Implementing PRO Evaluations in Cancer Clinical Trials

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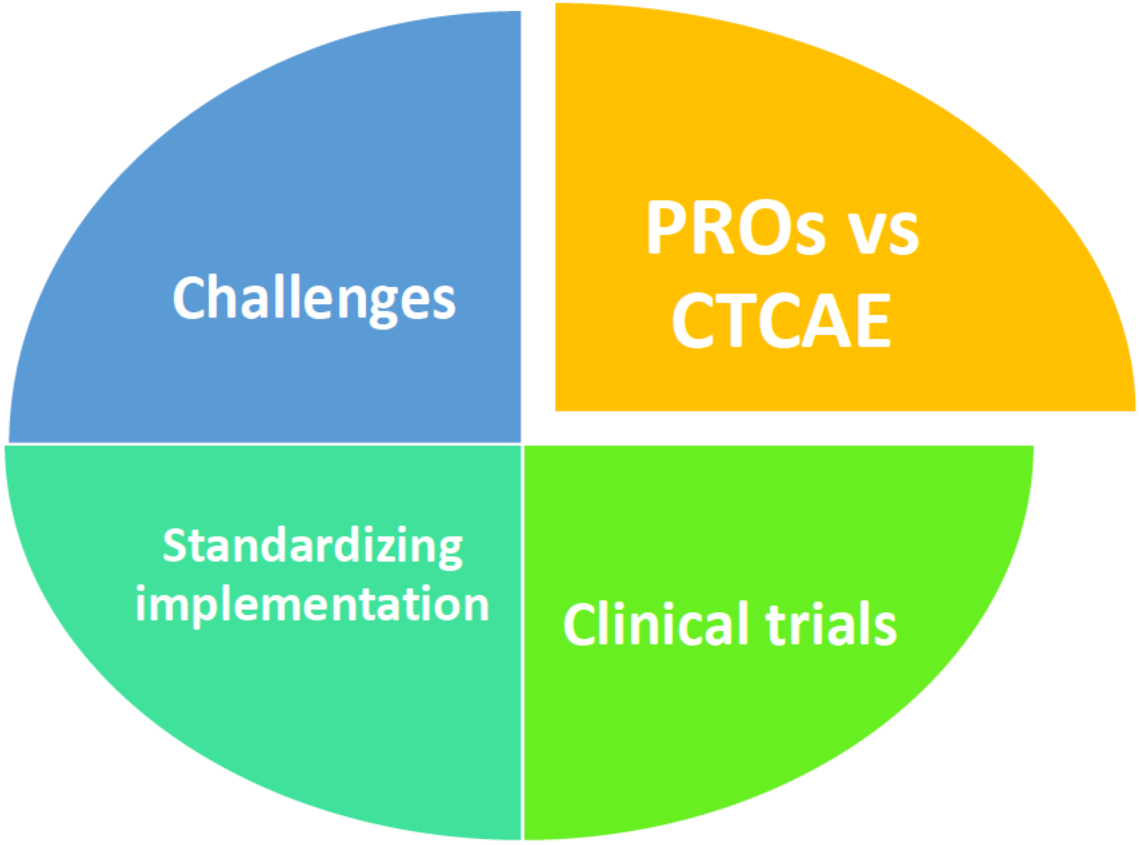
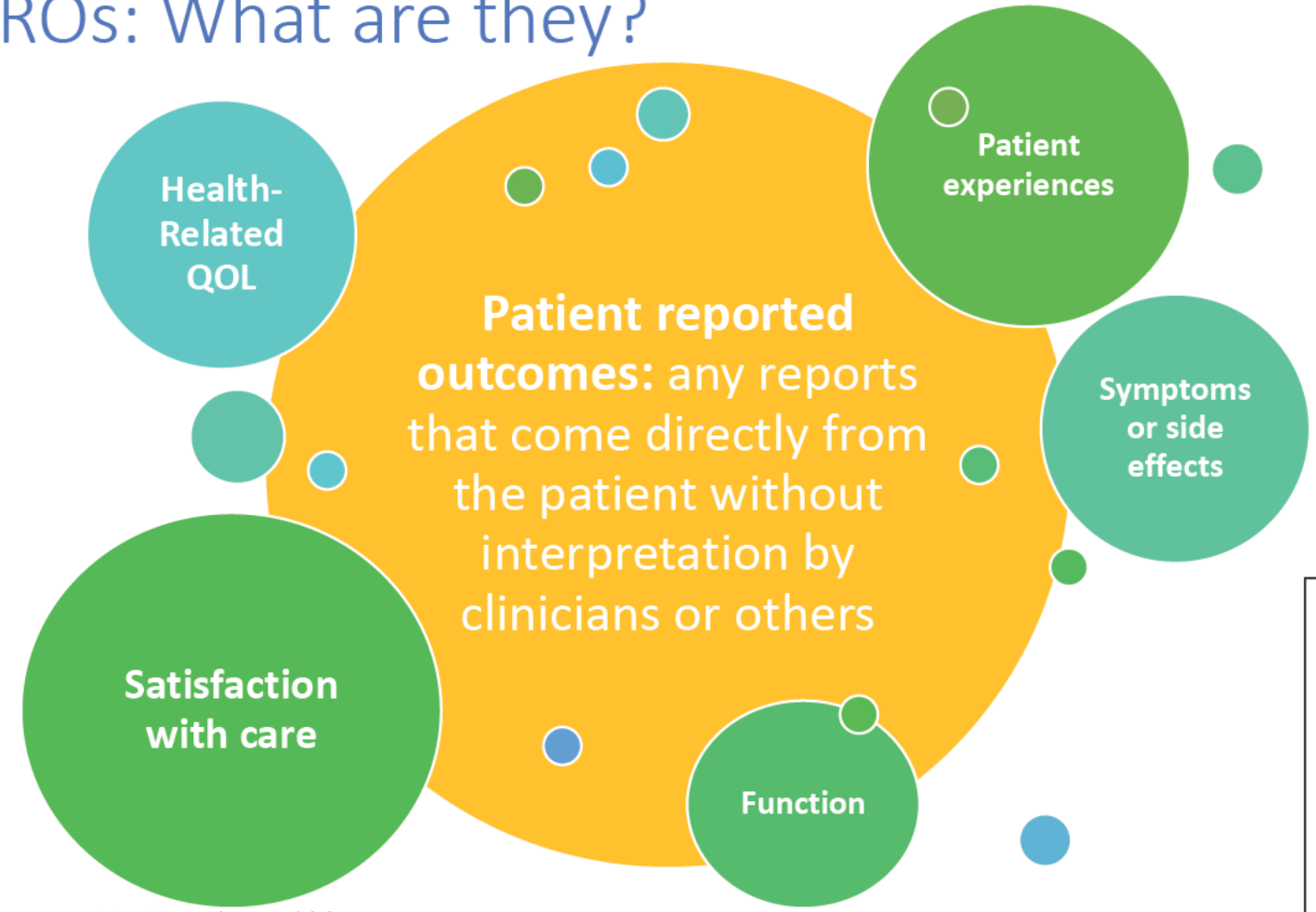
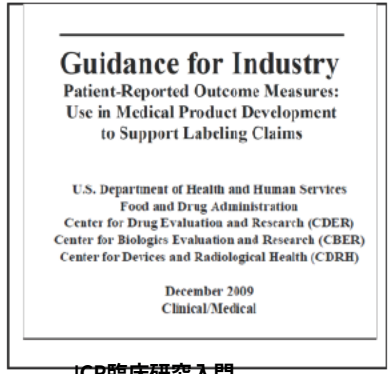
Overview



