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Patient-Reported Outcomes for Evaluating Toxicities (Adverse Events) in Cancer Clinical Research

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September 29, 2025

	Docetaxel 75 mg/m2 every 3 weeks	
ADVERSE REACTION	**ANY (%)**	**GRADE 3/4 (%)**
Anemia	67	5
Neutropenia	41	32
Thrombocytopenia	3	1
Infection	32	6
Epistaxis	6	0
Allergic Reactions	8	1
Neuropathy Sensory	30	2
Neuropathy Motor	7	2
Rash/Desquamation	6	0
Alopecia	65	N/A
Nail Changes	30	0
Nausea	41	3
Diarrhea	32	2
Stomatitis/Pharyngitis	20	1
Taste Disturbance	18	0
Vomiting	17	2
Anorexia	17	1
Cough	12	0
Dyspnea	15	3
Cardiac function	10	0
Fatigue	53	5
Myalgia	15	0
Tearing	10	1
Arthralgia	8	1

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Table from Docetaxel U.S. Drug Label

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Table from Docetaxel U.S. Drug Label

Standard Source of Adverse Event Data in Oncology Trials

- Common Terminology Criteria for Adverse Events (CTCAE)
- Item library, designed for clinicians to complete
- About 800 items total (10% of items are symptoms)

CTCAE/MedDRA Term	CTCAE Grade 1	CTCAE Grade 2	CTCAE Grade 3	CTCAE Grade 4
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated

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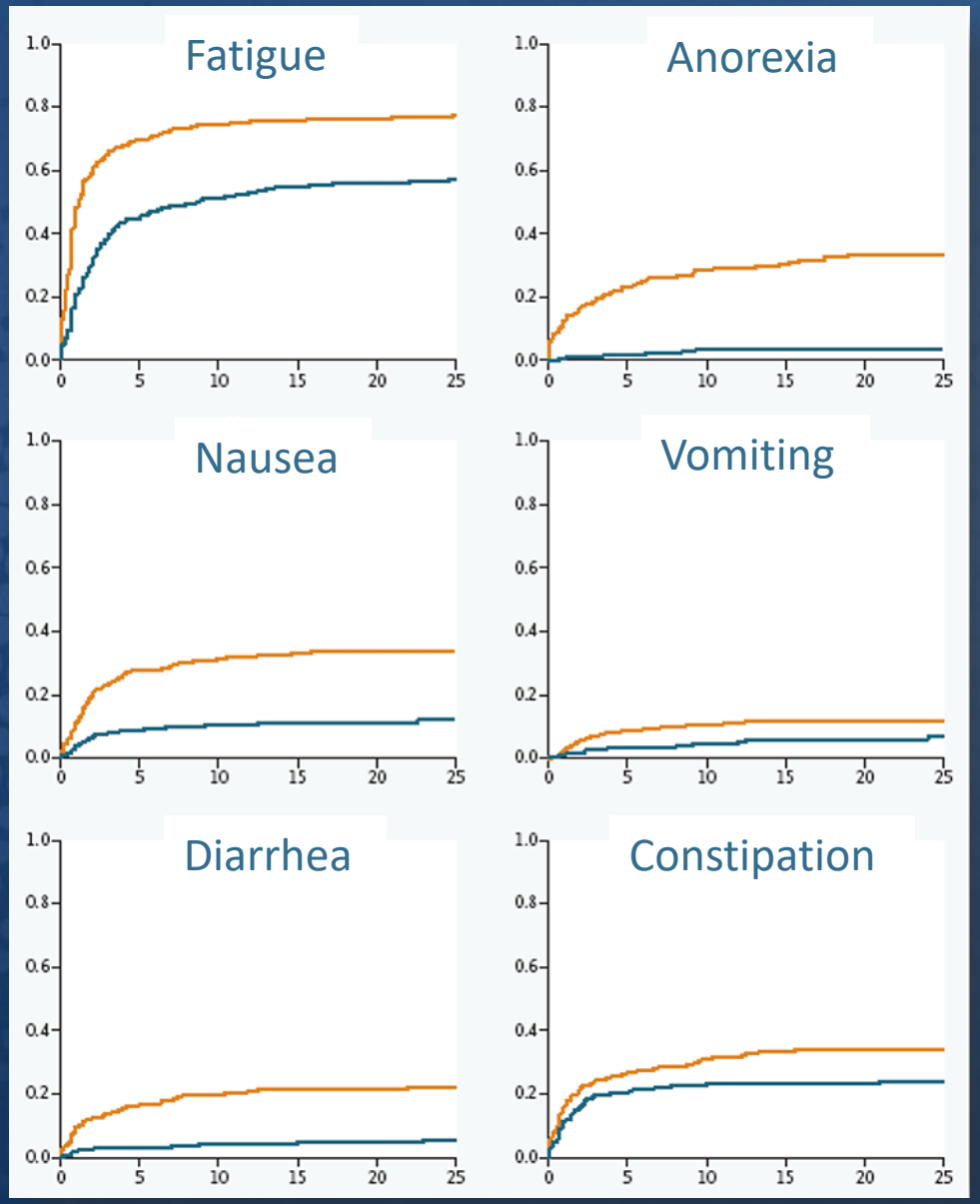
Investigators Under-Detect Symptomatic Toxicities

