ISOQOL

# Evolution of HRQoL Implementation in Clinical Trials

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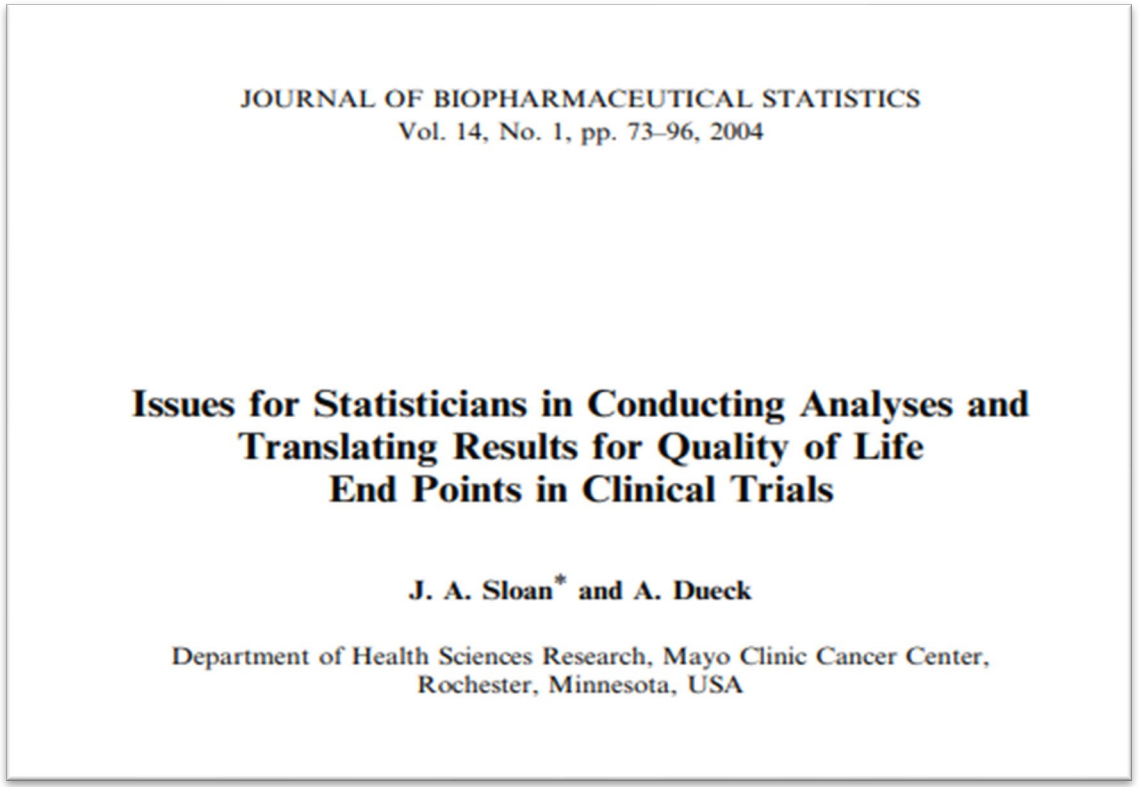
# Disclosures

- Formal
  - Employment: Mayo Clinic
  - Advisory board: Novartis
  - IDMCs: NIH, Breast International Group, Merck

- Informal
  - I’m a US-based biostatistician who implements PROs in cancer therapy clinical trials

# How it started…



JOURNAL OF BIOPHARMACEUTICAL STATISTICS
Vol. 14, No. 1, pp. 73–96, 2004

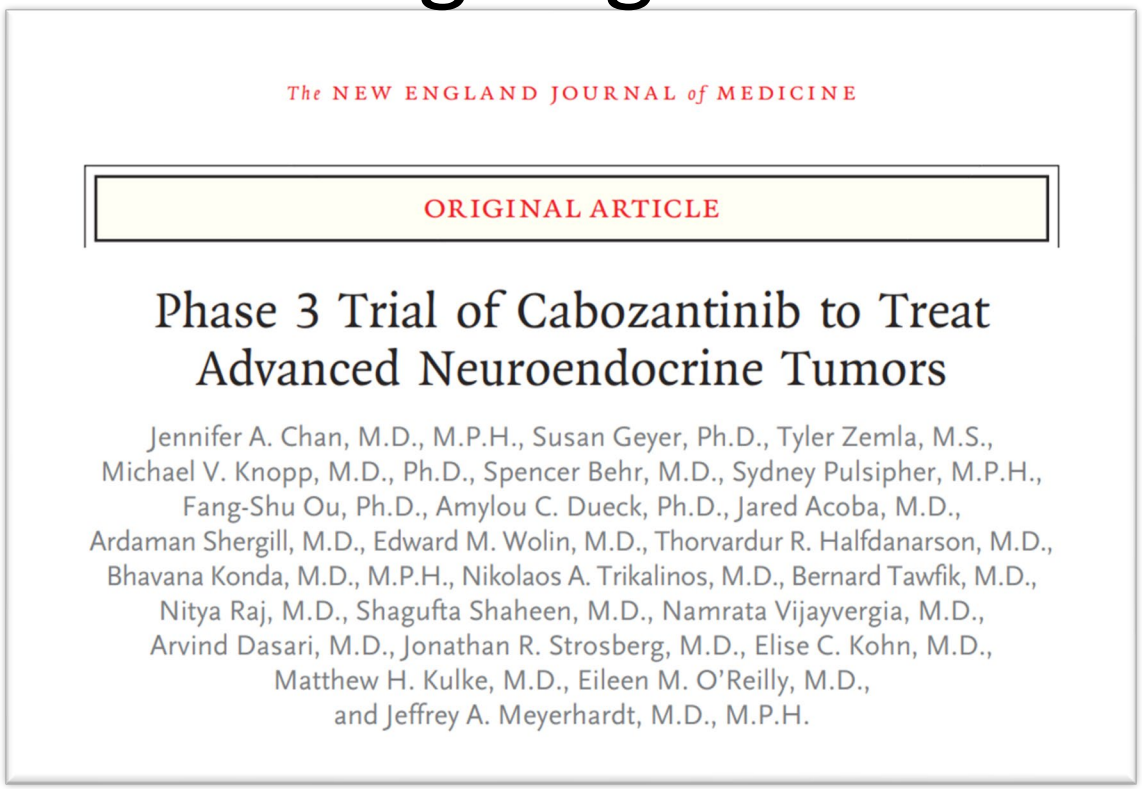
**Issues for Statisticians in Conducting Analyses and Translating Results for Quality of Life End Points in Clinical Trials**

