GWALTNEY consulting

Integrating Patient-Reported Outcomes

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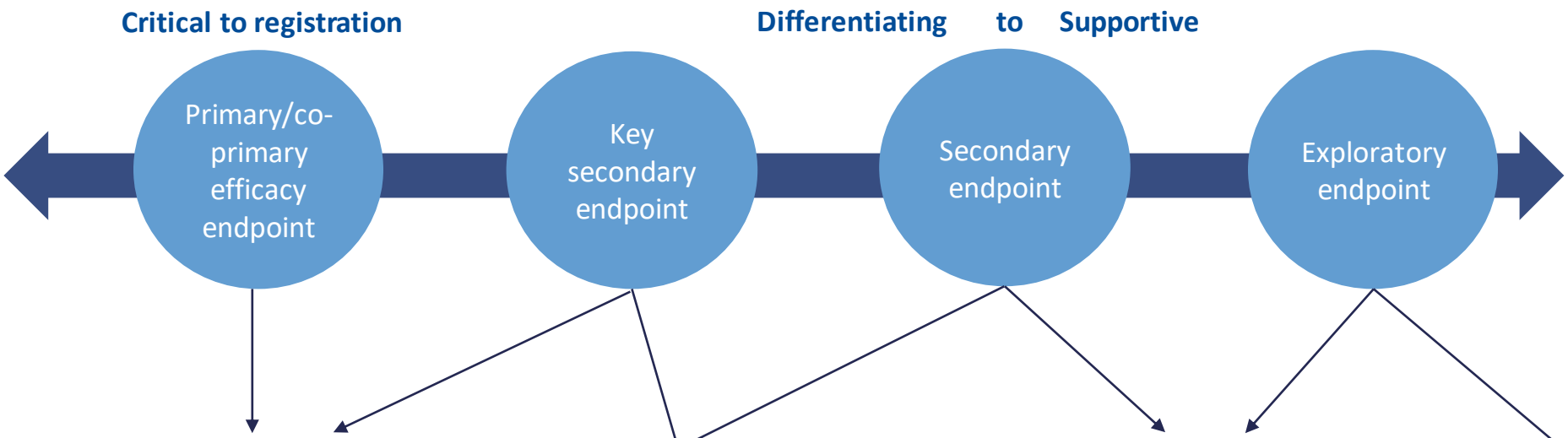
Patient-Reported Outcomes Can Be Used As Primary, Secondary, or Exploratory Endpoints In Oncology Trials

PRO-based endpoints can be viewed on a spectrum:



Myelofibrosis

- Symptom primary endpoint measured using the Myelofibrosis Symptom Assessment Form

NSCLC

- Symptom key secondary and secondary endpoints measured lung cancer symptom, health status and physical functioning improvement

Prostate Cancer

- Pain progression

GBM

- Health-related QOL

General Oncology

- Tolerability
- PRO-CTCAE symptom library

GUIDANCE DOCUMENT

Core Patient-Reported Outcomes in Cancer Clinical Trials

Draft Guidance for Industry

JUNE 2021

Download the Draft Guidance Document | Read the Federal Register Notice

III. CORE PATIENT-REPORTED OUTCOMES

To maximize the utility of submitted PRO information, we recommend collecting and separately analyzing the following core PROs:

- Disease-related symptoms
- Symptomatic adverse events
- Overall side effect impact summary measure
- Physical function
- Role function

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

Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ)

Table 2: Item Content for the *NSCLC-SAQ*

Domain	Item
Cough	1. How would you rate your coughing at its worst…?
Pain	2. How would you rate the worst pain in your chest…?
	3. How would you rate the worst pain in areas other than your chest…?
Dyspnea	4. How often did you feel short of breath during usual activities…?
Fatigue	5. How often did you have low energy…?
	6. How often did you tire easily…?
Appetite	7. How often did you have a poor appetite over the last 7 days?

https://www.fda.gov/media/119251/download

Getting the Dose Right: Optimizing Dose Selection Strategies in Oncology – An FDA-ASCO Virtual Workshop