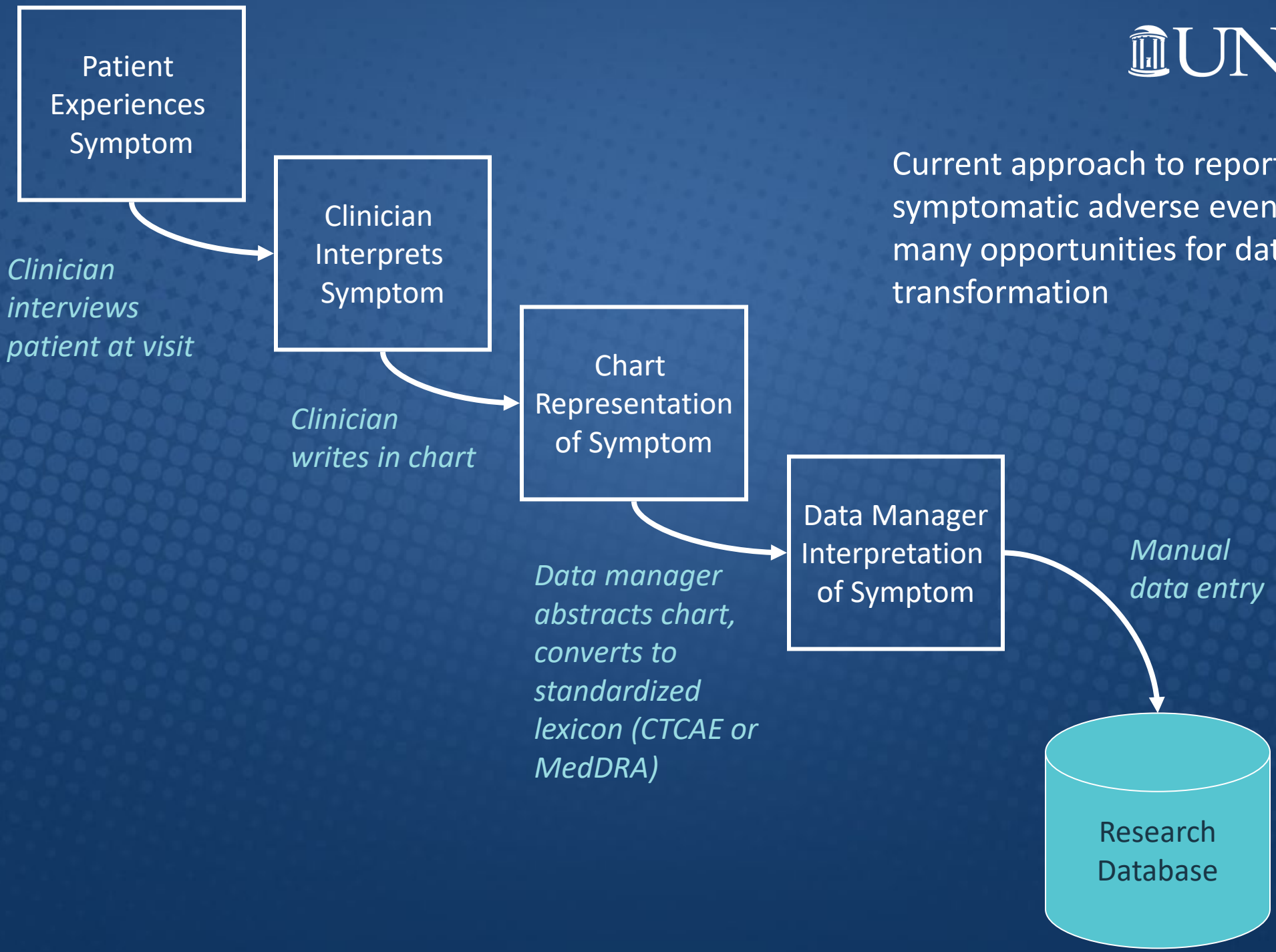


Consequence: Underestimation of true toxicity leading to imbalanced benefit:risk calculus

Patient-reported

Clinician-reported

Basch: NEJM, 2010



Current approach to reporting symptomatic adverse events in trials – many opportunities for data loss and transformation

Patient Experiences Symptom

Alternative patient-centered approach avoids data loss or misinterpretation

Patient direct reporting of symptoms

Low Reliability of Investigator-Reporting of Symptomatic Adverse Events

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Symptom	ICC	95% CI
Constipation	0.48	0.36; 0.58
Diarrhea	0.58	0.49; 0.66
Dyspnea	0.69	0.62; 0.75
Fatigue	0.50	0.39; 0.59