**J. A. Sloan* and A. Dueck**

Department of Health Sciences Research, Mayo Clinic Cancer Center, Rochester, Minnesota, USA

"Quality of life (QOL) end points in pharmaceutical clinical trials are at a crossroads…"

# How it's going…



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

**Phase 3 Trial of Cabozantinib to Treat Advanced Neuroendocrine Tumors**

Jennifer A. Chan, M.D., M.P.H., Susan Geyer, Ph.D., Tyler Zemla, M.S., Michael V. Knopp, M.D., Ph.D., Spencer Behr, M.D., Sydney Pulsipher, M.P.H., Fang-Shu Ou, Ph.D., Amylou C. Dueck, Ph.D., Jared Acoba, M.D., Ardaman Shergill, M.D., Edward M. Wolin, M.D., Thorvardur R. Halfdanarson, M.D., Bhavana Konda, M.D., M.P.H., Nikolaos A. Trikalinos, M.D., Bernard Tawfik, M.D., Nitya Raj, M.D., Shagufta Shaheen, M.D., Namrata Vijayvergia, M.D., Arvind Dasari, M.D., Jonathan R. Strosberg, M.D., Elise C. Kohn, M.D., Matthew H. Kulke, M.D., Eileen M. O'Reilly, M.D., and Jeffrey A. Meyerhardt, M.D., M.P.H.

Comment from the editor: "We would like to see quality of life data as part of the report at least in the supplement."

# HRQoL – from side show to main stage!

Image generated by ChatGPT

# Outline


Multi-stakeholder collaborative research

**Standardization efforts**

**Regulatory guidance**

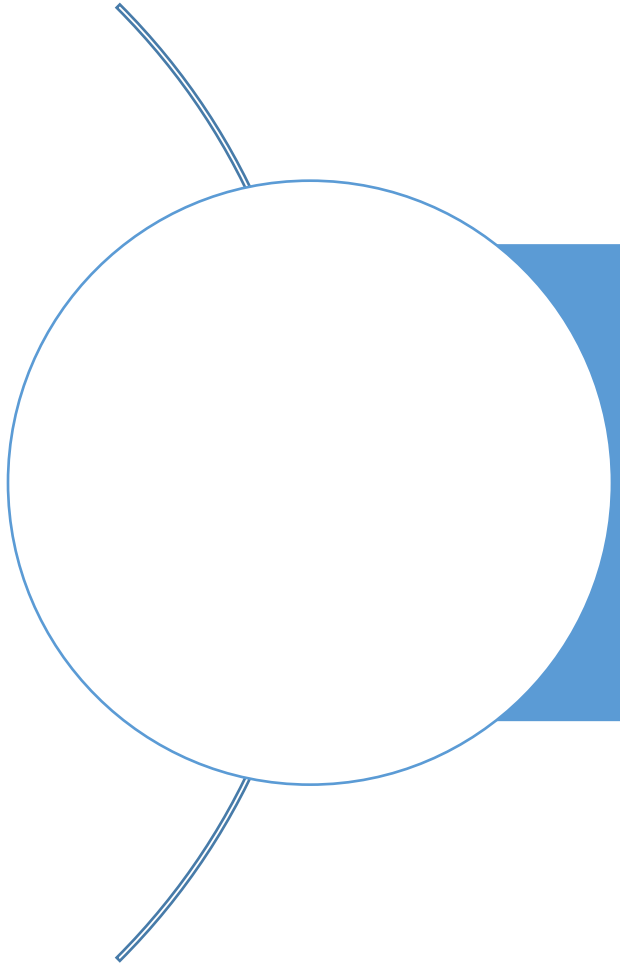
Federal/academic funding

Societies & patient research partners

# Standardization across the protocol lifecycle

- Protocol:  SPIRIT-PRO Extension
- Selecting Measures:  ISOQOL Recommendations & Others
- Statistical Analysis:  SISAQOL & Graphical Recommendations
- Reporting:  CONSORT-PRO Extension
- Education/Resources:  PROTEUS - Trials

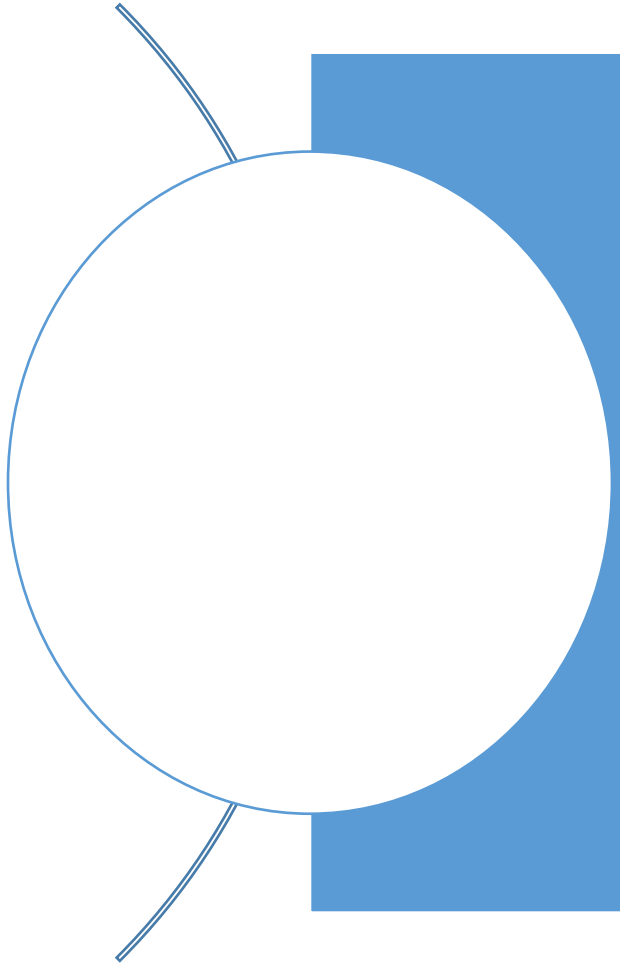
# Standardization across the protocol lifecycle



