Incorporating Patient-Reported Outcomes in Clinical Trials

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O'NEAL COMPREHENSIVE CANCER CENTER
UAB MEDICINE

Conflicts of Interest

- Royalties from UpToDate
- Consulting fees from Recordati and Pharmassentia
- Advisory board: Opna Bio, Seagen, Sobi, Electra

Objectives

At the end of the session, the participant should be able to

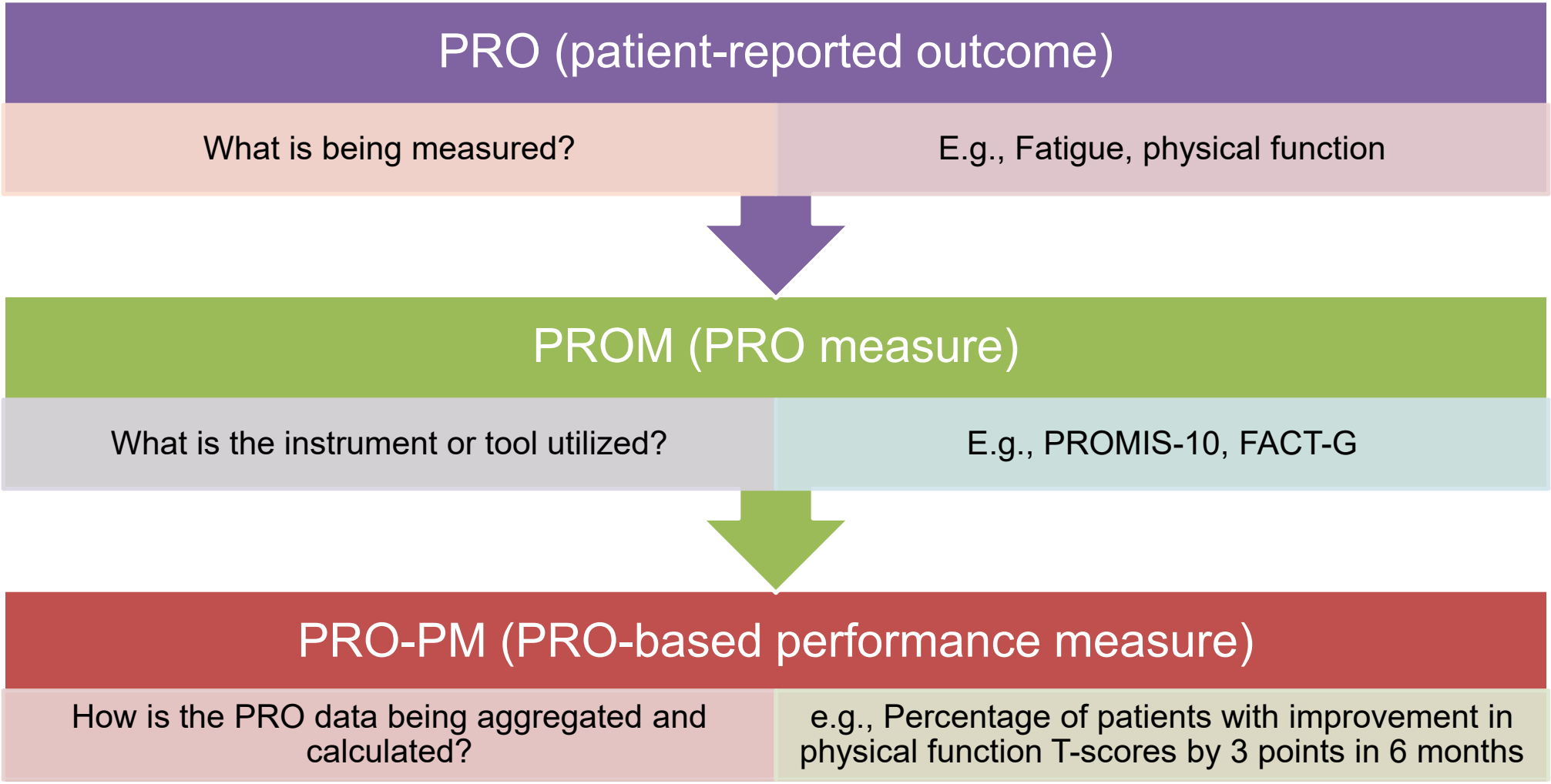
- Describe what PROs and PROMs are
- Recognize the importance of incorporating effective and efficient PROs in cancer clinical trials
- Identify appropriate strategies to include PROs in cancer clinical trials

