Regulatory Use of Patient-Reported Outcomes in Oncology

Vishal Bhatnagar, MD
Associate Director for Patient Outcomes
Oncology Center of Excellence

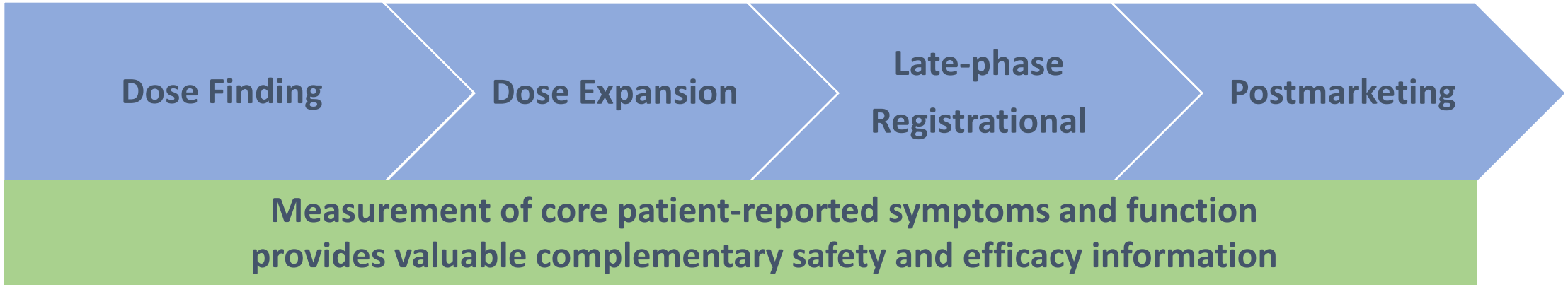
September 29, 2025

Disclosures

No disclosures

Content of this presentation represents current thinking and is subject to modification

Inclusion of Patient-Reported Outcomes During Oncology Product Development



FDA's Patient-Focused Drug Development Initiative

- Patients are uniquely positioned to inform understanding of the therapeutic context for drug development and evaluation
  - There is a need for more systematic ways of gathering patient perspective on their condition and treatment options

- Patient-Focused Drug Development (PFDD) is part of FDA commitments under PDUFA V and VI*

- 21st Century Cures includes important language about PFDD

*The sixth authorization of the Prescription Drug User Fee Act, enacted in 2017

Core PRO Outcomes

Overall Survival
Progression Free Survival
Overall Response Rate
Serum Biomarkers

CTCAE Safety Data
Dose Modifications

Hospitalizations
ED Visits
Morbid Procedures
Supportive Care Use

Clinician Reported and Biomarker Data

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

Patient Generated Data

Example Assessment Frequency

	Early treatment period												Continued Tx	
	BL	w2	w3	w4	w5	w6	w7	w8	M3	M4	M5	M6	M9	M12*
Symptomatic AE	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Single Item Side Effect Global	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Function	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Role Function	X		X		X		X		X	X	X	X	X	X
Disease Symptoms	X				X				X			X		X
Other HRQOL	X								X			X		X

*Assessments at further timepoints would be context dependent

Additional relevant items outside of the Core Outcomes may be necessary depending on context

What is the PRO Trial Objective?

- **What is your PRO Trial Objective?**
  - Describe the patient experience on treatment?
  - Inform Safety / Tolerability?
  - Inform Efficacy?

- **What is your U.S. regulatory goal for the PRO data?**
  - Supportive data for overall benefit:risk assessment?
  - Descriptive patient experience data in product label?
  - Make a claim of treatment benefit in product label?
    - Substantial evidence of efficacy or improved safety

Using PROs for Safety/Tolerability

2013 Crizotinib Visual Symptoms- VSAQ-ALK

"The majority of patients on the XALKORI arm in Study 1 (> 50%) reported visual disturbances; these visual disturbances occurred at a frequency of 4-7 days each week, lasted up to 1 minute, and had mild or no impact (scores 0 to 3 out of a maximum score of 10) on daily activities as captured in a patient questionnaire."