## Protocol:  SPIRIT-PRO Extension

- Calvert M, et al. JAMA. 2018; 319(5):483-494.
- PRO-specific protocol guidance
- 11 extensions and 5 elaborations when PROs are a primary or key secondary endpoint

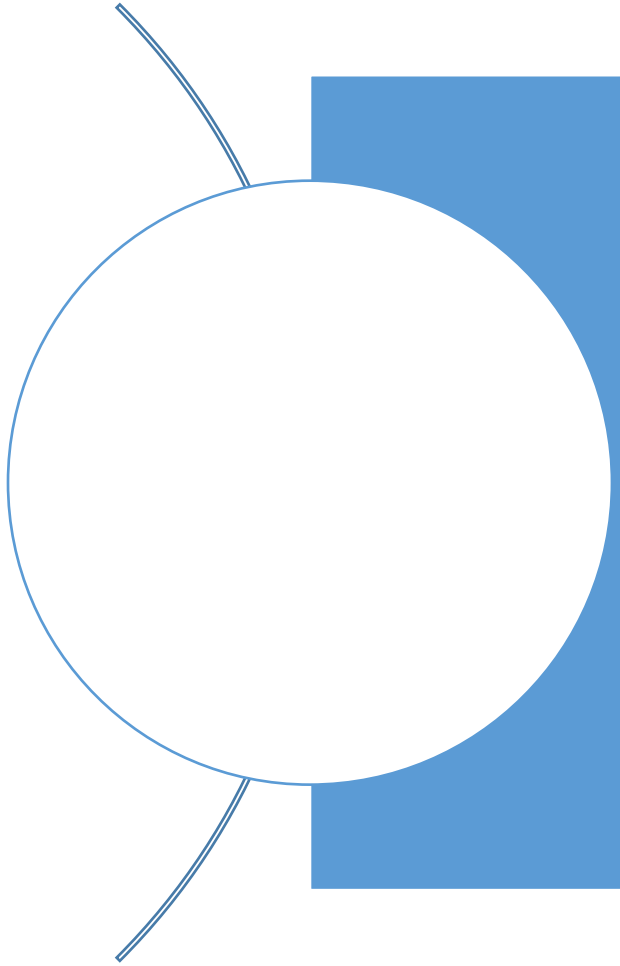
# Standardization across the protocol lifecycle



**Selecting Measures: ISOQOL Recommendations & Others**

- **ISOQOL recommendations:**
  - Reeve BB, et al. ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research. Qual Life Res. 2013; 22(8):1889-905.
- **Related review:** Crossnohere NL, et al. International guidance on the selection of patient-reported outcome measures in clinical trials: a review. Qual Life Res. 2021; 30(1):21-40.
- **Use of item libraries:** Piccinin C, et al. Recommendations on the use of item libraries for patient-reported outcome measurement in oncology trials: findings from an international, multidisciplinary working group. Lancet Oncol. 2023; 24(2):e86-e95.

# Standardization across the protocol lifecycle

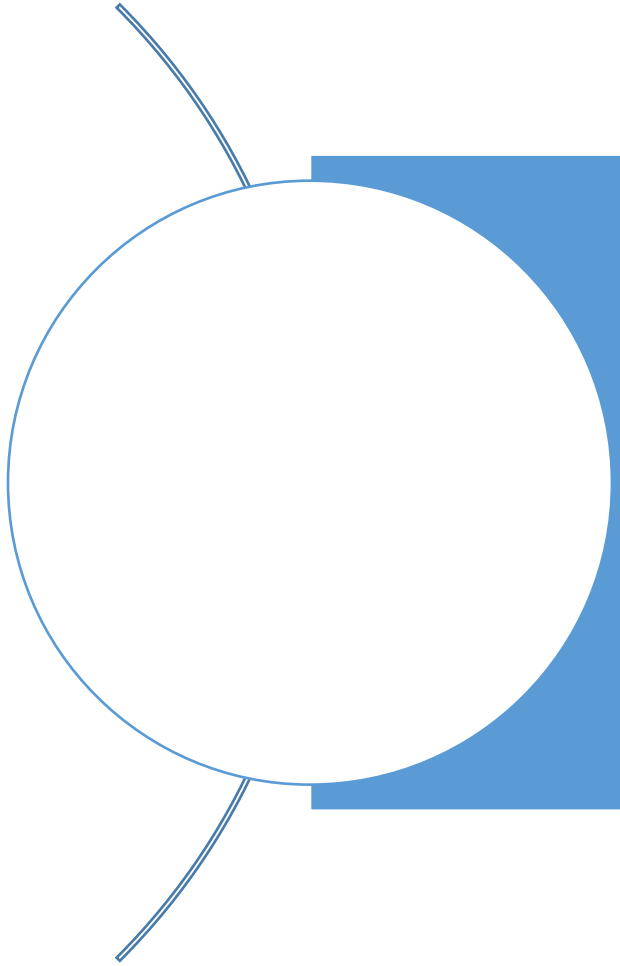


## Statistical Analysis: SISAQOL & Graphical Recommendations

- **SISAQOL-IMI:** **S**etting **I**nternational **S**tandards in **A**nalyzing Patient-Reported Outcomes and **Q**uality **o**f **L**ife Endpoints Data International multi-stakeholder consortium with shared interest in improving the standards for the statistical analysis of Patient-Reported Outcomes (PRO) - https://www.sisaqol-imi.org/
  - First recommendations published in 2020; second recommendations expected in 2025
  - Coens C, Pe M, et al. International standards for the analysis of quality-of-life and patient-reported outcome endpoints in cancer randomised controlled trials: recommendations of the SISAQOL Consortium. Lancet Oncol. 2020; 21(2):e83-e96.

- **Graphical recommendations:**
  - Snyder C, et al. Qual Life Res. 2019; 28(2):345-356.