PRO Definition

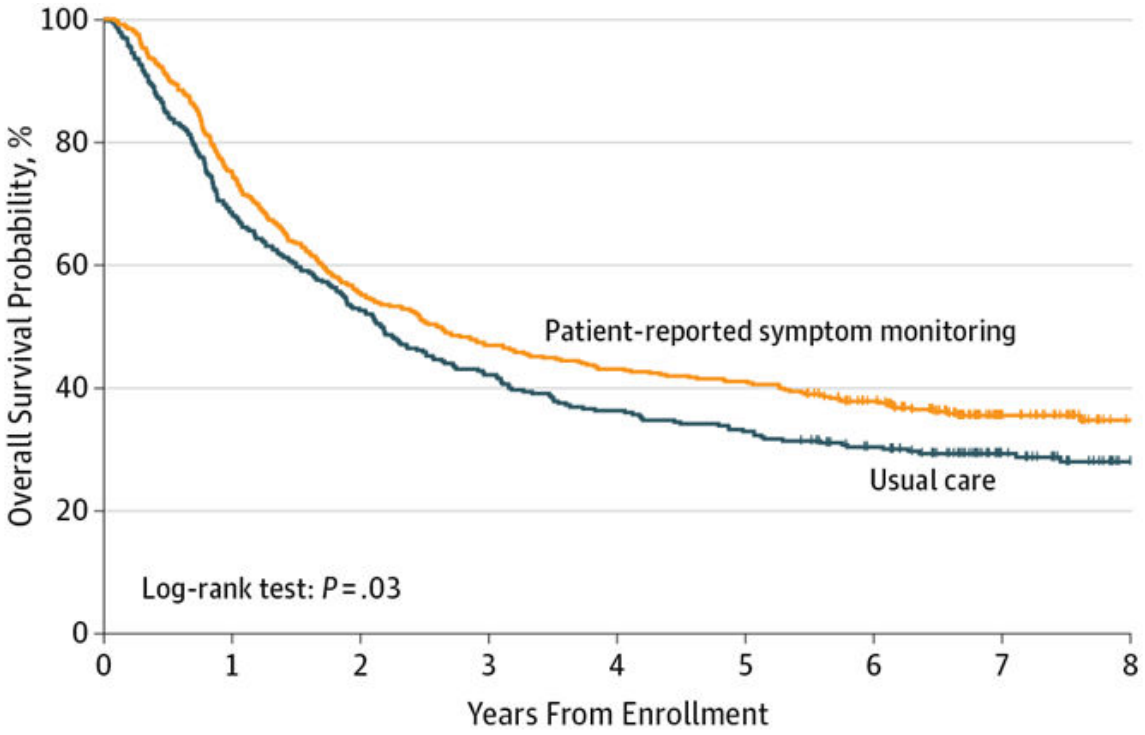
- **US- Food and Drug Administration (FDA)-** '*A PRO is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else.*'

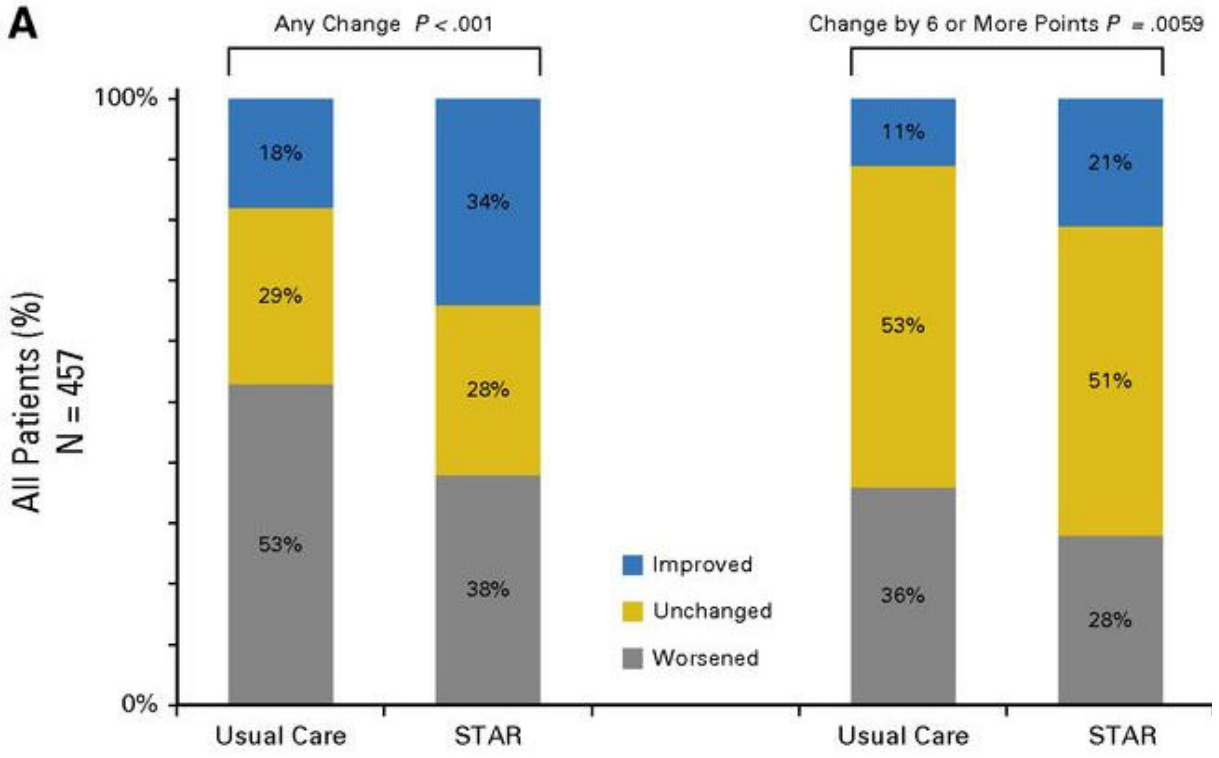
US FDA. *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*. 2009.

