U.S. FOOD & DRUG ADMINISTRATION

2022 FDA Update

Annual PRO Consortium Meeting

April 13, 2022

Agenda

- Introductions
- Clinical Outcome Assessment (COA) Qualification Program Metrics and Resources
- PFDD Update
- Patient-Focused Statistical Support (PFSS) and COA-related Guidances within FDA
- Topics of Interest Section
- Panel Discussion

Panelists and Speakers

- **Robyn Bent**, Director, Patient Focused Drug Development, CDER
- **Laura Lee Johnson**, Director Division of Biometrics III, Office of Translational Sciences, CDER
- **David Reasner**, Division Director, Division of Clinical Outcome Assessment, OND|ODES, CDER

Panel Moderator

- **Michelle Campbell**, Sr. Clinical Analyst for Stakeholder Engagement and Clinical Outcomes, Office of Neuroscience, OND, CDER

COA QUALIFICATION PROGRAM METRICS AND RESOURCES

COA Qualification Program

- Drug Development Tool Guidance
- COA DDT Qualification Stages and Timeframes
- COA DDT Qualification 2021 Metrics
- COA Qualification Program Resources

Qualification Program Introduction

Drug Development Tool (DDT) Guidance

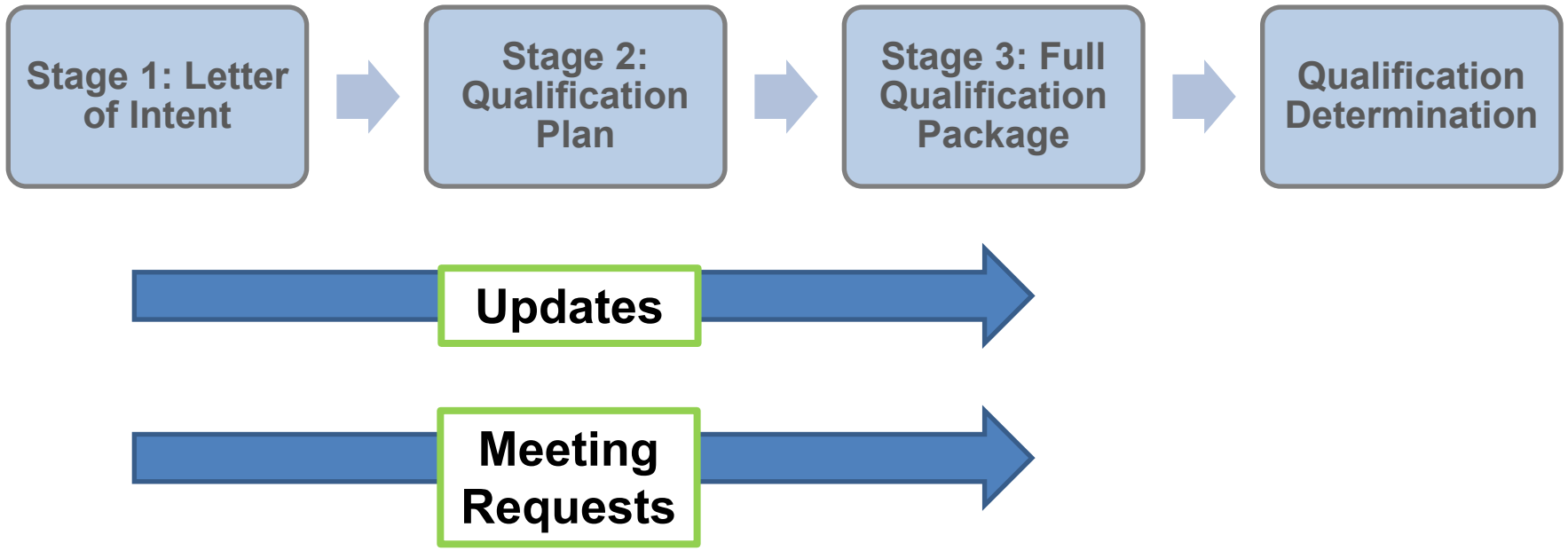
Qualification Process for Drug Development Tools Guidance for Industry and FDA Staff