Nausea	0.52	0.41; 0.60
Neuropathy	0.71	0.65; 0.76
Vomiting	0.46	0.34; 0.56

Atkinson/Basch: Qual Life Res, 2011

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Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events

Developed under contracts to the NCI

To provide a patient-reported adjunct to the CTCAE and improve the accuracy of symptomatic AE reporting in cancer clinical trials

https://healthcaredelivery.cancer.gov/pro-ctcae/

CTCAE → PRO-CTCAE

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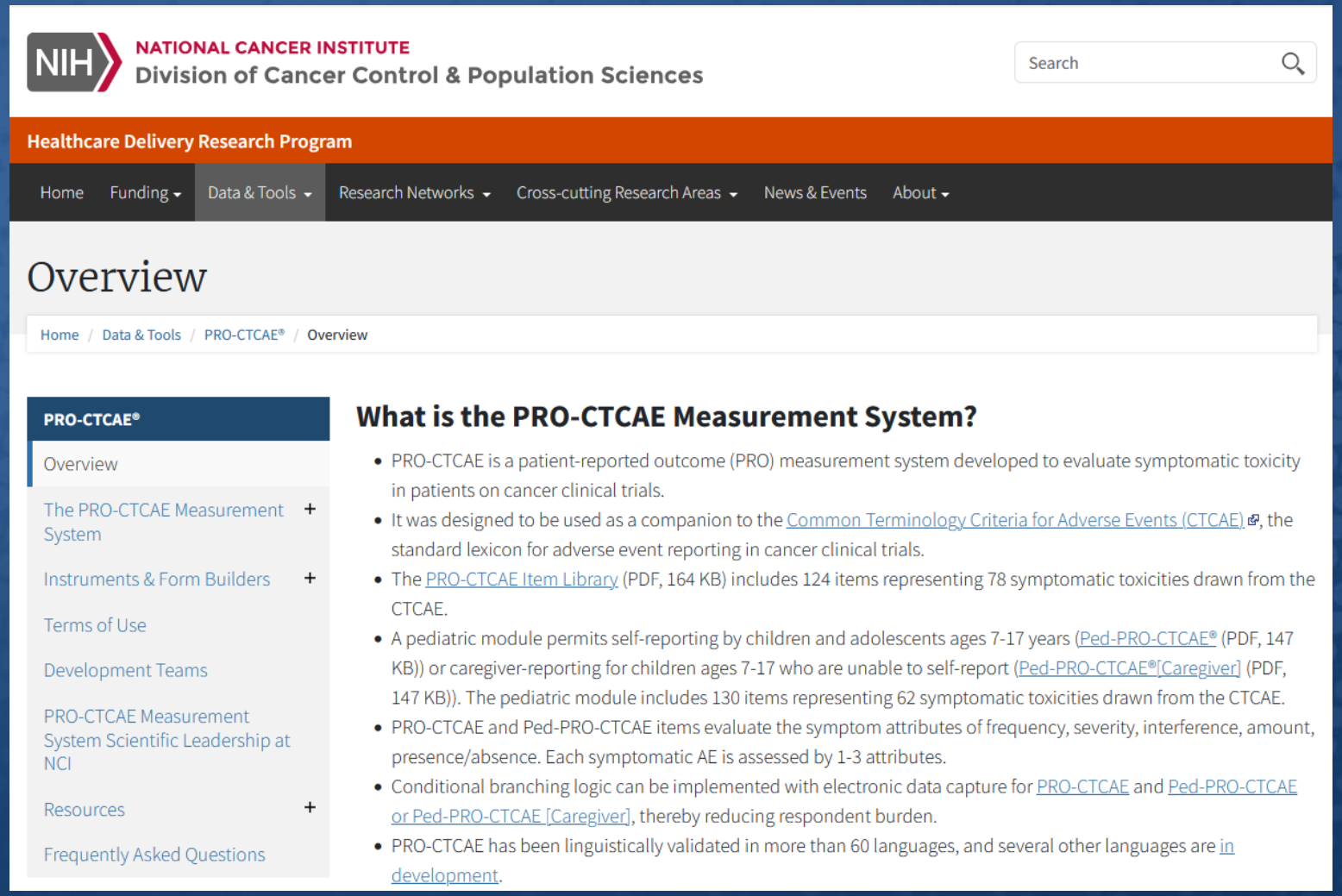
CTCAE/MedDRA Term	CTCAE Grade 1	CTCAE Grade 2	CTCAE Grade 3	CTCAE Grade 4
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated

Two Items	Responses
What was the severity of your MOUTH OR THROAT SORES at their worst?	None Mild Moderate Severe Very Severe
How much did MOUTH OR THROAT SORES interfere with your usual activities?	Not at all A little bit Somewhat Quite a bit Very much

PRO-CTCAE Item Library

- Released 2014
- 124 items representing 78 symptomatic adverse events
- Robust psychometric properties (validity, reliability, sensitivity)
- Available in >70 languages
- Publicly available (no fees)
- Now being included in drug development trials, FDA Guidance, drug labeling
- Pediatric version also available



https://healthcaredelivery.cancer.gov/pro-ctcae/

Example: 2023 ASCO Plenary
PROSPECT Trial (Alliance N1048)

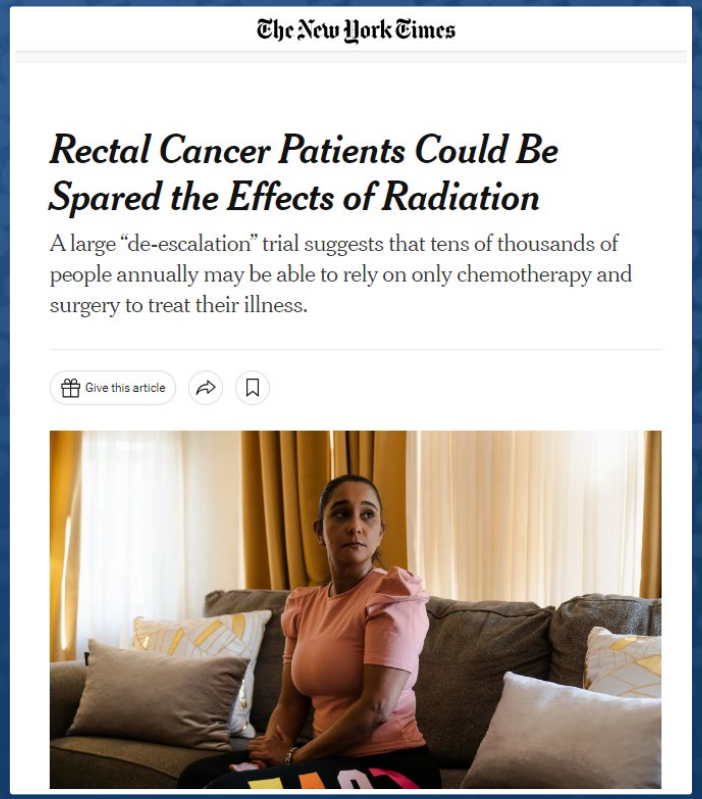
Design:

- RCT chemoradiotherapy vs chemotherapy only before resection of locally advanced rectal cancer
- 14 PRO-CTCAE symptomatic AEs

Findings:

- No difference in 5-Year DFS
- Substantial differences in PRO-CTCAE:
  - ChemoRT: Long term fatigue, neuropathy, sexual dysfunction
  - Chemo only: No long term symptomatic AEs
- Clinician reporting <u>did not detect</u> these differences

Patient compliance with PRO reporting: 92%


The New York Times

Rectal Cancer Patients Could Be Spared the Effects of Radiation

A large "de-escalation" trial suggests that tens of thousands of people annually may be able to rely on only chemotherapy and surgery to treat their illness.

Give this article

Schrag: NEJM 2023
Basch: JCO 2023

FRIENDS of CANCER RESEARCH

A FRIENDS OF CANCER RESEARCH WHITE PAPER

BROADENING THE DEFINITION OF TOLERABILITY IN CANCER CLINICAL TRIALS TO BETTER MEASURE THE PATIENT EXPERIENCE

OBJECTIVE

Robust safety and tolerability data are essential in cancer therapeutic studies, and some trials are specifically designed with a key objective of demonstrating improved safety and tolerability. The development of a clinical trial framework and data elements to demonstrate comparative safety and tolerability requires a suite of endpoints and approaches to enable meaningful interpretation of results for regulatory and clinical decision-making. Identification of data elements suitable for a comparative tolerability trial design would be useful across cancer clinical trial settings where a comprehensive characterization of safety and tolerability is a critical component in the evaluation of individual and collective patient benefit.

A multi-stakeholder working group was convened, including drug sponsors, regulators from the US and Europe, researchers, and patients, to develop a contemporary definition of tolerability that better encompasses the patient experience receiving a given treatment; to identify a broader array of data elements and methodologies that more fully characterize tolerability and to consider a trial design framework that includes patient endpoints and other clinical outcomes to support p regulatory and clinician decision-making, and direc in U.S. Food and Drug Administration (FDA) labelin this whitepaper were conceived to foster patient fo In particular, this whitepaper presents opportunitie of the patient's perspective on symptomatic advers impacts on work and daily activities and overall sid the use of clinical outcome assessments, including complement our understanding of safety and toler discussed in this whitepaper may extend into the b setting.