PROs: What are they?




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

Adapted from K. Kircheiner, ESTRO 2018

Toxicity measurement

PROs cover

- Analytic outcomes e.g. blood tests
- Clinician assessed signs e.g. rash
- Patient reported objective symptoms e.g. vomiting
- Patient reported subjective symptoms e.g. fatigue
- Patient reported impact on ADLs e.g. unable to work
- Patient reported multidimensional health concepts e.g. QOL

CTCAE covers

CTCAE is the gold standard for AE reporting in clinical trials
BUT…PROs are considered the gold standard for all symptoms which are not directly accessible to a physician (e.g. not observable / measurable)

Trotti et al. JCO 2007, Basch et al. Value Health 2012

PROs versus CTCAE

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During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4

PROs versus CTCAE

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Eye disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Corneal ulcer	-	-	Corneal ulcer without perforation in the affected eye	Perforation in the affected eye	-
Definition: A disorder characterized by an area of epithelial tissue loss on the surface of the cornea. It is associated with inflammatory cells in the cornea and anterior chamber. **Navigational Note:** -					
Dry eye	Asymptomatic; clinical or diagnostic observations only; symptoms relieved by lubricants	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL	-	-
Definition: A disorder characterized by dryness of the cornea and conjunctiva. **Navigational Note:** If corneal ulcer is present, grade under Eye disorders: Corneal ulcer.					

Asymptomatic; clinical or diagnostic observations only; symptoms relieved by lubricants

Support Care Cancer. 2016 August ; 24(8): 3669–3676. doi:10.1007/s00520-016-3297-9.