Final Guidance published in Nov 2020

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/qualification-process-drug-development-tools-guidance-industry-and-fda-staff

https://www.fda.gov/drugs/clinical-outcome-assessment-coa-qualification-program/clinical-outcome-assessments-coa-qualification-program-resources

New DDT Process: COA Qualification Stages



Each of the three milestone submissions should be a stand-alone package.

New DDT Process: COA Qualification Timeframes

Qualification Stage	Timeframe
Letter of Intent (LOI)	3 months (calendar days)
Qualification Plan (QP)	6 months (calendar days)
Full Qualification Package (FQP)	10 months (calendar days)

CDER conducts a reviewability assessment, and the review begins when a reviewable memo issued.

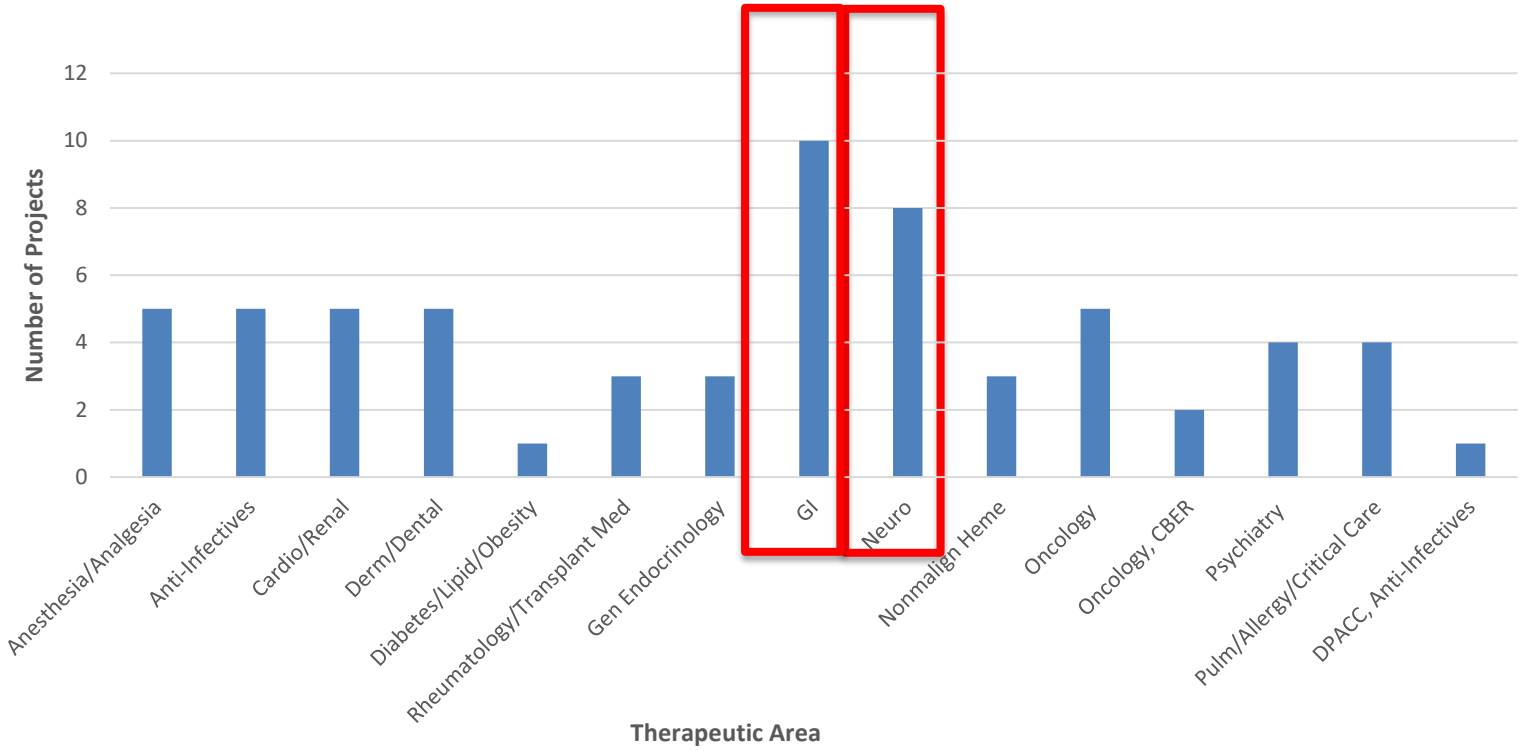
Qualification Program Metrics

Number of COA DDT Projects

- As of March 22, 2022, the total number of projects in the program totaled 64

- Accepted 0 LOIs between 1/1/21 – 3/22/22
  - Pre-LOI Meetings, LOI revisions, and restarting (or withdrawing) existing DDTs

COA DDT Projects by OND Clinical Review Divisions



DDT Projects by COA Type

COA Type	Number
PRO Measures	41
Other*	9
PerfO Measures	6
ObsRO Measures	3
ClinRO Measures	4
PRO/ObsRO	1

*Digital Health Technologies (DHTs) not falling into other categories (e.g., activity monitors)

Number of 2021 DDT Submissions

Type	Number (2018)	Number (2019)	Number (2020)	Number (2021)
Letter of Intents (LOIs)	10	18	22	7
Qualification Plans (QPs)	2	8	15	10
Full Qualification Packages (FQPs)	2	0	2	2
Updates	13	9	9	13
Meeting Requests	7	5	10	13

COA DDT Research Grants Update