PRO, PROM, and PRO-PM



Importance of PROs





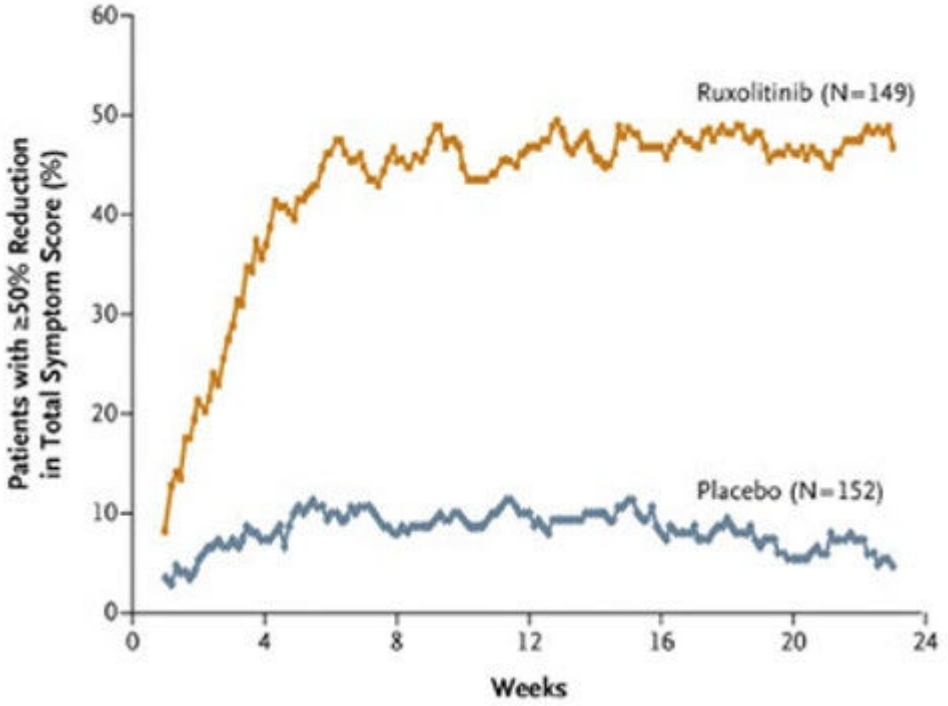
Association with overall survival and health-related quality of life
Even more relevant with increased use of surrogate endpoints

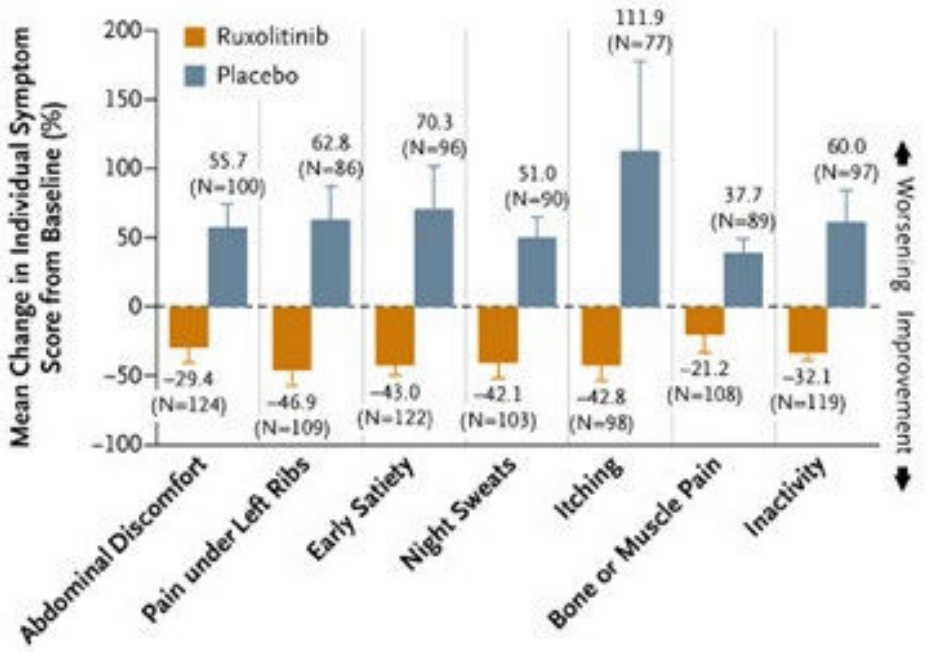
Basch E, et al. JAMA. 2017 Jul 11;318(2):197-198
Basch E, et al. J Clin Oncol. 2016 Feb 20;34(6):557-6

Balitsky AK, et al. JAMA Netw Open. 2024 Aug 1;7(8):e2424793

Successful use of a PROM in oncology trial

Modified Myelofibrosis Symptom Assessment Form (MFSAF)





Verstovsek S, et al. N Engl J Med. 2012 Mar 1;366(9):799-807.

Use of PROs in clinical trials - The problem

Inadequate and heterogeneous protocol and reporting standards

- 32% checklist items met in protocols (missing rationale, objectives, etc.)
- 22% checklist items met in publications (missing hypothesis, validity, reliability, etc.)