# Standardization across the protocol lifecycle



## Reporting: CONSORT-PRO Extension

- https://www.equator-network.org/reporting-guidelines/consort-pro/
- Calvert M, et al. JAMA. 2013; 309(8):814-22.
- Five checklist items recommended
  - PROs be identified as a primary or secondary outcome in the abstract
  - PRO hypotheses be provided
  - PRO instrument's validity/reliability be provided/cited
  - Statistical approach for dealing with missing data be explicitly stated
  - PRO-specific limitations/generalizability be discussed

# Standardization across the protocol lifecycle

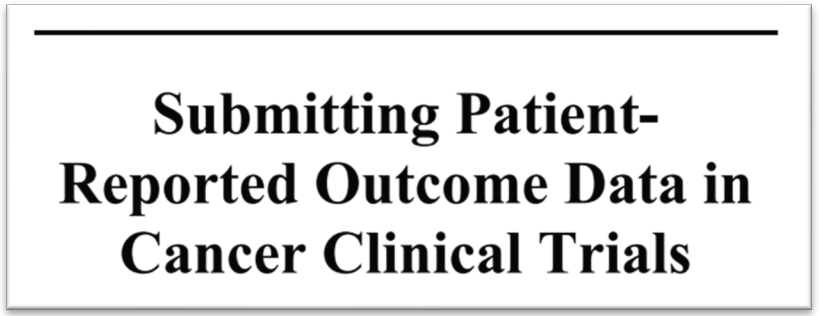
## Education/Resources: PROTEUS – Trials

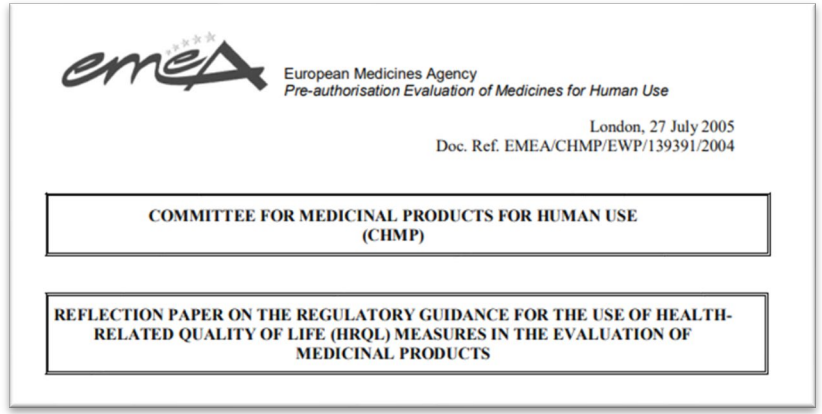
- Patient-Reported Outcomes Tools: Engaging Users & Stakeholders
- https://theproteusconsortium.org/proteus-trials/
- PROTEUS Handbook. Prepared by The University of Sydney Quality of Life Office for the PROTEUS-Trials Consortium. Available at TheProteusConsortium.org.

# Regulatory Guidance


Guidance for Industry

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

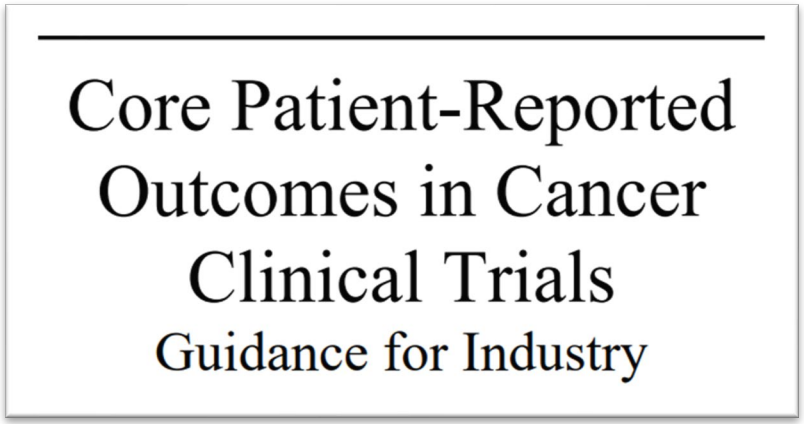

Submitting Patient-Reported Outcome Data in Cancer Clinical Trials


European Medicines Agency
*Pre-authorisation Evaluation of Medicines for Human Use*

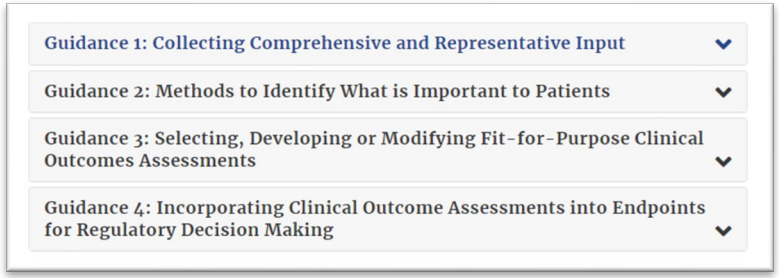
London, 27 July 2005
Doc. Ref. EMEA/CHMP/EWP/139391/2004

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

REFLECTION PAPER ON THE REGULATORY GUIDANCE FOR THE USE OF HEALTH-RELATED QUALITY OF LIFE (HRQL) MEASURES IN THE EVALUATION OF MEDICINAL PRODUCTS


Core Patient-Reported Outcomes in Cancer Clinical Trials

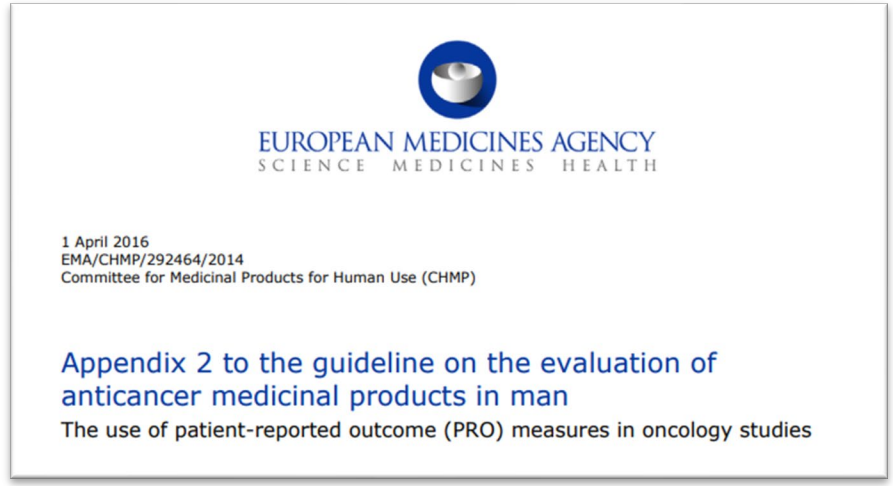
Guidance for Industry


Guidance 1: Collecting Comprehensive and Representative Input

Guidance 2: Methods to Identify What is Important to Patients

Guidance 3: Selecting, Developing or Modifying Fit-for-Purpose Clinical Outcomes Assessments

