEUS

Mr. Q (3)

- During chemotherapy, Mr. Q's clinic monitored his functioning and symptoms via remote weekly reporting
- These symptom reports enabled Mr. Q and his doctor to track how he was doing and address issues early on
- He successfully completed the full-course of chemotherapy
- 5 years after diagnosis, he is still cancer-free

PROTEUS

Questions & Discussion