Missing PRO publications

- 38% not published
- 39% missing in primary publication

Delayed PRO reporting

- 54% published after 4 years of primary publication
- 36% 5-8 years later

Publication bias

- Publishing only better or stable PROs

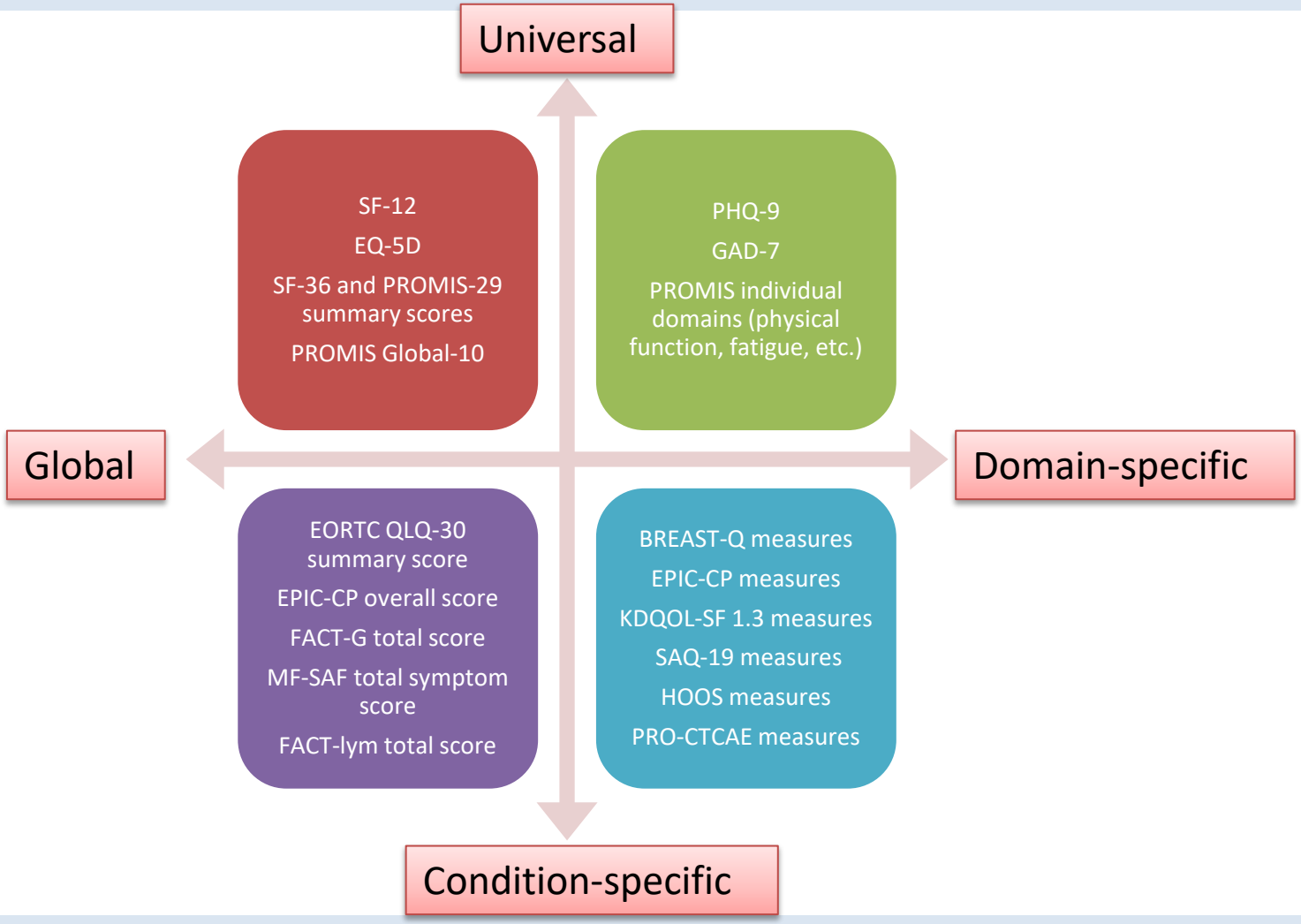
Kyte D, et al. J Natl Cancer Inst. 2019 Nov 1;111(11):1170-1178
Patel K, et al. JAMA Netw Open. 2024 Jun 3;7(6):e2414425
Al Hadidi S, et al. Blood Adv. 2021 Nov 23;5(22):4630-4633
Marandino L, et al. Ann Oncol. 2018 Dec 1;29(12):2288-2295.

FDA guidance on PROs

- *'FDA acknowledges the added value of incorporating PRO measurement of symptoms and functional impacts into the benefit/risk assessment in appropriately designed trials; however, heterogeneity in PRO assessment strategies has lessened the regulatory utility of PRO data from cancer trials.'*

US FDA. *Core Patient-Reported Outcomes in Cancer Clinical Trials Guidance for Industry*. 2024

Many types of PROMs: ‘what’ and ‘for whom’



Liu JB, et al. Health Aff Sch. 2024 Mar 27;2(4):qxae038.