The Association between Clinician-Based Common Terminology Criteria for Adverse Events (CTCAE) and Patient-Reported Outcomes (PRO): A Systematic Review

Thomas M. Atkinson, Ph.D.[1], **Sean J. Ryan, M.A.**[1,2], **Antonia V. Bennett, Ph.D.**[3], **Angela M. Stover, Ph.D.**[3], **Rebecca M. Saracino, MA**[1], **Lauren J. Rogak, MA**[1], **Sarah T. Jewell, MLS**[5], **Konstantina Matsoukas, MLS**[1], **Yuelin Li, PhD**[1], and **Ethan Basch, MD, MPh**[1,3]

- 28 studies including direct comparisons between CTCAE and PRO ratings
- Poor to moderate correlations between PRO and clinician reported toxicity
- PROs provide unique and complementary information

Mapping EORTC Quality of life Item library to CTCAE

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ISOQOL 2020 VIRTUAL

CTCAE ⇔ PRO

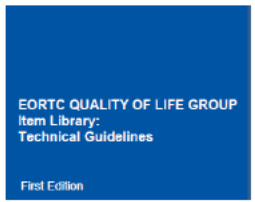
Oral sessions

Use of the Common Terminology Criteria for Adverse Events (CTCAE) framework to summarize symptomatic toxicities in the European Organisation for Research and Treatment of Cancer (EORTC) Item Library

Date: 12:03 AM–11:00 PM Oct 24, 2020 (US – Central) / 7.03AM Oct 24 – 6AM Oct 25, 2020 CET

Session Details: Oral Brief Session 202: Methods I

Authors: Claire Piccinin, Andrew Bottomley, Mogens Groenvold, Dagmara Kuliś, Galina Velikova, & Alexandra Gilbert



EORTC

Mapping EORTC Quality of life group (QLG) Item library to CTCAE

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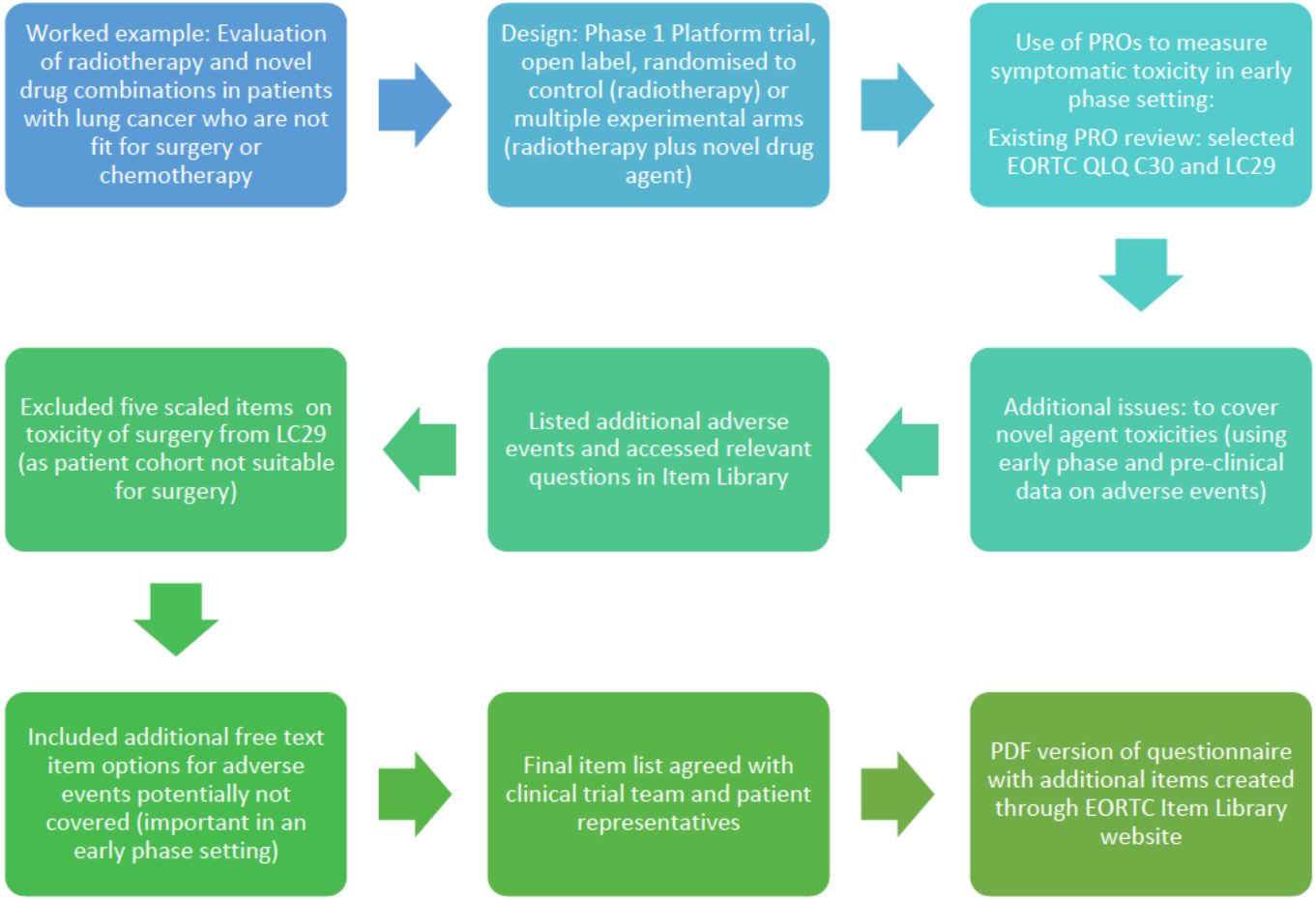
- 950 items in EORTC QLG Item library (e.g. generic, disease specific)
  - e.g. Did you have diarrhoea?
- 838 adverse events in CTCAE
  - e.g. Diarrhoea
- Extensive coverage of adverse events: 625 items (65.7%) mapped onto an adverse event, covering 207 different adverse event items
- 320 items covering issues not covered by CTCAE – e.g. body image, QOL, impact on activities of daily living
- Standardised framework between two commonly used systems in clinical trials