CONTRIBUTORS

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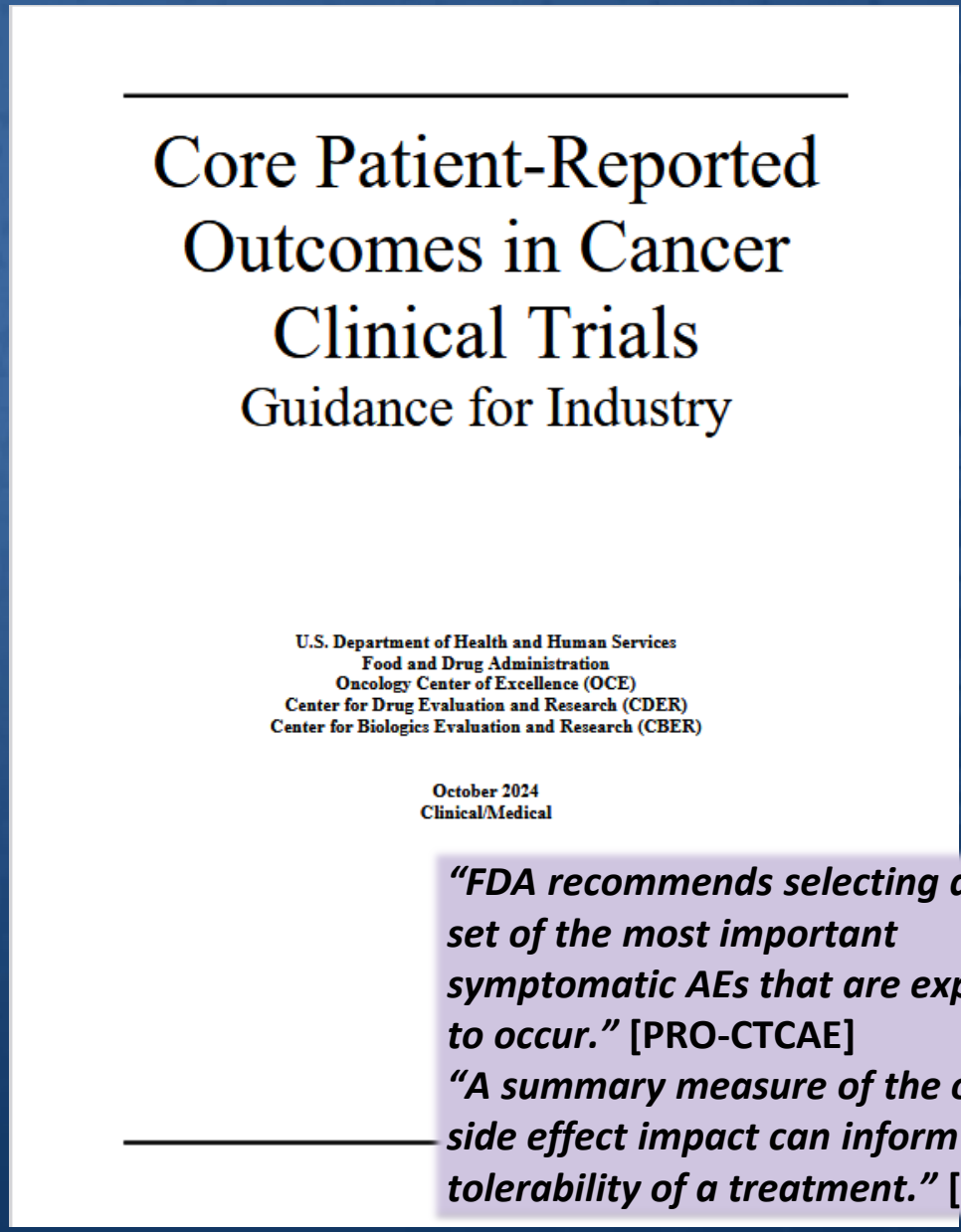
"A complete understanding of tolerability should include direct measurement from the patient on how they are feeling and functioning while on treatment."



Core Patient-Reported Outcomes in Cancer Clinical Trials

Guidance for Industry

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)

October 2024
Clinical/Medical

"FDA recommends selecting a concise set of the most important symptomatic AEs that are expected to occur." **[PRO-CTCAE]**
"A summary measure of the overall side effect impact can inform the tolerability of a treatment." **[GP5]**

Conclusions

Patient reporting of adverse events improves the accuracy and patient-centeredness of clinical trials.

Methods are well established for phase 3 trials and real-world studies; less defined in early-phase for dose-finding (area of active development work).

Continued FDA encouragement for drug developers to use PRO tools is essential for continued uptake.

The NEW ENGLAND JOURNAL of MEDICINE

PERSPECTIVE

The Missing Voice of Patients in Drug-Safety Reporting

Author: Ethan Basch, M.D. Author Info & Affiliations

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A patient wants to know about symptoms she may have from a prescription drug she is taking. Consulting the label's "Adverse Reactions" section, she finds a wealth of data. Little does she realize that this information, largely collected during clinical trials, is based almost entirely on clinicians' impressions of patients' symptoms — not on patients' own firsthand reports of their experiences with the drug.

The current drug-labeling practice for adverse events is based on the implicit assumption that an accurate portrait of patients' subjective experiences can be provided by clinicians' documentation alone. Yet a substantial body of evidence contradicts this assumption, showing that clinicians systematically downgrade the severity of patients' symptoms, that patients' self-reports frequently capture side effects that clinicians miss, and that clinicians' failure to note these symptoms results in the occurrence of preventable adverse events.[1,2]

Selected References

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