Key contributors of global HRQoL

HRQoL can have components that may not be associated with treatment like mental health or social health

Adapted from Kluetz PG, et al. Clin Cancer Res. 2016 Apr 1;22(7):1553-8

Longitudinal HRQoL in histiocytic neoplasms

On targeted treatments

PROMIS 29+2	Baseline Scores	Repeat Scores
Summary Scores		
Physical health summary	46.2	46.6
Mental health summary	45.8	49.1
PROPr	0.364	0.409
Domain Scores		
Pain Interference	53.5	52.6
Pain Intensity	54.1	53.1
Depression/Sadness	50.2	46.7
Fatigue	55.4	52.3
Anxiety/Fear	52.9	48.7
Sleep Disturbance	54.9	53.9
Social Roles	47.2	50.9
Physical Function	46.5	46.3
Cognitive Function	49.5	50.2

Observation alone

PROMIS 29+2	Baseline Scores	Repeat Scores
Summary Scores		
Physical health summary	49.7	51.1
Mental health summary	51.4	52.9
PROPr	0.472	0.542
Domain Scores		
Pain Interference	52.4	48.5
Pain Intensity	51.6	51.3
Depression/Sadness	47.9	47.2
Fatigue	48.8	47.5
Anxiety/Fear	50.5	47.5
Sleep Disturbance	52.2	51.9
Social Roles	55.6	56.4
Physical Function	49.1	50.4
Cognitive Function	51.4	51.6

*Unpublished

Guidelines for PROs

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

Reporting of Patient-Reported Outcomes in Randomized Trials
The CONSORT PRO Extension

Consensus Statement https://doi.org/10.1038/s41591-024-02

Recommendations to address respondent burden associated with patient-reported outcome assessment

Patient-Reported Outcomes

Best Practices for the Electronic Implementation and Migration of Patient-Reported Outcome Measures

Florence D. Mowlem, PhD, Celeste A. Elash, MS, Kelly M. Dumais, PhD, Estelle Haenel, PhD, Paul O'Donohoe, MSc, Jennifer Olt, PhD, Alexandra V. Kalpadakis-Smith, PhD, Ben James, BA (Hons), Grazia Balestrieri, BA, Kayci Becker, Melissa C. Newara, MS, Scottie Kern, BSc (Hons), on behalf of the Electronic Clinical Outcome Assessment Consortium

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

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

Core Patient-Reported Outcomes in Cancer Clinical Trials
Guidance for Industry

Choosing the right PRO measure

Relevance

- To study population and disease

Reliability

- Test-retest or intra-interviewer reliability
- Internal consistency
- Inter-reviewer reliability

Validity

- Content validity (i.e., measures the concept of interest)
- Construct validity (i.e., ability to perform as expected based on logical relationships between measures)

Ability to detect change

- Instrument's sensitivity to change over time in response to interventions

Core PROs

Disease symptoms	• NSCLC-SAQ, MF-SAF
Symptomatic adverse events	• PRO-CTCAE
Overall side effect impact	• GP5 from FACIT, Q168 from EORTC
Physical function	• PROMIS item bank
Role function	• EORTC QLQ-C30 role function scale

US FDA. *Core Patient-Reported Outcomes in Cancer Clinical Trials Guidance for Industry*. 2024

Protocol development and analysis plan

Administrative

- PRO-specific research question and rationale
- PRO objectives (primary vs. secondary vs. exploratory)

Methods: participants, interventions, and outcomes

- PRO-specific eligibility criteria
- Specific domains/concepts used to evaluate the intervention
- Analysis metric
- Schedule of PRO assessments and rationale for time points

Methods: data collection, management, and analysis

- Justify PRO instrument, describe domains, items, scale, and scoring
- Data collection plan, including mode (paper vs. electronic)
- Strategies for minimizing and handling missing data
- PRO analysis methods, including plans for addressing type I/multiplicity error

Monitoring

- PRO monitoring plan during the study (e.g., will the PI be notified)
- Explain in participant consent form

Calvert M, et al. JAMA. 2018 Feb 6;319(5):483-494.

PRO assessment frequency

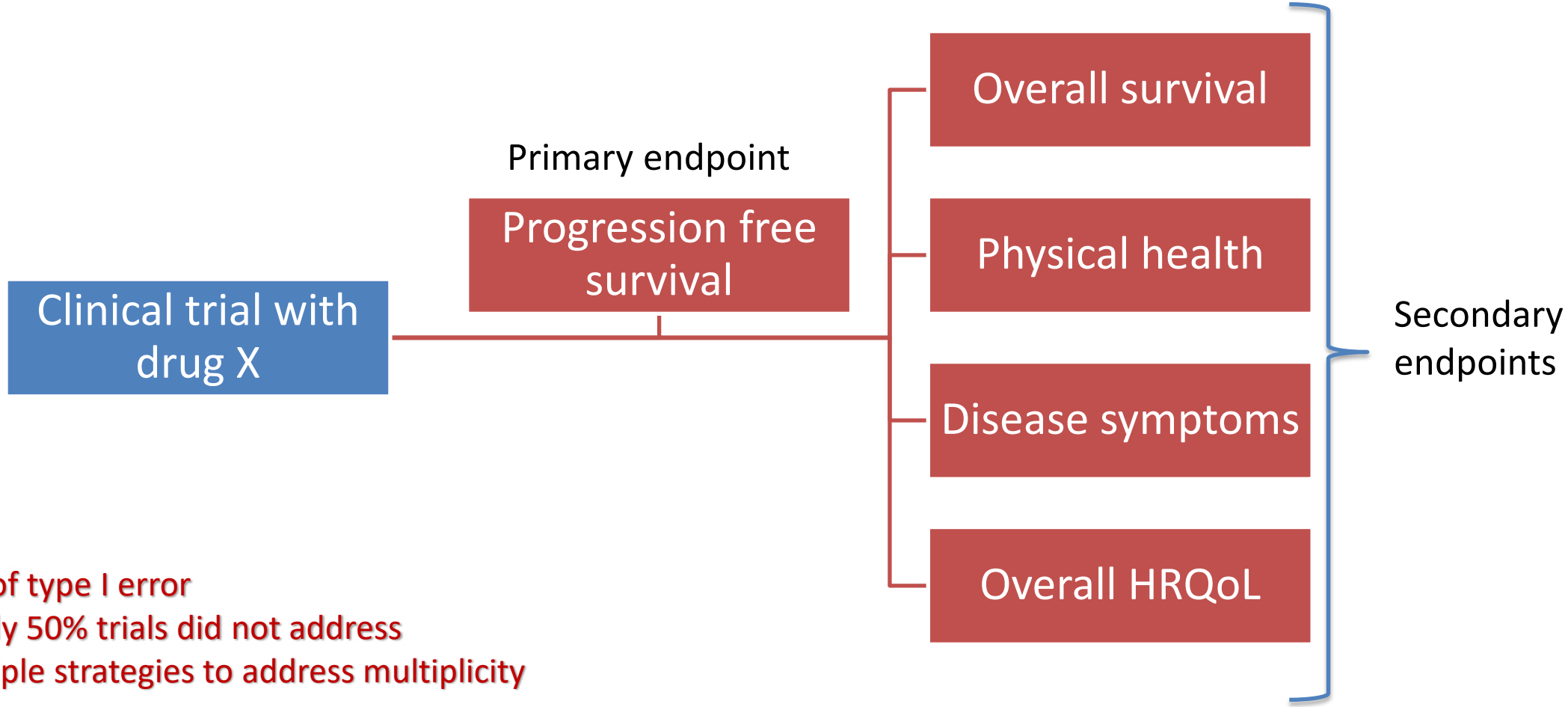
Key considerations:

- Baseline assessment as reference point
- PRO assessment frequency higher in the beginning as the participant receives more treatments
- Assessment frequency should take into account the study treatment schedule
- Different assessment frequencies can be selected for each core concept

Visits(a) / Investigations	Patients involved	Screening	Post (+/-) chemo pre (+/-) RT	Post (+/-) RT	1 yr	2 yr	3 yr	4 yr	5 yr	6 yr	7 yr	8 yr	9 yr	10 yr	Recurrence[2]
		Baseline 1	2	3	4	5	6	7	8	9	10	11	12	13	
Informed consent	All	X													
Medical history & examination (b)	All	X		X	X	X	X	X	X	X	X	X	X	X	X
Staging tests	All	X													
Contralateral mammography	All	X			A mammogram of the opposite breast, if appropriate, is recommended at least in alternate years for 10 years from the date of mastectomy										
Blood sampling	If consented to TRANS-SUPREMO	X													X
Tumour paraffin block from primary tumour[1]	All	X													
Tumour paraffin block at recurrence if available[2]	All														X
Acute/ Late morbidity[3]	All			X	X	X	X	X	X	X	X	X	X	X	
Cardiac symptoms and examination	If consented to cardiac sub study	X	X[4]	X	X				X					X	X
Blood sampling for BNP	If consented to cardiac sub study	X	X[4]	X	X				X					X	X
Electrocardiogram	If consented to cardiac sub study	X			X[5]				X[5]					X	X[5]
Echocardiogram (c)	If consented to cardiac sub study	X			X[5]				X[5]					X	X[5]
QOL and EQ5D economic assessment (d)	If consented to QOL sub study	X			X	X			X					X	

Calvert M, et al. JAMA. 2018 Feb 6;319(5):483-494
https://www.supremo-trial.com

The multiplicity issue



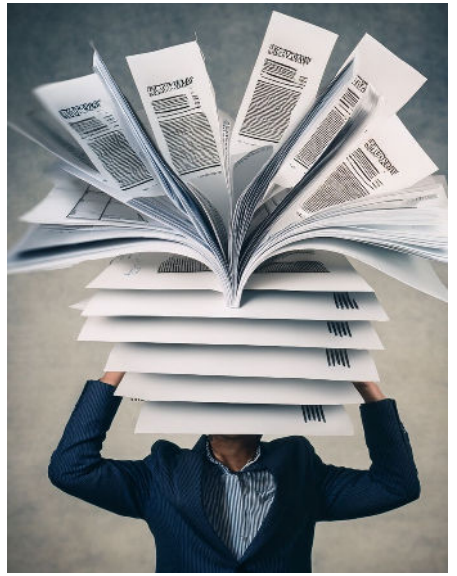
Risk of type I error
Nearly 50% trials did not address
Multiple strategies to address multiplicity

Coens C, et al. Lancet Oncol. 2020 Feb;21(2):e83-e96
Hamel JF, et al. Eur J Cancer. 2017 Sep:83:166-176.