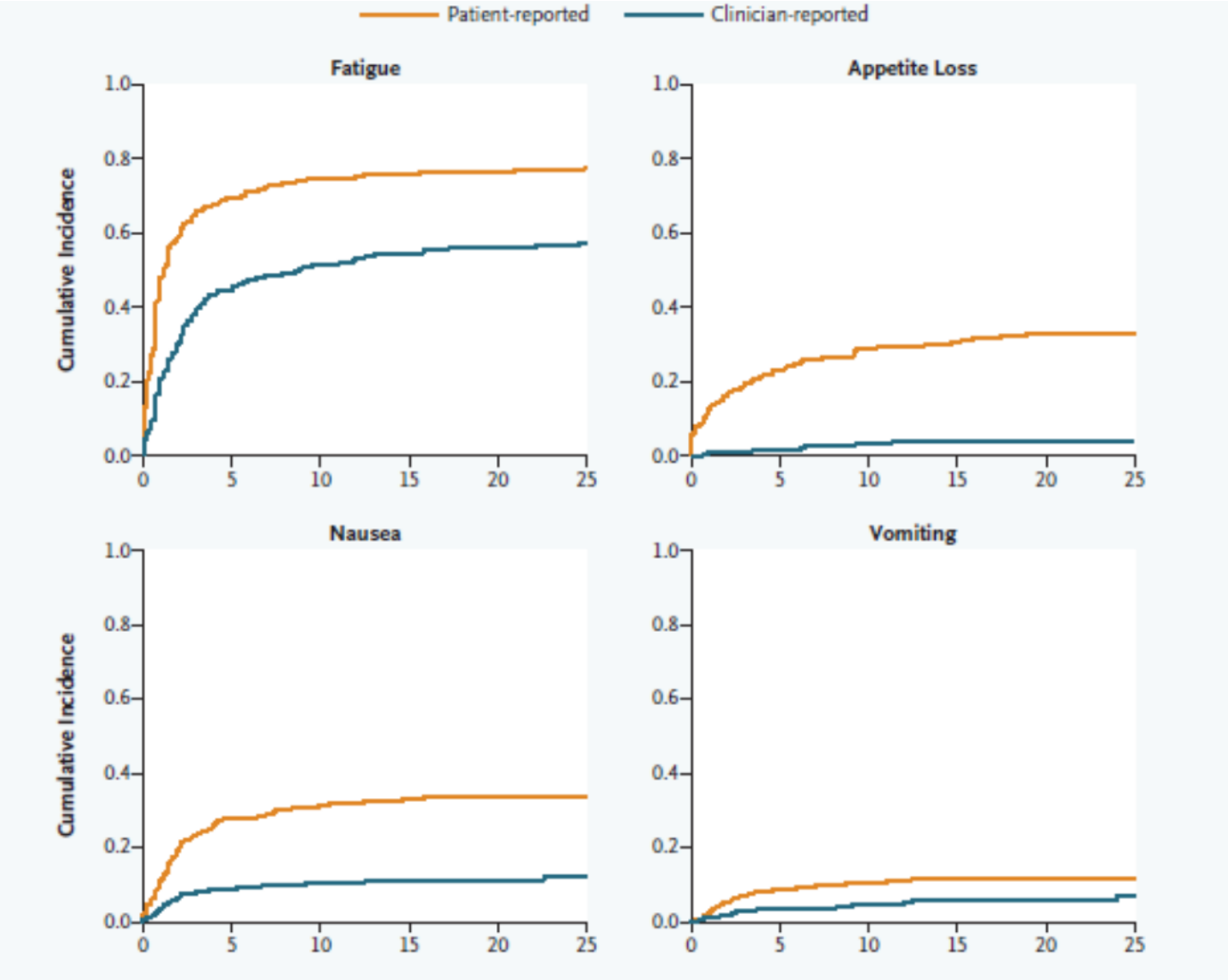
MAY 3 - 5, 2022

Adding patient-reported outcomes data to clinician-reported adverse events in early cancer drug trials could better inform dose selection and optimization, US Food and Drug Administration officials said at a recent meeting on optimizing dose selection strategies.

Pink Sheet, May 9, 2022

Clinicians Often Underestimate Symptomatic Toxicities

- Oncologists consistently underreported adverse reactions experienced by patients
- Important to obtain clinician AND patient perspectives on symptomatic toxicities when evaluating the safety and tolerability of new oncology treatments



Basch E. The missing voice of patients in drug-safety reporting. N Engl J Med. 2010 Mar 11;362(10):865-9

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Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE®)

- Developed to evaluate symptomatic toxicities by self-report in adults, adolescents and children participating in cancer clinical trials
- Item library includes 124 items representing 78 symptomatic toxicities
- Characterizes the frequency, severity, interference, and presence/absence of symptomatic toxicities
- A subset of items from the library can be selected for use in a particular study; do NOT need to administer all items
- Available in over 30 languages

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

Patient-Reported Outcomes version Of The Common Terminology Criteria For Adverse Events (PRO-CTCAE™)

QUICK GUIDE TO THE ITEM LIBRARY*

Oral	
Dry mouth	S
Difficulty swallowing	S
Mouth/throat sores	SI
Cracking at the corners of the mouth (cheilosis/cheilitis)	S
Voice quality changes	P
Hoarseness	S

Gastrointestinal	
Taste changes	S
Decreased appetite	SI
Nausea	FS
Vomiting	FS
Heartburn	FS
Gas	P
Bloating	FS
Hiccups	FS
Constipation	S
Diarrhea	F
Abdominal pain	FSI
Fecal incontinence	FI

