FDA Annual Update

Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Ninth Annual PRO Consortium Workshop

Silver Spring, MD
April 25, 2017

Disclaimer

The views expressed in this presentation are those of the speaker, and do not necessarily represent an official FDA position

Presenters/Panelists

Presenters:

- Michelle Campbell, PhD, Reviewer and Scientific Coordinator, COA Staff, OND
- Elektra Papadopoulos, MD, MPH, Associate Director, COA Staff, OND

Panelists:

- Theresa Mullin, PhD, Associate Director for Strategic Initiatives, CDER
- Laura Lee Johnson, PhD, Acting Director Division of Biometrics III, OB, OTS

QUALIFICATION PROGRAM UPDATES

COA Staff

- **Associate Director for Clinical Outcome Assessments:**
  Elektra Papadopoulos, MD, MPH

- Regulatory Project Manager:
  - Kim Chiu, PharmD
  - Kristina Luong, PharmD

- DDT Qualification Scientific Coordinator:
  - Michelle Campbell, PhD

- Team Lead
  - Selena Daniels, PharmD, MS
  - Wen-Hung Chen, PhD

- Reviewers:
  - Michelle Campbell, PhD
  - Yasmin Choudhry, MD
  - Ebony Dashiell-Aje, PhD
  - Julia Ju, PharmD, PhD
  - Sarrit Kovacs, PhD
  - Susan Pretko, PharmD, MPH

- ORISE Fellow:
  - Parima Ghafoori, PharmD
  - Yujin Chung, PharmD

Recent COA Qualification Statements

- *Symptoms of Major Depressive Disorder Scale*
  - November 2017

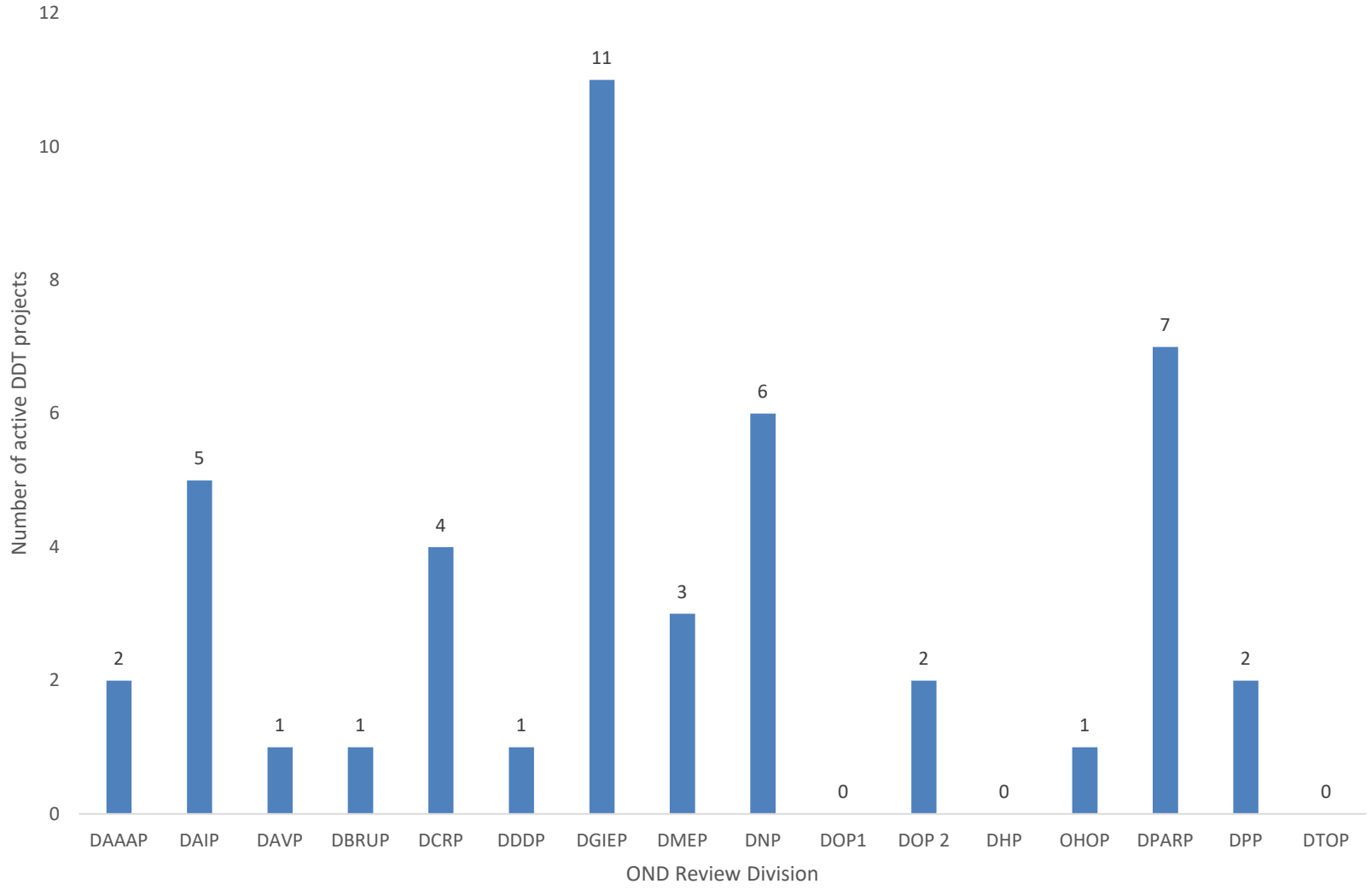
- *Non-Small Cell Lung Cancer Symptoms Assessment Questionnaire*
  - April 2018