Guidance 4: Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision Making


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 April 2016
EMA/CHMP/292464/2014
Committee for Medicinal Products for Human Use (CHMP)

Appendix 2 to the guideline on the evaluation of anticancer medicinal products in man

The use of patient-reported outcome (PRO) measures in oncology studies

https://www.fda.gov/media/77832/download;
https://www.fda.gov/media/149994/download;
https://www.fda.gov/media/173581/download;
https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical

https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-regulatory-guidance-use-health-related-quality-life-hrql-measures-evaluation-medicinal-products_en.pdf;
https://www.ema.europa.eu/en/documents/other/appendix-2-guideline-evaluation-anticancer-medicinal-products-man_en.pdf

# Core Outcomes

Overall Survival
Progression Free Survival
Overall Response Rate
Serum Biomarkers

CTCAE Safety Data
Dose Modifications

Hospitalizations
ED Visits
Morbid Procedures
Supportive Care Use

Disease Symptoms

Symptomatic Adverse Events

Overall Side Effect Impact

Physical Function:

Ability to Carry Out Activities that Require Physical Effort

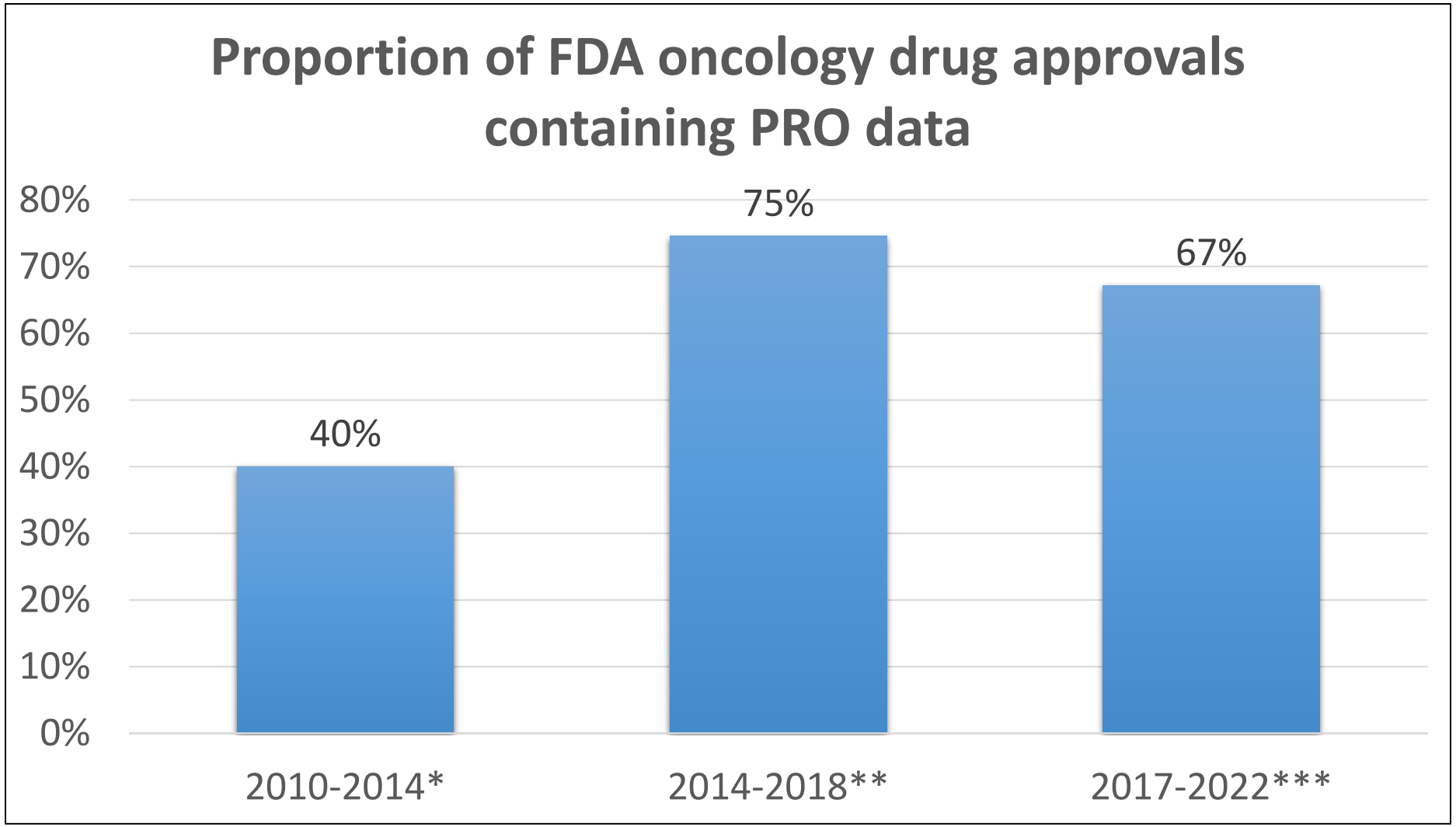
Role Function:

Ability to Work and Perform Leisure Activities

Clinician Reported and Biomarker Data

Patient Generated Data

Slide from: FDA WORKSHOP: 9th Annual Clinical Outcome Assessment in Cancer Clinical Trials Workshop
https://www.fda.gov/media/180339/download




*Gnanasakthy A, et al. J Clin Oncol. 2016; 34(16):1928-34.
**Gnanasakthy A, et al. Contemp Clin Trials. 2022; 120:106860.
***Ge C, et al. EClinicalMedicine. 2023; 59:101953.