PRO-CTCAE is not CTCAE

CTCAE

Grade 1 Diarrhea	Grade 2 Diarrhea	Grade 3 Diarrhea	Grade 4 Diarrhea	Grade 5 Diarrhea
Increase of <4 stools per day over baseline	Increase of 4-6 stools per day over baseline; IV fluids indicated <24hrs	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization	Life-threatening consequences (e.g., hemodynamic collapse)	Death

PRO-CTCAE

In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (diarrhea)?

○ Never ○ Rarely ○ Occasionally ○ Frequently ○ Almost constantly

Individual Toxicity versus Overall Side Effect (OSE) Measure

- Drugs cause many symptomatic side effects (e.g., rash, diarrhea, neuropathy)
- How an individual “weighs” one over the other can differ
- Could an overall side effect measure be a useful summary metric?

Possible Options from Commonly Used Item Libraries Include:

- FACT GP5 Question: “I am bothered by the side effects of treatment”
- EORTC Q168: “To what extent have you been troubled with side-effects from your treatment”

PRO-CTCAE, OSE Bother included in Oncology Product Labeling

ITOVEBI (inavolisib)
approved October 10, 2024

Indication: in combination with palbociclib and fulvestrant for the treatment of adults with endocrine-resistant, PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, as detected by an FDA-approved test, following recurrence on or after completing adjuvant endocrine therapy.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/219249s000lbl.pdf

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

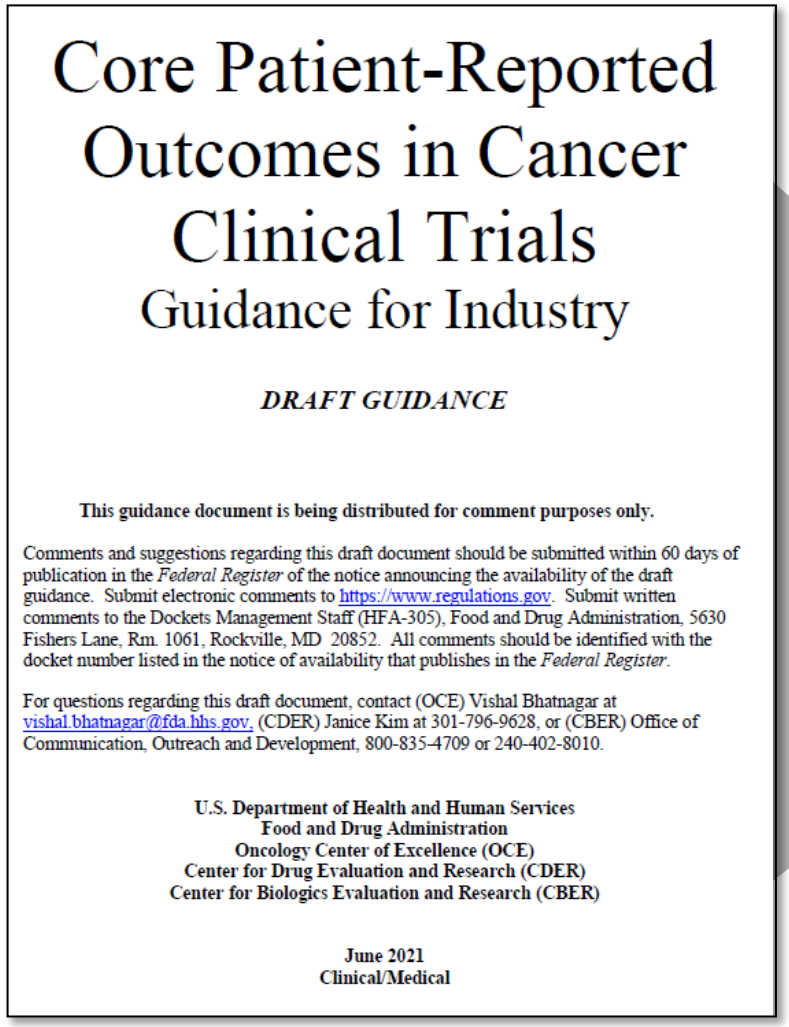
Symptom (Attribute)[a]	Any Symptom Before Treatment (%)[b]		Any Worsening on Treatment (%)[c]		Worsening to Score 3 or 4 (%)[d]	
	ITOVEBI + P + F (N=148)[e]	Placebo + P + F (N=152)[e]	ITOVEBI + P + F (N=148)[e]	Placebo + P + F (N=152)[e]	ITOVEBI + P + F (N=148)[e]	Placebo + P + F (N=152)[e]
Diarrhea (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