- 1 COA DDT Research Grant was awarded in FY2021 and 1 was deferred
  - For developers of DDTs with an accepted LOI who are working towards the next qualification submission
- FY2022: **May 3, 2022,** application due date
  - Funding opportunity announcement: PAR-21-178

Other COAQP Updates

Sign-Up! to the **COAQP Email Listserv** for timely updates and announcements such as:

- Newly qualified COAs
- Updates to existing COAQP resources (e.g., LOI outline edits)
- COAQP process changes (e.g., switching electronic submission portals)

https://public.govdelivery.com/accounts/USFDA/subscriber/new?topic_id=USFDA_531

Are you interested in Patient-Centered Outcomes?

U.S. FOOD & DRUG ADMINISTRATION

dcoa@fda.hhs.gov

Title 21 Vacancy Announcement
Department of Health and Human Services (HHS)
Food and Drug Administration (FDA)
Center for Drug Evaluation and Research (CDER)
Office of New Drugs (OND)
Office of Drug Evaluation Science (ODES)
Division of Clinical Outcome Assessment (DCOA)

Application Period: *Open throughout 2022*

Area of Consideration: United States Citizenship is required. You must be a U.S. Citizen or U.S. National. Foreign nationals or legal permanent residents are not eligible for consideration.

Position: Social Science Analyst

Series: AD-0101

Location(s): Silver Spring, MD

Salary: *Depending on level*

Work Schedule: Full Time **Cures**
Band(s): Band D [*or Band C*]

Full Performance Band Level:

Band D [*or Band C*]

Travel Requirements: 25% or less

Bargaining Unit: 3591

Relocation Expenses Reimbursement: You may qualify for reimbursement of relocation expenses in accordance with agency policy.