**Inavolisib label** (approved 10/10/2024 with palbociclib and fulvestrant for treatment of endocrine-resistant, PIK3CA-mutated, HR-positive, HER2-negative, advanced breast cancer)

**Table 5: Patient-Reported Symptoms Assessed by PRO-CTCAE in INAVO120**

| Symptom (Attribute)[a] | Any Symptom Before Treatment (%)[b] | | Any Worsening on Treatment (%)[c] | | Worsening to Score 3 or 4 (%)[d] | |
|---|---|---|---|---|---|---|
| | ITOVEBI + P + F (N=148)[e] | Placebo + P + F (N=152)[e] | ITOVEBI + P + F (N=148)[e] | Placebo + P + F (N=152)[e] | ITOVEBI + P + F (N=148)[e] | Placebo + P + F (N=152)[e] |
| Diarrhea (frequency), % | 23 | 15 | 78 | 49 | 32 | 8 |
| Nausea (frequency), % | 21 | 21 | 59 | 50 | 20 | 11 |
| Vomiting (frequency), % | 9 | 6 | 35 | 26 | 6 | 3.3 |
| Fatigue (severity), % | 72 | 69 | 72 | 58 | 32 | 22 |
| Mouth sores (severity), % | 11 | 14 | 74 | 52 | 30 | 9 |
| Decreased appetite (severity), % | 38 | 28 | 78 | 55 | 26 | 12 |

At Cycle 2 Day 15, the proportion of patients with MBI responses of “not at all” were 25% in the ITOVEBI with palbociclib and fulvestrant arm and 53% in the placebo with palbociclib and fulvestrant arm. Through 31 cycles of treatment, patients in the ITOVEBI with palbociclib and fulvestrant arm reported more side effect bother compared to the placebo with palbociclib and fulvestrant arm.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/219249s001lbl.pdf

OMERACT®
Outcome Measures in Rheumatology

nature reviews rheumatology



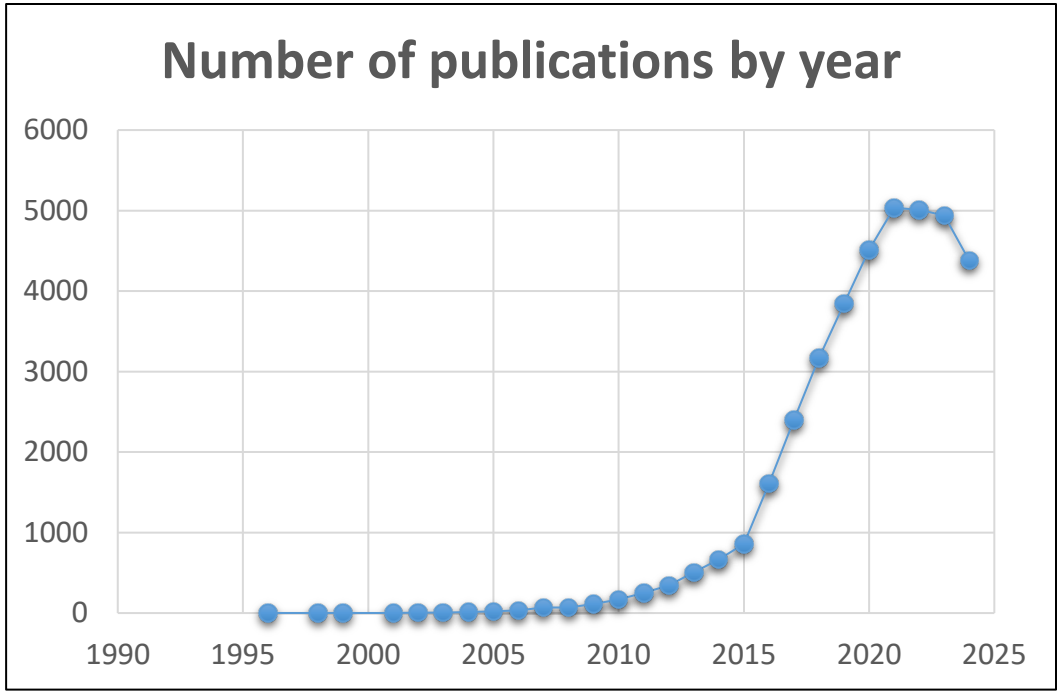
Review Article | Published: 01 September 2015