EORTC
European Organisation for Research and Treatment of Cancer
The future of cancer therapy

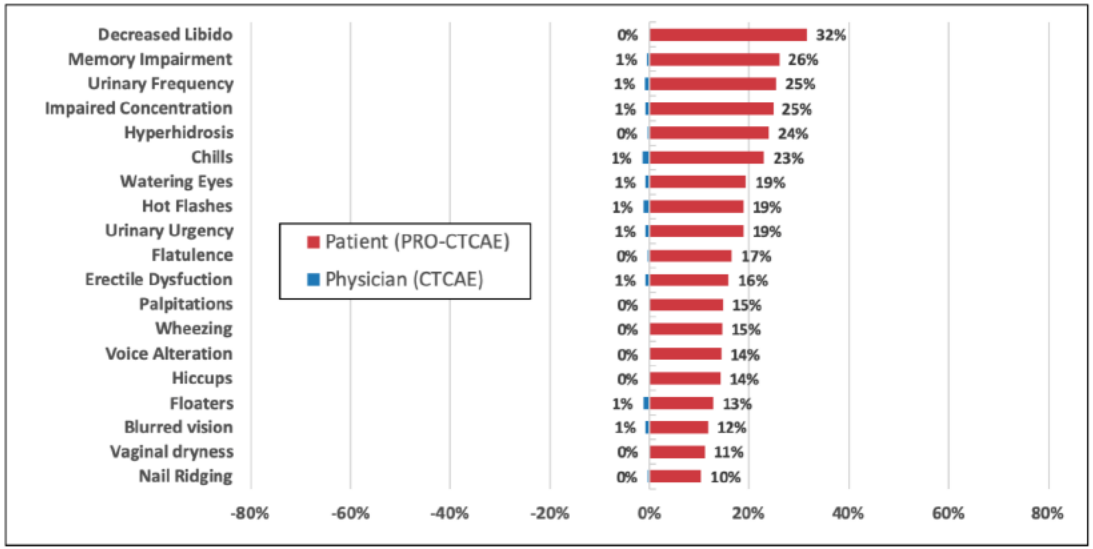


Phase 1 trials: highlighting difference in reporting of toxicity

- Solid tumour (mix), Phase I trials at Princess Margaret Cancer Center, Toronto
- Completed 80 item PRO-CTCAE™ tablet-based survey

1) Baseline (n=243)
2) mid-cycle 1 (n=191)
3) mid-cycle 2 (n=118; 49%)

- Multiple different systemic treatments



Courtesy of Veitch, ESMO 2019

AE reporting for items occurring with a patient frequency ≥10% and physician frequency ≤1%

Veitch et al 2021 JNCI

Findings

50 PRO-CTCAE items with patients reporting ≥10%

Under reporting of sexual health, cognition and urination

Poor-fair agreement:

Fatigue, pain, insomnia

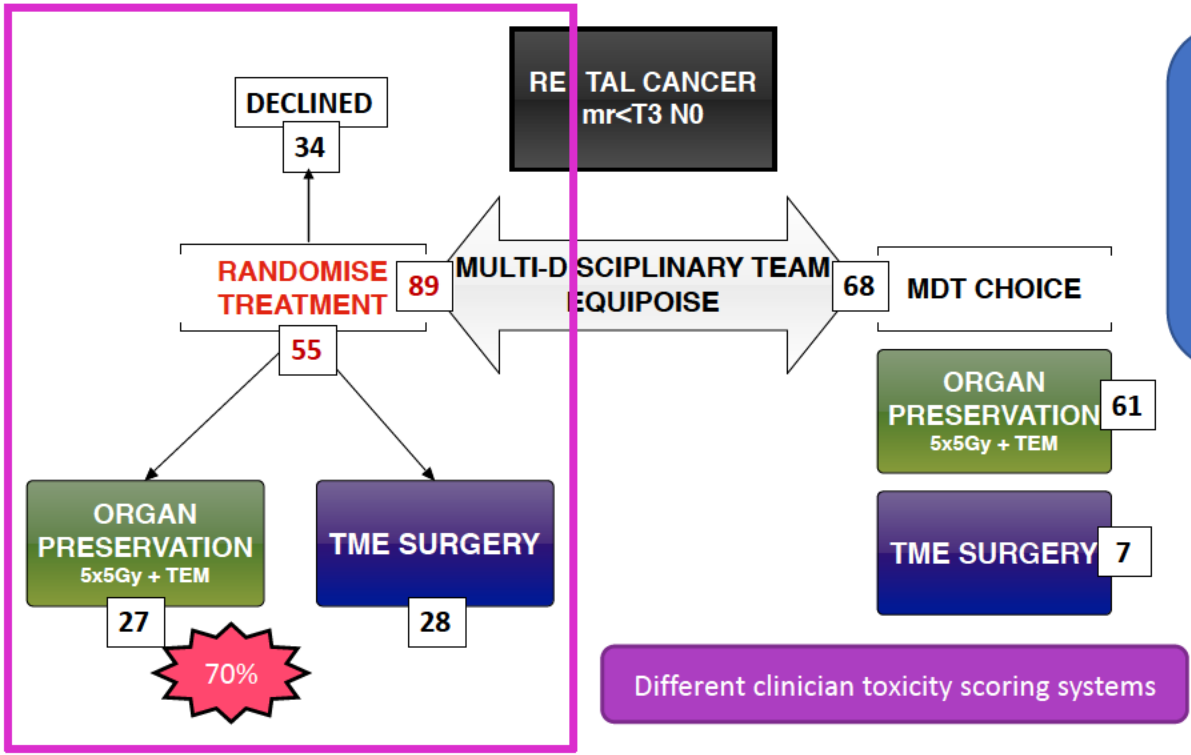
Moderate agreement:

Nausea and vomiting, rash, dyspnoea

Validation in larger cohort

Veitch et al 2021 JNCI

Comparison of different treatment modalities: TREC, Ph2 feasibility RCT

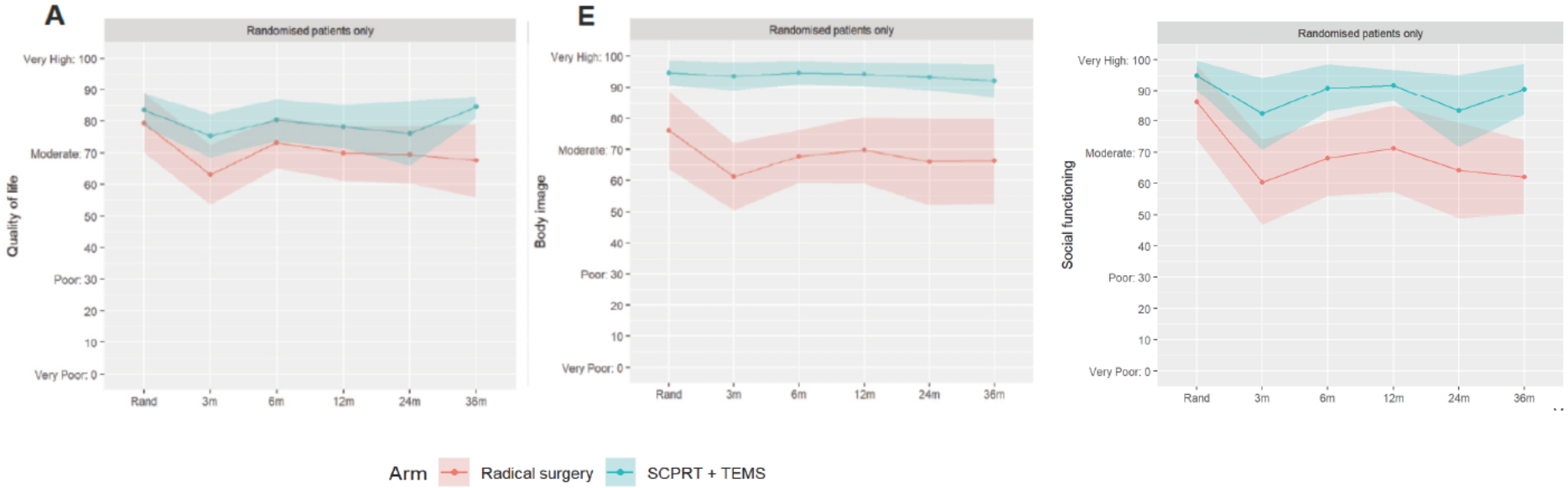


- Surgery is SOC but option for organ preservation is preferable for many patients/clinicians
- First RCT to compare OP to SOC toxicity with PROs