Symptom (Attribute)	Baseline Presence		Post-baseline Presence	
	ITOVEBI + P + F (N=148)[e]	Placebo + P + F (N=152)[e]	ITOVEBI + P + F (N=148)[e]	Placebo + P + F (N=152)[e]
Rash (yes), %	5	5	50	38

ITOVEBI+P+F = ITOVEBI with palbociclib and fulvestrant arm; Placebo+P+F = placebo with palbociclib and fulvestrant arm.
[a] The symptom attribute scoring is defined by amount/frequency/severity with a score of 0 = 'not at all'/'never'/'none'; 1 = 'a little bit'/'rarely'/'mild'; 2 = 'somewhat'/'occasionally'/'moderate'; 3 = 'quite a bit'/'frequently'/'severe'; 4 = 'very much'/'almost constantly'/'very severe'.
[b] The percentage of patients whose symptom score before treatment was 1-4.
[c] The percentage of patients whose symptom score increased during treatment, with respect to their score before treatment.
[d] The percentage of patients whose symptom score increased to 3 or 4 during treatment, with respect to their score before treatment.
[e] The number of patients who provided a score before treatment and at least one on-treatment score.

Patient-reported overall side-effect impact was assessed using the Modified Bother Item (MBI). Patients provided a response to "I am bothered by side effects of treatment," and at baseline the proportion of patients with MBI responses of "not at all" were 70% in the ITOVEBI with palbociclib and fulvestrant arm and 76% in the placebo with palbociclib and fulvestrant arm. 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.