US FDA. *Multiple Endpoints in Clinical Trials Guidance for Industry* 2024

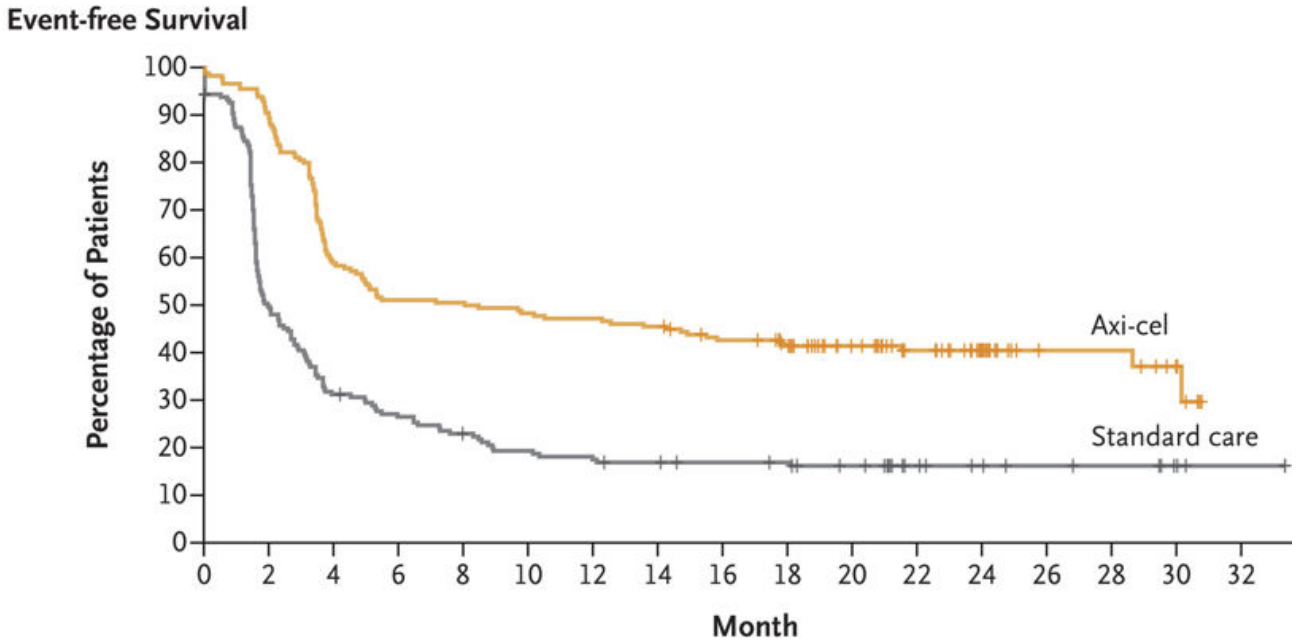
Respondent burden

Participant engagement	Early patient involvement in selection of measures
	Inform participants about the reason for PROM collection and who will have access
PROM length	May not be associated with burden
	Participants may prefer longer forms if they capture concepts that matter to them and inform care
PROM content	If selecting more than 1 PROM, avoid overlapping constructs
	Consideration for the recall period
Training of study staff	Staff may be reluctant to administer PROMs due to perceived burden even though the participants are willing to complete them

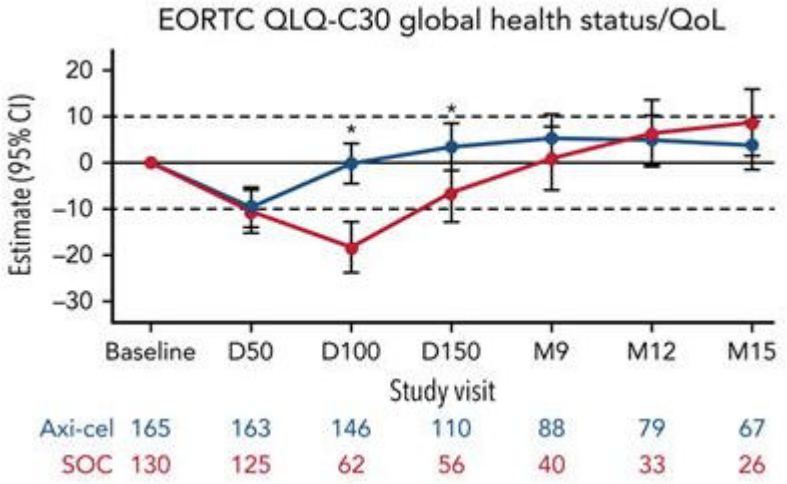


Aiyegbusi OL, et al. Nat Med. 2024 Mar;30(3):650-659.
Ettridge K, et al. Qual Life Res. 2021 Feb;30(2):407-423
Shepshelovich D, et al. Oncologist. 2019 Apr;24(4):e146-e148.
Retzer A, et. al. Cancer Med. 2021 Aug;10(16):5475-5487

Timely reporting of PROs: Zuma-7



Epub: Dec 2021



Epub: July 2022
(Submitted Jan 2022)

Locket FL, et al. N Engl J Med. 2022 Epub Dec 2021;386(7):640-654.
Elsawy M, et al. Blood. Epub July 2022;140(21):2248-2260

Take away suggestions

- PROs are vital to allow the incorporation of patient voice in clinical trials
- Existing PRO assessments and reporting are too heterogeneous
- Ethical imperative to evaluate cancer therapies rigorously, including PROs
- Pre-specify clearly all planned endpoints, data management plans, analysis plans
- Informed consent applies to PROs, patient engagement critical
- Timely reporting of PROs is critical in the era of surrogate endpoints