Bach et al, Lancet Gastro Hep, 2021

PRO results

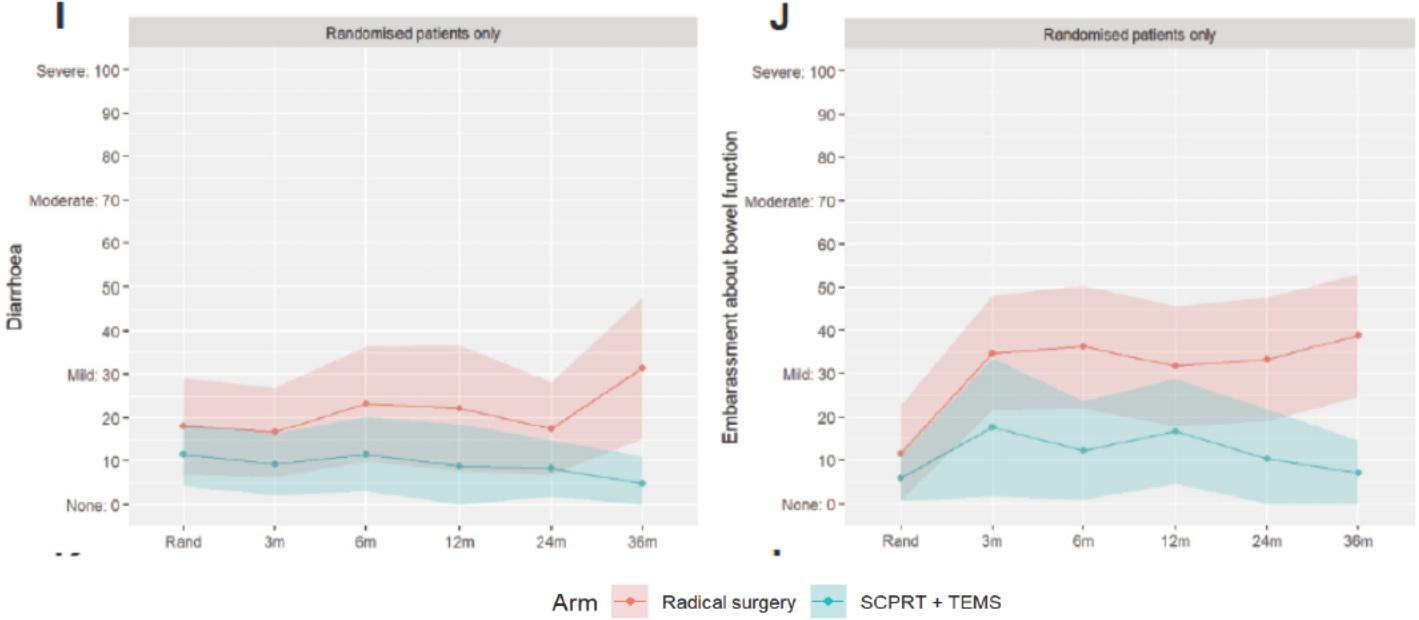
Higher score = better function
Mean and 95% CI shown



Ability to measure the impact on patients' QOL, social function and body image to understand patient experience with two treatment options

Bach et al, Lancet Gastro Hep, 2021

PRO results



Higher score = worse symptoms

Mean and 95% CI shown

- Ability to compare symptomatic toxicity between radiotherapy and surgery
- CTCAE lexicon is not used/developed for use in surgical practice
- Understand patient experience over time

Bach et al, Lancet Gastro Hep, 2021

The ‘EPic’ Study

- 1,141 cancer trials on the UK National Institute for Health Research (NIHR) Portfolio 2001-2014
- Cancer trials on the NIHR portfolio including a PRO as either a primary or secondary outcome
- **Final sample:** 228 trials collecting PROs, recruiting in 72 countries.
- 160 trials had published results by June 2017
- **At a mean of 6.43 year’s follow-up from trial closure, 38% (61/160;95% CI 31% - 46%) had failed to publish their PRO findings**
- These trials included 49,568 participants
- Even where results published – significant delays and reporting quality poor

49,568 participants

MACMILLAN CANCER SUPPORT

Courtesy of D. Kyte; from Kyte et al, JNCI, 2019

Standardisation of PROs in Clinical trials

PROs in Grant applications Snyder et al 2021	• Top issues to include in grant applications to ensure appropriate coverage in costs and staff considerations
SPIRIT-PRO Calvert et al 2018	• Developing PRO protocols for clinical trials • Based on systematic review, expert panel and Delphi process
SISAQOL Coen et al 2020	• Guidance on analysis and reporting of PRO data • Based on systematic review, SISAQOL international consortium
CONSORT-PRO Calvert et al 2013	• CONSORT reporting quality • 'Visualising PRO data'

Background/ Objectives

- PRO specific hypotheses: 1º or 2º
- Rationale for VALIDATED PRO tool
- Background of existing PRO findings

Methods

- Reliability and validity of PRO instrument; language
- Method of collection: paper/electronic/reminders (cost implications)
- Sample size considerations: 1º (consider attrition)
- A priori hypotheses – specific items for consideration
- Missing data (and consider how to minimize)