This position is being filled under a stream-lined hiring authority, Title 21, Section 3072 of the 21st Century Cures Act. The candidate selected for this position will serve under a career or career-conditional appointment and be paid under the provisions of this authority.
Additional information on 21st Century Cures Act can be found here:
21st Century Cures Act Information

Patient-Focused Drug Development

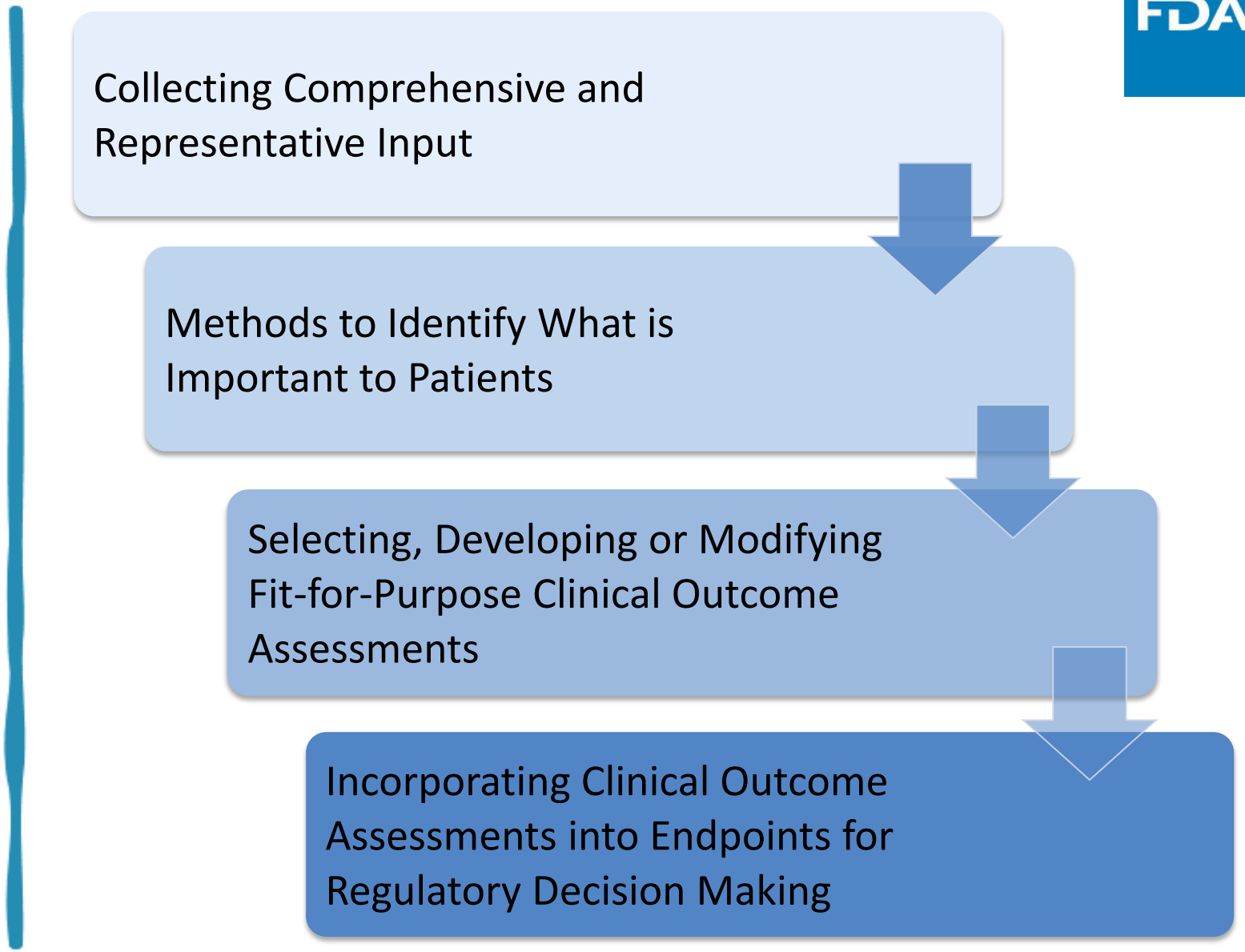
April 2022

CAPT. Robyn Bent, Director
Patient Focused Drug Development Program
Center for Drug Evaluation and Research (CDER)

Updates on Selected PFDD Efforts

1. Patient Focused Drug Development
2. PFDD Guidance Documents
3. Standard Core Clinical Outcome Assessment and Endpoints Grant Program
4. International Council for Harmonisation PFDD Reflection Paper

Methodologic Guidance Documents



https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical

PFDD Guidance 1: Collecting Comprehensive and Representative Input

Guidance 1

Guidance 2

Guidance 3

Guidance 4

- Whom do you get input from, and why?
- How do you collect the information?