OCE Core Outcomes Guidance



Core Patient-Reported Outcomes in Cancer Clinical Trials

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

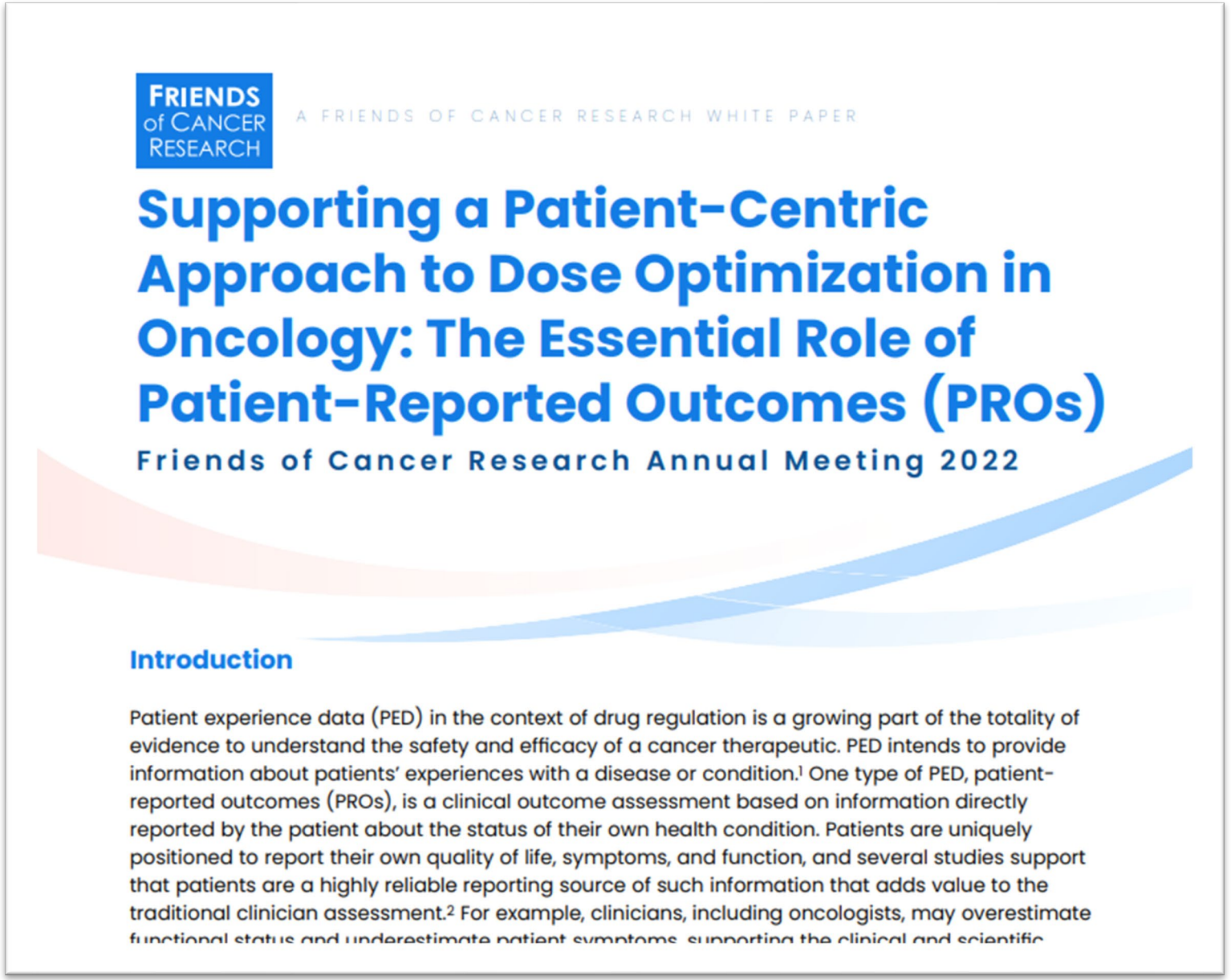
Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (OCE) Vishal Bhatnagar at vishal.bhatnagar@fda.hhs.gov, (CDER) Janice Kim at 301-796-9628, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

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)

June 2021
Clinical/Medical

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/core-patient-reported-outcomes-cancer-clinical-trials



FRIENDS of CANCER RESEARCH

A FRIENDS OF CANCER RESEARCH WHITE PAPER

Supporting a Patient-Centric Approach to Dose Optimization in Oncology: The Essential Role of Patient-Reported Outcomes (PROs)

Friends of Cancer Research Annual Meeting 2022

Introduction

Patient experience data (PED) in the context of drug regulation is a growing part of the totality of evidence to understand the safety and efficacy of a cancer therapeutic. PED intends to provide information about patients' experiences with a disease or condition.[1] One type of PED, patient-reported outcomes (PROs), is a clinical outcome assessment based on information directly reported by the patient about the status of their own health condition. Patients are uniquely positioned to report their own quality of life, symptoms, and function, and several studies support that patients are a highly reliable reporting source of such information that adds value to the traditional clinician assessment.[2] For example, clinicians, including oncologists, may overestimate functional status and underestimate patient symptoms, supporting the clinical and scientific

https://friendsofcancerresearch.org/wp-content/uploads/Supporting_Patient-Centric_Approach_Dose_Optimization_Oncology-PROs.pdf

Summary

- Patient-reported outcomes and healthcare utilization can complement standard efficacy and safety measures
- PRO concepts should be well understood; instruments should be fit-for-purpose and well-defined
- Tolerability can be assessed in all oncology trials, including dose escalation and expansion
- Item libraries can be used to parsimoniously meet the respective needs of regulators, payors, and all stakeholders.
- Well-collected and meaningful PRO information should be communicated to patients, caregivers, and providers

Acknowledgements

Richard Pazdur

Angelo De Claro, Tamy Kim

OCE staff

CDER Office of Biostatistics

CDER Patient Focused Drug Development Staff

Patients, Caregivers, and Advocates