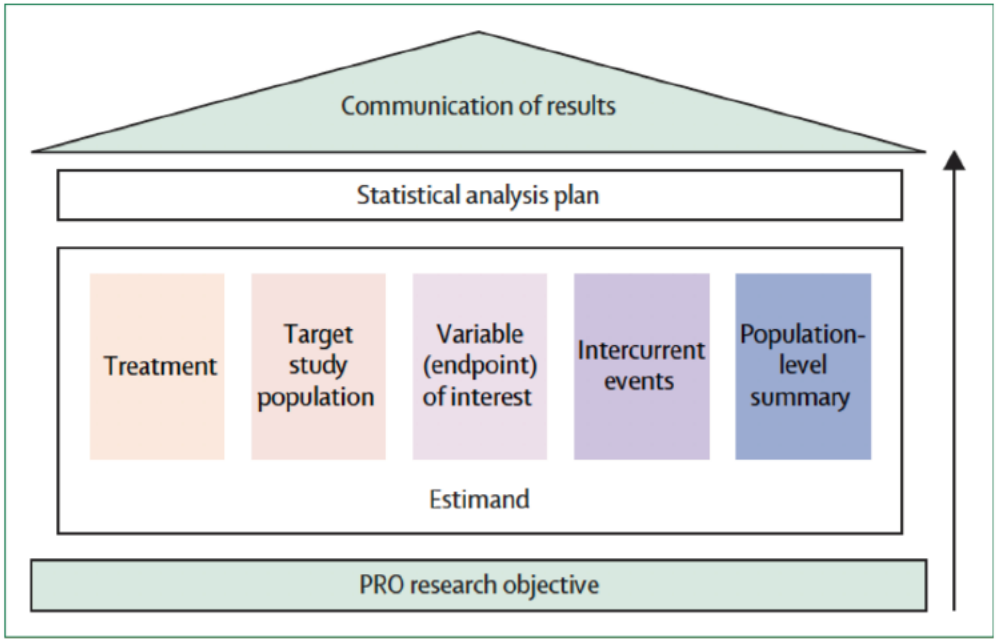
Results

- Baseline/completion number/all data (supplementary)
- Corrections for multiple testing
- Analysis of longitudinal data
- Presentation: graphs/tabular

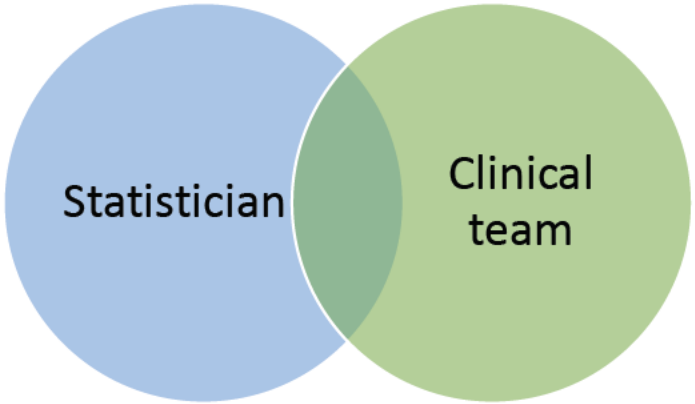
Discussion

- PRO specific, limitations,
- Consider generalizability
- Data interpretation integrated

Estimands Framework for PROs in Clinical trials



"An estimand (ICH E9(R1) addendum, 2019) is something that has to be estimated"



Fiero et al Lancet Onc 2020

Estimands Framework for PROs in Clinical trials

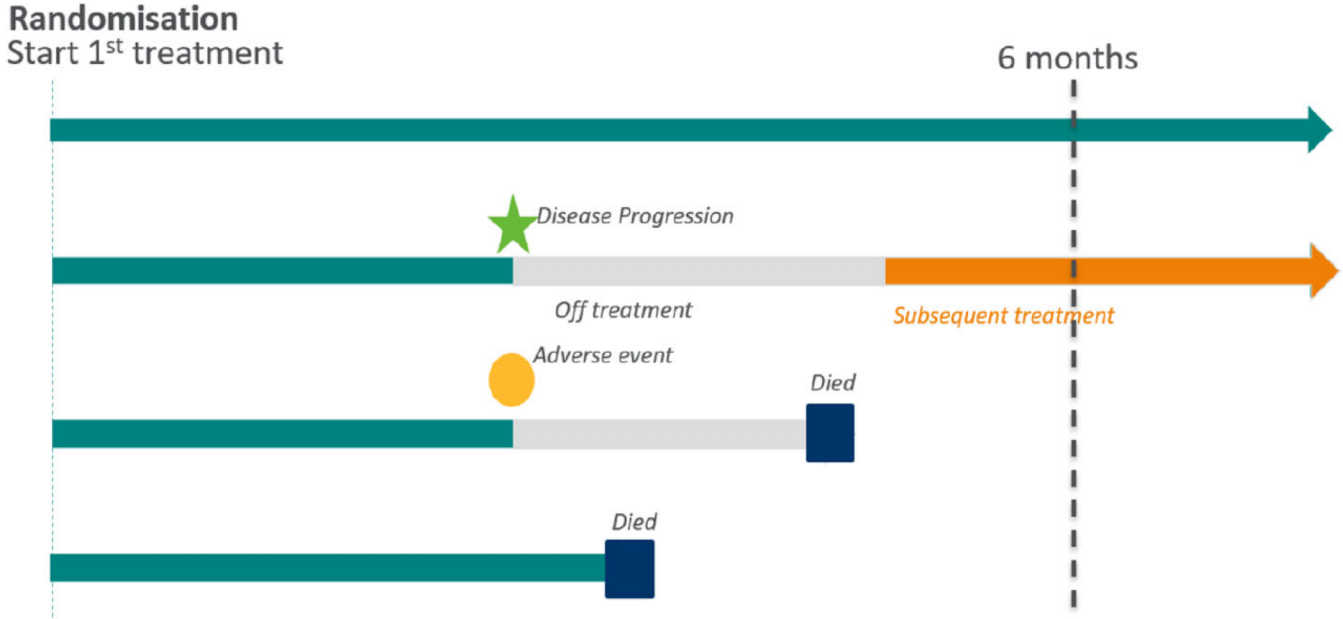
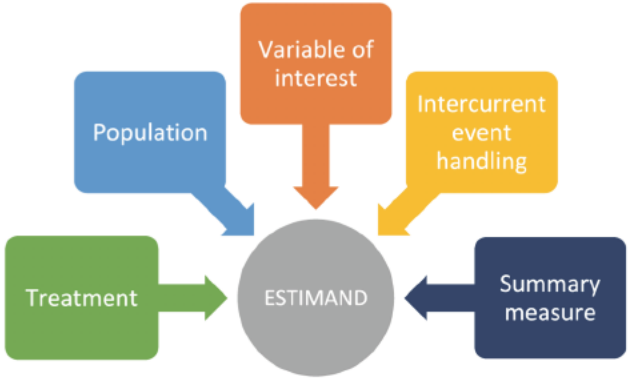