Status:

- Workshop held on December 18, 2017
- Issued Draft Guidance in June 2018 and Final Guidance in June 2020

PFDD Guidance 2: Methods to Identify What is Important to Patients

- What do you ask, and why?
- How do you ask non-leading questions that are well-understood by a wide range of patients and others?

Status:

- Workshop held on October 15-16, 2018
- Issued Final Guidance in February 2022

PFDD Guidance 3: Select, Develop or Modify Fit-for-Purpose Clinical Outcome Assessments

- How do you decide what to measure in a clinical trial and select or develop fit-for-purpose clinical outcome assessments (COAs) ?

Status:

- Workshop held on October 15-16, 2018
- Discussion Document published

Guidance 1

Guidance 2

Guidance 3

Guidance 4

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

- Once you have a COA measurement tool and a way to collect data using it, what is an appropriate clinical trial endpoint?

Status:

- Workshop held on December 6, 2019
- Discussion Document published

Standard Core COA Grant Program

- **Goal:** Enable development of standard core sets of measures of disease burden and treatment burden for a given area or across therapeutic areas —that would be made publicly available at nominal or no cost
- Currently funding 5 grants:
  - **Migraine** Clinical Outcome Assessment System (MiCOAS)
  - Clinical Outcome Assessments for **Acute Pain** Therapeutics in Infants and Young Children (COA APTIC)
  - Northwestern University Clinical Outcome Assessment Team (NUCOAT) – **Physical Function**
  - Preparing a Clinical Outcomes Assessment Set for Nephrotic Syndrome (Prepare-NS)- **Fluid Overload**
  - Expanding the Observer-Reported **Communication** Ability (ORCA) Measure

https://www.fda.gov/drugs/development-approval-process-drugs/cder-pilot-grant-program-standard-core-clinical-outcome-assessments-coas-and-their-related-endpoints

FDA Participants in the Grant Program

- Multiple Therapeutic Review Divisions
- DCOA
- PFSS
- Office of Biostatistics (non-PFSS)
- Other Centers
- PFDD Staff

Types of COAs Being Developed

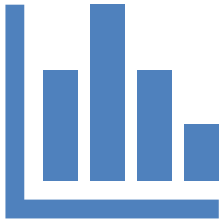
PATIENT-REPORTED OUTCOME MEASURES

OBSERVER-REPORTED OUTCOME MEASURES (PARENTS/CAREGIVERS)

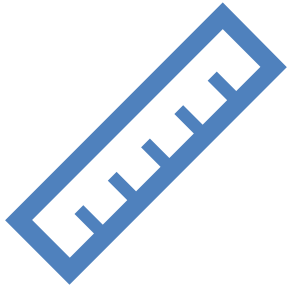
PERFORMANCE OUTCOME MEASURES

Where are the Measures Coming From?