# Patient-reported outcomes in core domain sets for rheumatic diseases

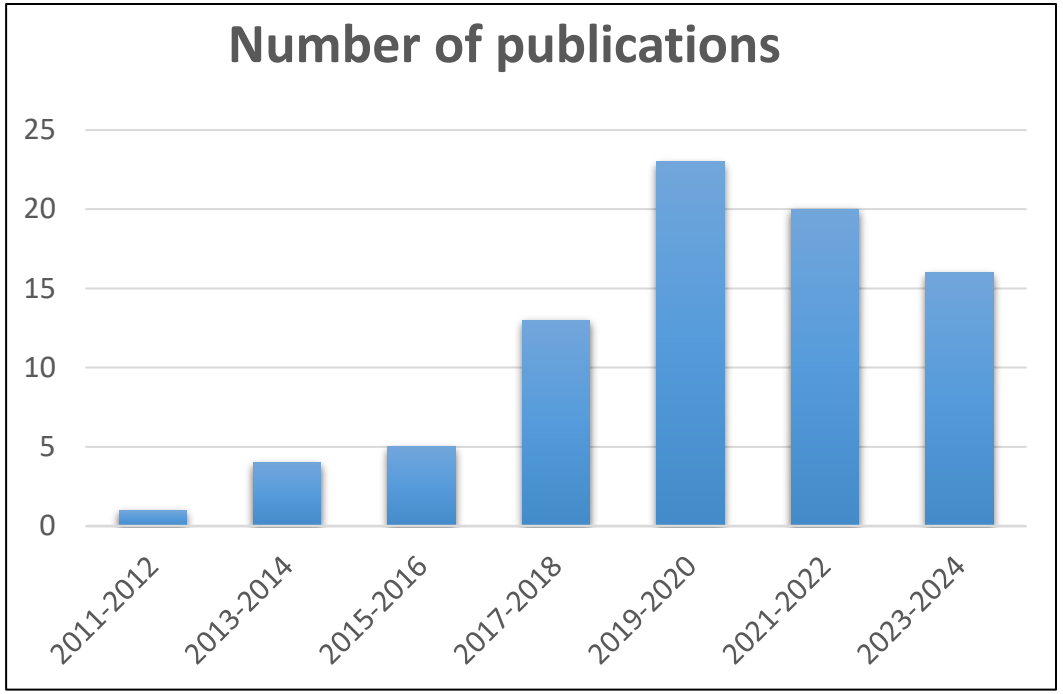
Lilian H. D. van Tuyl ✉ & Maarten Boers

*Nature Reviews Rheumatology* **11**, 705–712 (2015) | Cite this article

# But does this translate into HRQoL making it to the main stage?

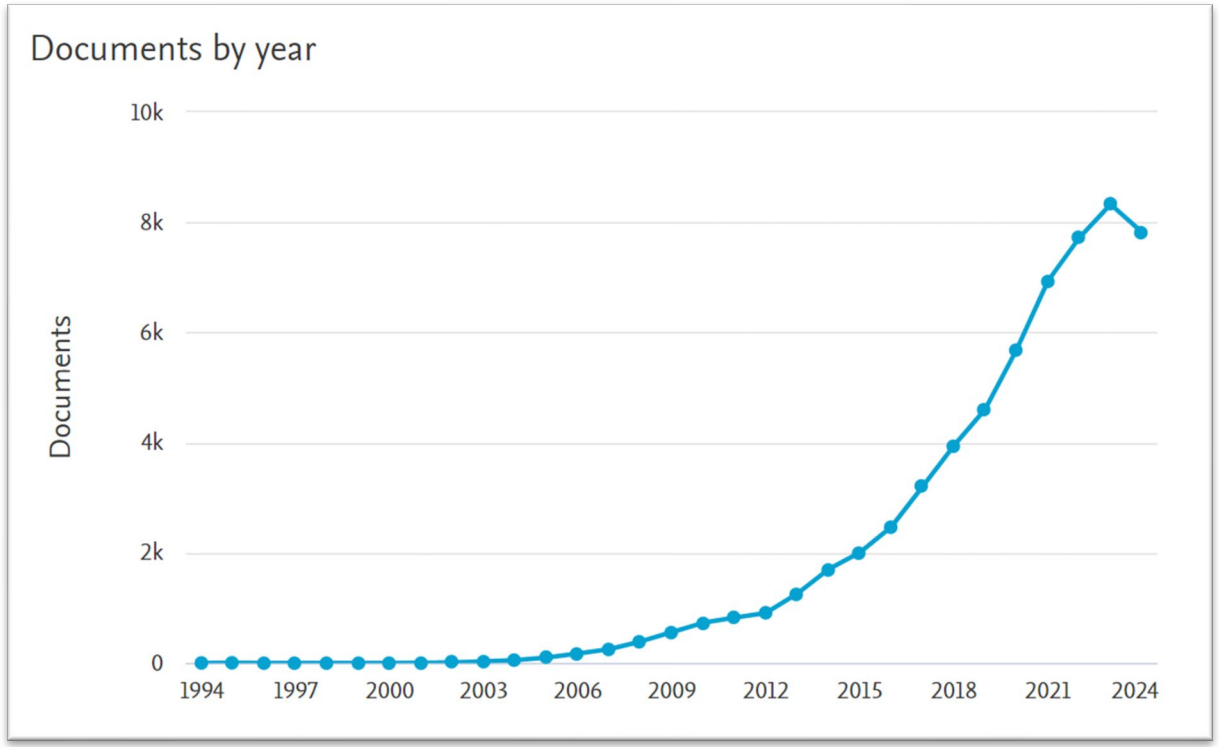


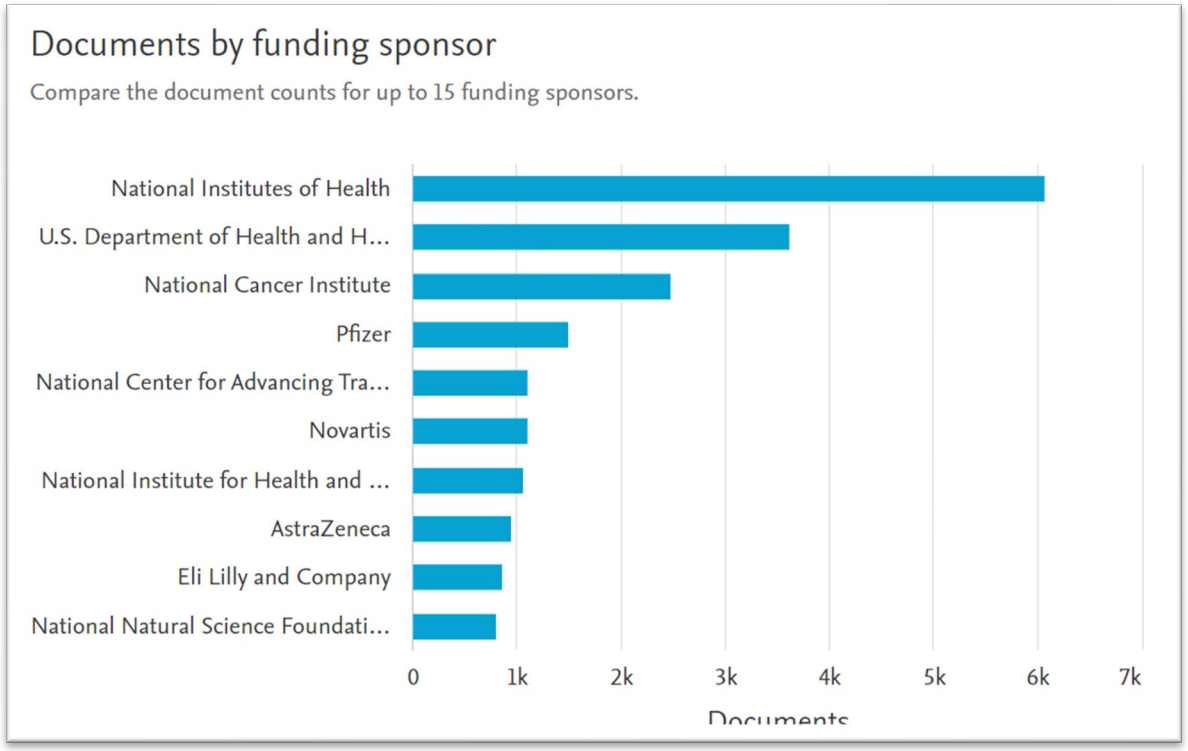

"patient-reported outcome" in **Pubmed**




"patient-reported outcome" AND "clinical trial" AND in a top cancer journal (J Clin Onc, Lancet Onc, Ann Onc, JNCI, JAMA Onc, Blood) in **Pubmed**