Fig. 3 Illustrative Patient treatment journeys

Lawrance et al, J PROs, 2020

Estimands Framework for PROs in Clinical trials

"In patients with previously untreated advanced indolent non-Hodgkin lymphoma ***what is the a between-group*** *difference in mean patient-reported lymphoma-related symptoms, as measured by change from baseline in FACT-LymS score,* ***after*** *treatment with obinutuzumab-based chemo-immunotherapy compared with treatment with rituximab-based chemo-immunotherapy therapy, at 30 months after randomisation or until death (whichever occurs first), regardless of treatment discontinuation?"*



Lawrance et al, J PROs, 2020

PROTEUS

Patient-Reported Outcomes Tools:
Engaging Users and Stakeholders

Home | About PROTEUS | Tools and Resources for Using PROs in Clinical Trials | Additional Helpful Resources | Contact Us

Patient-Reported Outcomes Tools: Engaging Users & Stakeholders

The PROTEUS Consortium promotes tools and resources to optimize the use of patient-reported outcomes (PROs) in clinical trials to ensure that patients, clinicians, and other decision-makers can make the best decisions about treatment options.

- PROs in Grant applications paper
- PROs in clinical practice

Value of PROs: RCTs of PROs in clinical practice

Authors	Patient sample	Patient well-being	Communication	Satisfaction with care
McLachlan 2001	N=450	Reduction in depression	NA	--
Detmar 2002	N=214	--	+	--
Velikova 2004	N=286	Improved QOL	+	--
Rosenbloom 2007	N=213 nurses	--	-/+	--
Carlson 2010	N=585 N=549	Reduced distress	+	NA
Berry 2011	N=660	NA	+	NA
Berry 2014	N=585 N=549	Reduced distress	NA	NA
Basch 2015	N=766	Improved QOL Fewer ER visits	NA	NA
Basch 2018	N=766	Improved 1yr overall survival (+5months)	NA	NA
Absolom 2021	N=509	Improved QOL & symptom control; benefits in adjuvant setting	NA	NA

Benefits: PROs in clinical trials

Systematic toxicity measurement

- Developed to measure trajectory
- Impact of intervention
- Useful when comparing interventions which have different clinician measurement tools

Patient experience

- Impact on QOL and function (ADLs)
- Wider range and milder symptoms

Benefits to patient

- Symptom support
- Communication

Challenges with PROs

Integration of Complex data

- Electronic: IT, training, infrastructure
- Optimal methodology: relevant VALIDATED PRO, hypothesis, design to ensure high response rates and use of results (trials and practice), analysis (e.g. Estimands, missing data, additional items

Not diagnostic

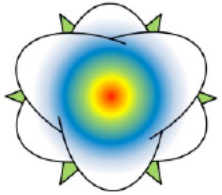
- Symptomatic measurement, not diagnostic
- Unable to measure non-symptomatic toxicity

Other Limitations

- CTCAE mapping (Standardised framework)
- Comparisons between different PRO tools

Summary

PROs	• Effective method of systematically collecting symptomatic toxicity data in clinical trials and impact on QOL • Benefits in addition to clinician toxicity monitoring
Benefits	• Benefits at an individual and systemic level
Standards	• Excellent resources available • PROTEUS consortium
Challenges	• Historically poor quality reporting • Complex real world implementation



Thank you....
Any questions?