Respiratory	
Shortness of breath	SI
Cough	SI
Wheezing	S

Cardio/Circulatory	
Swelling	FSI
Heart palpitations	FS

Cutaneous	
Rash	P
Skin dryness	S
Acne	S
Hair loss	A
Itching	S
Hives	P
Hand-foot syndrome	S
Nail loss	P
Nail ridging	P
Nail discoloration	P
Sensitivity to sunlight	P
Bed/pressure sores	P
Radiation skin reaction	S
Skin darkening	P
Stretch marks	P

Neurological	
Numbness & tingling	SI
Dizziness	SI

Visual/Perceptual	
Blurred vision	SI
Flashing lights	P
Visual floaters	P
Watery eyes	SI
Ringing in ears	S

Attention/Memory	
Concentration	SI
Memory	SI

Pain	
General pain	FSI
Headache	FSI
Muscle pain	FSI
Joint pain	FSI

Sleep/Wake	
Insomnia	SI
Fatigue	SI

Mood	
Anxious	FSI
Discouraged	FSI
Sad	FSI

Genitourinary	
Irregular periods/vaginal bleeding	P
Missed expected menstrual period	P
Vaginal discharge	A
Vaginal dryness	S
Painful urination	S
Urinary urgency	FI
Urinary frequency	FI
Change in usual urine color	P
Urinary incontinence	FI

Sexual	
Achieve and maintain erection	S
Ejaculation	F
Decreased libido	S
Delayed orgasm	P
Unable to have orgasm	P
Pain w/sexual intercourse	S

Miscellaneous	
Breast swelling and tenderness	S
Bruising	P
Chills	FS
Increased sweating	FS
Decreased sweating	P
Hot flashes	FS
Nosebleed	FS
Pain and swelling at injection site	P
Body odor	S

Attributes	
F: Frequency	I: Interference
S: Severity	P: Presence/Absence
A: Amount	

NIH National Cancer Institute

*Complete library of items available at: https://healthcaredelivery.cancer.gov/pro-ctcae

Version date: 3/11/2020

Examples of PRO-CTCAE Items

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please select the one response that best describes your experiences over the past 7 days…

1. PRO-CTCAE® Symptom Term: Dry mouth				
a. In the last 7 days, what was the SEVERITY of your DRY MOUTH at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

2. PRO-CTCAE® Symptom Term: Difficulty swallowing				
a. In the last 7 days, what was the SEVERITY of your DIFFICULTY SWALLOWING at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

9. PRO-CTCAE® Symptom Term: Nausea				
a. In the last 7 days, how OFTEN did you have NAUSEA?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
b. In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

How to Implement PRO-CTCAE Items in a Clinical Trial

- PRO-CTCAE items are publicly available for use in clinical research – no licensing fees
- Items can be administered on paper or electronically
- PRO-CTCAE data are complementary to existing safety assessments reported by clinicians using the CTCAE – BOTH should be reported
- Patient and clinician reports do NOT need to be harmonized
- Item selection and timing of assessment are critical design decisions
- Consider weekly assessment during key periods in the trial or at other crucial timeframes based upon knowledge of the anticipated toxicity profile
- Items should be analyzed separately and descriptively - there are no rules for combining item scores into a single score or analyzing data longitudinally

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

Resources When Selecting PRO-CTCAE Items in Dose-Finding Studies

- Prior Phase 1 studies: Adverse events reported as grades 1 or 2 and occurring in >=10% of sample
- Adverse event profiles of compounds with similar MOA
- Adverse event profiles of most common treatments of disease (new treatment would likely be combined with or tested against common treatments)
- Adverse reactions that are of most concern to patients with the condition
- Adverse reactions identified by expert stakeholder groups (National Cancer Institute's Symptom Management and Health-Related Quality of Life Steering Committee)
- Animal studies

Trask PC. Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events: Methods for item selection in industry-sponsored oncology clinical trials. Clin Trials. 2018

Alternatives to PRO-CTCAE

- FACT and FACIT condition- and symptom-specific measures
  - FACT-G: I am bothered by side effects of treatment
- MD Anderson Cancer Center condition- and symptom-specific measures
- EORTC condition-specific measures
- Condition-specific measures include a mix of items assessing disease- and treatment-related symptoms
- Same symptom (e.g., fatigue) can be a symptom of both disease and treatment – important to consider the timing of the assessments to distinguish between the two

Conclusions

- PROs can be useful in examining effectiveness and symptomatic toxicities from a patient perspective in dose selection studies
- Several measures are available to capture effects on symptoms and function
- PRO-CTCAE is a widely used item library including items that evaluate symptomatic toxicities – do NOT require additional validation
- “Implementing” vs. “Integrating” PROs
  - Processes for including PRO measures in studies are easier to articulate than determining how to use PRO data in concert with other endpoints to make dose selection decisions

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Thank You!