Utilize existing measures



Modify existing measures



Create new measure(s)

Information About Individual Grants

- MiCOAS (https://vpgcentral.com/micoas/)
  - MiCOAS - Acute Lit Review Report
  - Acute Report Appendix
  - MiCOAS - Preventive Lit Review Report
  - Preventive Report Appendix
- NUCOAT (https://sites.northwestern.edu/nucoat/)
  - NORD Presentation
- COA-APTIC (https://dcri.org/coa-aptic/)
- Expanded ORCA (https://populationhealth.duke.edu/research/center-health-measurement/expanding-observer-reported-communication-ability-orca-measure)
- Prepare-NS (https://www.prepare-ns.org/)

International Council for Harmonisation (ICH) PFDD Reflection Paper

Goal: Harmonize approaches, methods, and standards to advance incorporation of patient perspective in drug development globally

This Reflection Paper proposes development of ICH guidelines to address:

- What to measure (meaningful to patients) in a clinical trial, e.g., clinical outcome assessments
- Methods for elicitation or collection of assessments looking at patients' perspectives on alternative outcomes or other specified alternative attributes

https://www.ich.org/page/reflection-papers

PATIENT FOCUSED STATISTICAL SUPPORT (PFSS) INTRODUCTION & OTHER GUIDANCES OF INTEREST

Patient-Focused Statistical Support

Who are we?


Lili Garrard (TL)


Monica Morell


Weimeng Wang


Marian Strazzeri


Xin Yuan

FDA

- Team home: CDER/OTS/Office of Biostatistics
- Consult: across FDA; primarily for CDER/OND
- Work closely with DCOA (we both have psychometricians)
- Clinical, statistical team, or DCOA may request a consult

What We Do


Review
Support
Policy and Guidance
Research
Communications

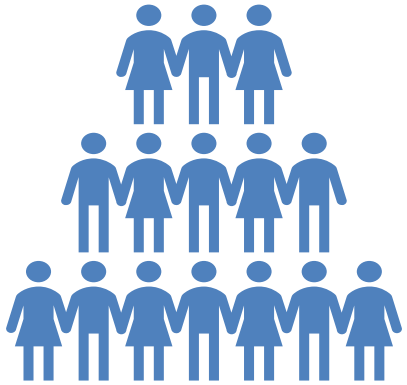
We are Hiring

Looking for COA and quantitative patient preference expertise

All Levels

Email resume to CDEROTSHIRES@fda.hhs.gov and cc laura.johnson@fda.hhs.gov

Guidances of Interest



All COVID-related guidances

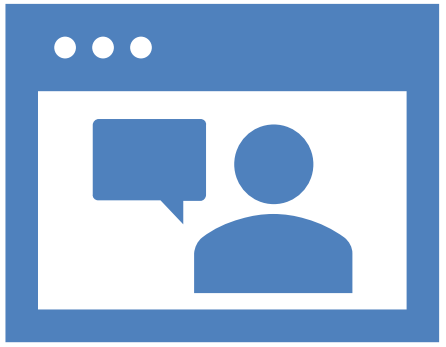
FDA Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency

Statistical Considerations [talk to division]

Guidances of Interest

CDRH & CBER Principles for Selecting, Developing, Modifying, and Adapting Patient-Reported Outcome Instruments for Use in Medical Device Evaluation

CDRH & CBER Patient Engagement in the Design and Conduct of Medical Device Clinical Studies



Oncology Core Patient-Reported Outcomes in Cancer Clinical Trials (Draft)

Digital Health Technologies for Remote Data Acquisition in Clinical Investigations (Draft)

Topics of Interest

PERCENT CHANGE (FROM BASELINE OR OTHER PLACES)