PRO guidelines and resources

Trial design

Data collection, analysis, and reporting

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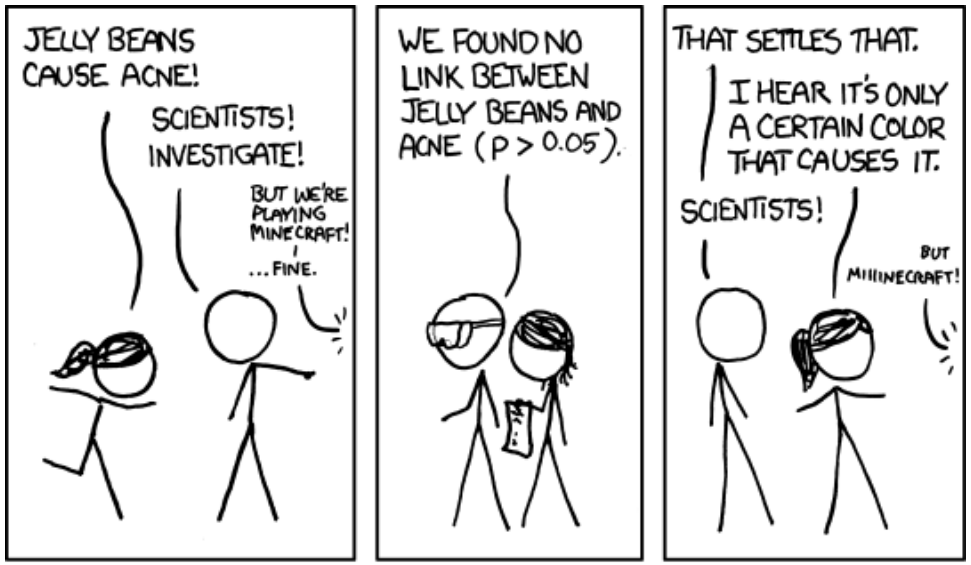

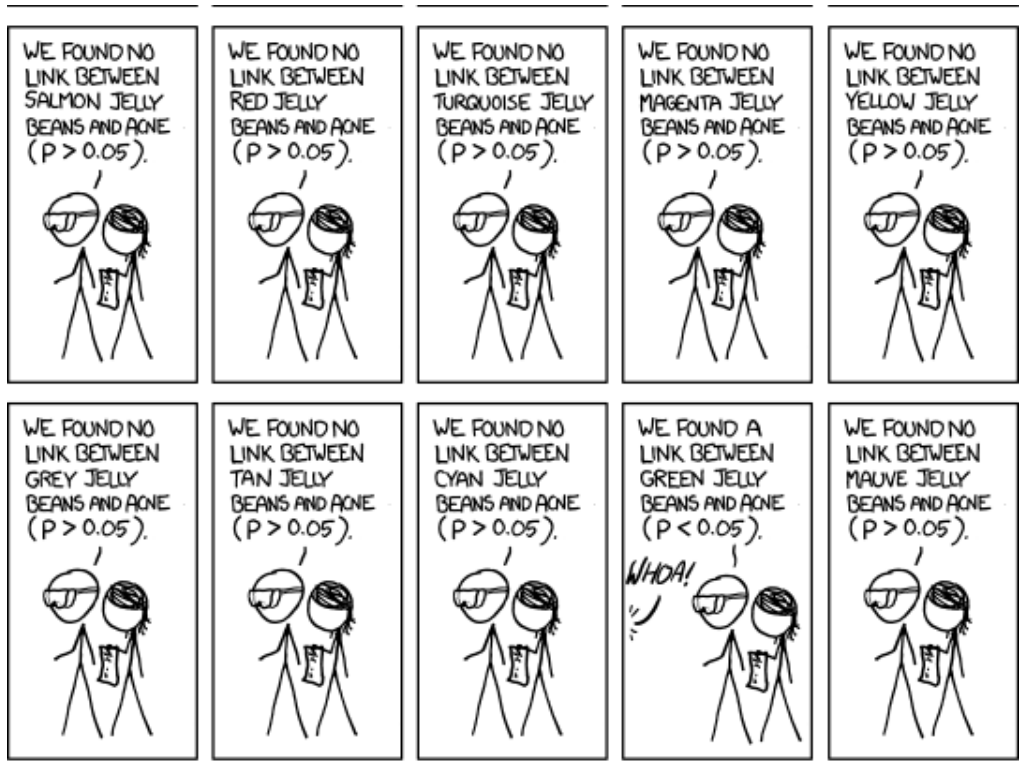

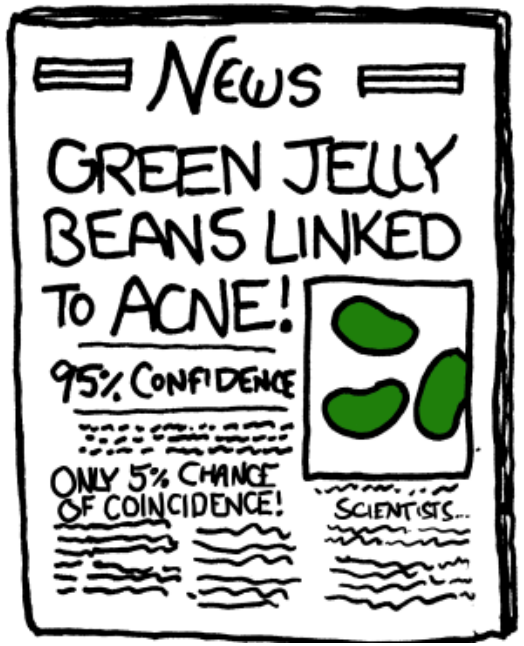

https://xkcd.com/882/