# N=59,789 articles (1994-2024)




"patient-reported outcome" AND "clinical trial" in **SCOPUS** limited to articles

# Highly cited studies

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Early Palliative Care for Patients with Metastatic Non–Small-Cell Lung Cancer

Jennifer S. Temel, M.D., Joseph A. Greer, Ph.D., Alona Muzikansky, M.A., Emily R. Gallagher, R.N., Sonal Admane, M.B., B.S., M.P.H., Vicki A. Jackson, M.D., M.P.H., Constance M. Dahlin, A.P.N., Craig D. Blinderman, M.D., Juliet Jacobsen, M.D., William F. Pirl, M.D., M.P.H., J. Andrew Billings, M.D., and Thomas J. Lynch, M.D.

**Table 2. Bivariate Analyses of Quality-of-Life Outcomes at 12 Weeks.***

| Variable | Standard Care (N=47) | Early Palliative Care (N=60) | Difference between Early Care and Standard Care (95% CI) | P Value† | Effect Size‡ |
|---|---|---|---|---|---|
| FACT-L score | 91.5±15.8 | 98.0±15.1 | 6.5 (0.5–12.4) | 0.03 | 0.42 |
| LCS score | 19.3±4.2 | 21.0±3.9 | 1.7 (0.1–3.2) | 0.04 | 0.41 |
| TOI score | 53.0±11.5 | 59.0±11.6 | 6.0 (1.5–10.4) | 0.009 | 0.52 |

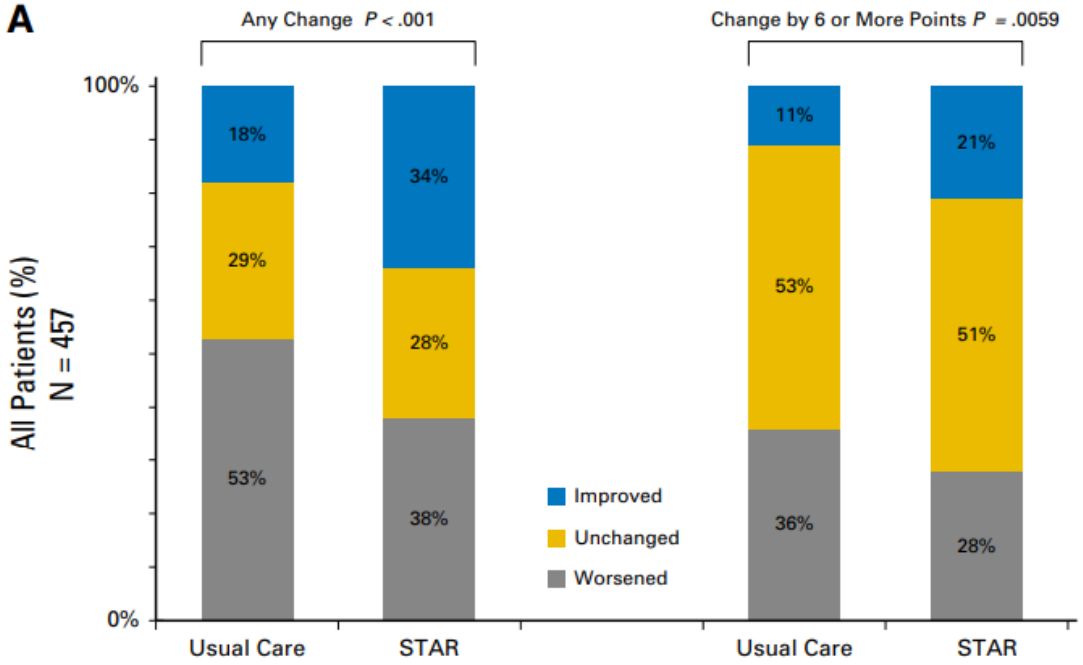
# Highly cited studies

VOLUME 34 · NUMBER 6 · FEBRUARY 20, 2016

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

## Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial

*Ethan Basch, Allison M. Deal, Mark G. Kris, Howard I. Scher, Clifford A. Hudis, Paul Sabbatini, Lauren Rogak, Antonia V. Bennett, Amylou C. Dueck, Thomas M. Atkinson, Joanne F. Chou, Dorothy Dulko, Laura Sit, Allison Barz, Paul Novotny, Michael Fruscione, Jeff A. Sloan, and Deborah Schrag*



# Highly cited studies

- Cancer therapy clinical trials
  - Motzer RJ, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med. 2007; 356(2):115-24.
  - Sequist LV, et al. Phase III Study of Afatinib or Cisplatin Plus Pemetrexed in Patients With Metastatic Lung Adenocarcinoma With EGFR Mutations. J Clin Oncol. 2023; 41(16):2869-2876.
  - Raymond E, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med. 2011; 364(6):501-13.
  - Kasivisvanathan V, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. N Engl J Med. 2018; 378(19):1767-1777.
- PROMIS papers
  - Cella D, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. J Clin Epidemiol. 2010; 63(11):1179-94.
  - Cella D, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS): progress of an NIH Roadmap cooperative group during its first two years. Med Care. 2007;45(5 Suppl 1):S3-S11.
- COSMIN papers
  - Mokkink LB, et al. The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. J Clin Epidemiol. 2010; 63(7):737-45.
  - Mokkink LB, et al. The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. Qual Life Res. 2010; 19(4):539-49.


Image generated by ChatGPT

# So all the work is done, right??!!

- PROs in early phase trials
- Tolerability analysis
  - Recommended core set from US FDA/NCI
  - Statistical analysis approaches from NCI Moonshot Treatment Tolerability Consortium
- Second set of SISAQOL recommendations expected soon
- Consensus EORTC interpretation guidelines in development
- Other core outcomes (e.g., patient-reported physical function)
- PROs in decentralized trials, evolving technology, and other future innovations in measurement

# THANKS!

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https://duecklab.github.io/

@BiostatGirl