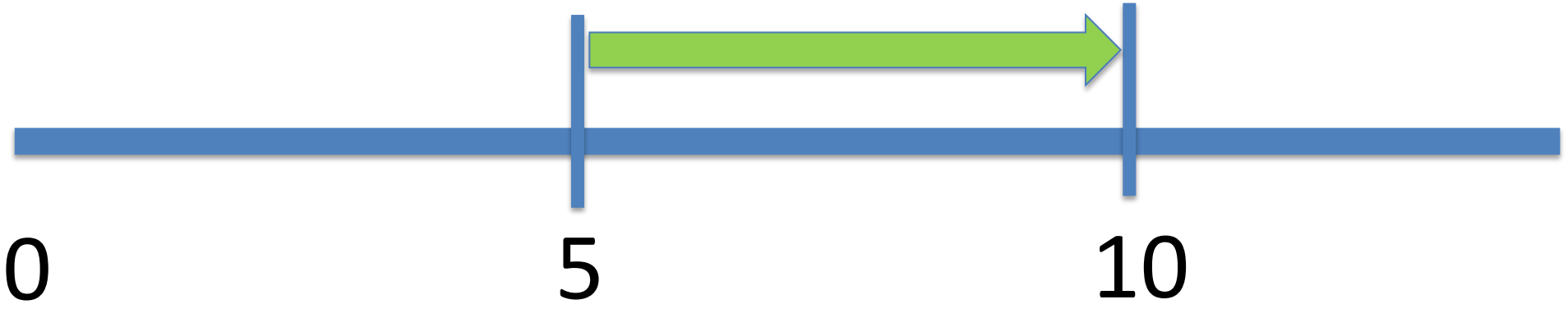
Percent Change

- Use evidence from the context of use
  - 15%, 30%...arbitrary
  - If 100% = resolved though? Is frequently clinically meaningful
    - No anchor (if all resolved, all well, then….)
- What is the actual change that is clinically meaningful, and how is that determined across the spectrum of people in the study (or outside it)?


0
5
10

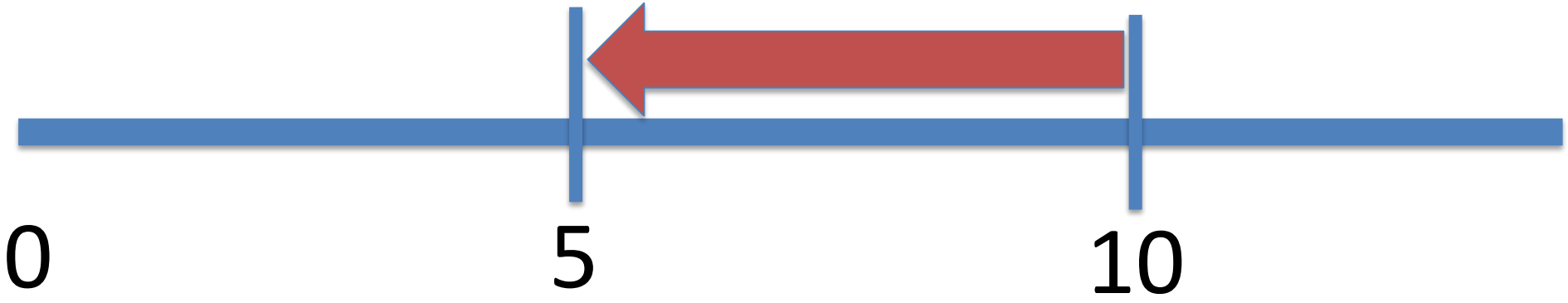
+5

100% change!



-5

-50% change!



Pop Quiz!

- You are the FDA Reviewer. Is there
  A. No overall change
  B. Overall improvement

Notes

- In both cases, the absolute change is 5
- Average change on the original scale (0) indicates no overall change
- Percent change is very different: +100% and -50%
- Average percent change ([+100 – 50]/2 = +25%) suggests an overall improvement

- At least there was not a 0 at baseline
- What if the patients started at 1? 2? Is 15, 30, 50% change meaningful? If the scale is 0-1000?

Percent Change: Not from Baseline?

- Is percentage change from baseline always/necessarily computed using a patient's baseline score in the denominator? Could one use the total or highest possible score in the denominator instead to help surmount asymmetry and possible 0s in the denominator?
  - Not seen often
  - Addresses a different idea than percent change from baseline

Percent Change: Could it work?

- Treatment effect expected to be multiplicative rather than additive (e.g., treatment improves symptom severity 20% above what it would have been without treatment)
  - Logarithmic or similar transformation could be applied to continuously distributed COA scores prior to comparing groups (Senn 2007).
- Randomized withdrawal and go back on therapy once see x% change
  - Can see (not uncommonly) people who would qualify to enroll in the study are not allowed back on therapy

If you still want Percent Change, do not forget

- Compared to landmark scores or change-from-baseline scores, percent change-from-baseline scores may have highly non-normal distributions that can be challenging to model

Summary: Percent Change

- Think about all numeric scenarios and what they mean
- Provide the evidence and the rationale
  - ≠ someone else did it or said you could do it
- Is the method of determining meaningful change directly considering the patient voice?

PRO-CTCAE AND CTCAE

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

50

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

○ Never ○ Rarely ○ Occasionally ○ Frequently ○ Almost constantly

Slide/graphics from Vishal Bhatnagar, FDA OCE

See Clin Cancer Res 2018 Apr 15;24(8):1780-4. Use of PRO measures to inform tolerability in oncology trials: Implications for clinical review, IND safety reporting and clinical site inspections, Kim J, Singh H, Ayalew K, Borror K, Campbell M, Johnson LL, Karesh A, Khin NA, Less JR, Menikoff J, Minasian L, Mitchell SA, Papadopoulos EJ, Piekarz RL, Prohaska KA, Thompson S, Sridhara R, Pazdur R, Kluetz PG

ANCHOR-BASED ANALYSES & ALTERNATIVE SCORING

Considerations for Anchor-Based Analyses

- Anchor-based methods are the primary methods we use to interpret meaningful within-patient score change.
- **Anchor-based methods should be supplemented with anchor-based empirical CDF and PDF curves.**
- Other methods (e.g., **exit interviews)** may be explored to complement the anchor-based methods or when anchor-based methods are not feasible or when anchor-based results are challenging to interpret (e.g., **sparsity**).

External anchor scales should have the following properties (1)

- Selected anchor scales should be associated with the target COA endpoint in a way that addresses the question of clinical meaningfulness of the target COA endpoint.
  - **For example, for an endpoint measuring a specific aspect of the disease, an anchor scale measuring the same concept (i.e., the aspect of the disease specified in the endpoint, as opposed to global status of the disease) provides the most direct evidence.**
- The anchor scale should be easier to interpret than the COA endpoint itself and meaningful to patients.

External anchor scales should have the following properties (2)

- The anchor scale's response categories should be distinct and non-overlapping and should represent meaningful differences among adjacent response categories.
  - **For example, an anchor scale that uses a 0-10 numeric rating scale would not be easy to interpret and would not be an appropriate anchor scale in most contexts.**
- An example of a commonly used response scale for rating severity is none, mild, moderate, or severe.

External anchor scales should have the following properties (3)

- **The anchor scale's recall period should be consistent with the assessment time period of the prespecified endpoint to the extent possible.**
  - Additionally, the selected anchors should be assessed at comparable time points as the target COA endpoint.

Interpretation of clinically meaningful within-patient change is critical

- Provide the text of the item stem and the response categories
- Submit the patient-facing version when available
- Provide multiple anchors for each key efficacy endpoint
- Consider the interpretability of the eCDF plots… clutter, annotation, directionality of improvement, sparsity, etc.
- Balance patient burden, study operations, and the varying recall periods for quality data

Considerations for Alternative Scoring (1)

- Alternative scoring provides an approach to better understand problematic items or structure
- Supplemental analyses with alternative endpoints aid interpretation of the developer's endpoint
- **Alternative scoring is different than instrument modification as all items should be understood and completed without a negative impact on the instrument**

Considerations for Alternative Scoring (2)

- **Consider a supplemental analysis excluding problematic item(s) for an alternative endpoint.**
  - Example: Qualitative research in a new context of use indicates that an item has an excessive ceiling or floor effect. Consider whether the item is positioned to assess improvement or worsening.
- **Placing the alternative endpoint in an endpoint model rather than the developer's endpoint necessarily has a higher burden for supportive evidence.**

Panel Discussion with Q&A