CONGRATULATIONS!

COA Qualification Submissions Received January 2017-2018

COA DDT Qualification Program Submission Type Received	Number
Letters of Intent	9
Other Submissions	46
Review Packages	2
TOTAL	57

Number of Active DDT Projects by Division as of 2017-2018 (n=44)



Overview of 21st Century Cures (21CC) Legislation and PDUFA VI: Impacts on DDT Qualification Activities

Highlights

- 21st Century Cures and PDUFA VI increasingly places FDA as an *active participant* in drug development, broadening our traditional regulatory role
- Requires expanded efforts to enhance drug development
  - *Patient-focused drug development*: collect / analyze patient experience, to use in designing drug development programs (endpoints), and in regulatory decision making (endpoints and risk/benefit considerations)
  - *Novel, innovative trial designs*: use of complex adaptive and other novel trial designs – and how such clinical trials can be used to satisfy the substantial evidence standard
  - *Real world evidence*: using data regarding use or potential benefits and risks of a drug derived from sources other than randomized clinical trials – in support of new indications and post-approval study requirements
  - ***Drug development tools: biomarkers and COAs***

21ST CC DDT PROCESS (SECTION 3011): WHAT'S DIFFERENT?

- New important features, but also much continuity with existing DDT programs
- Formalizes a process defined by three submissions. "Accept" or "Not Accept" decision for each:
  - Letter of Intent (LOI)
  - ***Qualification Plan (QP)***
  - Full Qualification Package (FQP)
- Requires setting and implementing "reasonable timeframes" for the FDA review of each submission type

TRANSPARENCY PROVISIONS

Under 21CC, DDT qualification becomes a transparent public process:

- All interested parties know what tools are in development, stage of development, and FDA determinations including rationale

- Information about the submission and FDA's determination including recommendations will be posted on DDT website

- For legacy projects, we plan to post only new information after transition (e.g., we will not make public information prior to legislation enactment or to agreement to transition to 507)

21st CC: Acceptance of a COA into Qualification

- Prioritization and acceptance decision for each submission (LOI, QP, FQP) based upon scientific merit:
  - Does the COA DDT fill a critical measurement gap (i.e., is drug development stalled or slowed)?
  - Does the proposed COA DDT represent significant improvement over currently available, acceptable COA DDTs?
  - Is the COA patient centric (i.e., measures something of relevance and importance to patients in their daily lives that is not being evaluated in that clinical context due to lack of acceptable assessments)?

Content Focus for Submission types

- LOI Submission: Proposed COU, any current instrument development, area of unmet need

- QP Submission: Completed qualitative work, draft instrument, scoring and conceptual framework. Psychometric analysis protocol

- FQP Submission: Review of all data to support the DDT for the COU (qualitative and quantitative)

Three-tiered internal review

- **DDT Program Assessment and Recommendations**
  - Work with requestor to clarify DDT, COU, and project proposal
  - Provide tool-specific recommendations based on past and ongoing projects

- **Discipline-specific SME Assessment and Recommendations**
  - Includes OND division management participation
  - Evaluate based on regulatory precedent, current disease-specific challenges, and level of impact on drug development programs

- **CDER DDT Committee Assessment, Recommendations, and Decision**
  - Opportunity for broad senior CDER input early and throughout in the process
  - Work towards greater consistency across therapeutic areas and divisions

What is Currently Happening?

- Letter sent to submitters in Legacy Program (pre 21st CC)
  - June 2017
  - Explained changes under 21st CC
  - 41 submitters were contacted
  - 32 submitters agreed to follow the new 21st CC process
  - 7 submitters could not be reached via email or have not yet provided a response
  - 3 DDTs will continue to follow the legacy process

What is Currently Happening?

- Transitioning Legacy Programs
  - Mapping to new process
  - Identifying what is needed to reach next milestone
- Transition will take time
- Accepting new LOIs under 21st CC

OVERVIEW OF CDER PFDD GUIDANCE SERIES AND OTHER UPDATES

Elektra Papadopoulos, MD, MPH
Associate Director Clinical Outcome Assessments Staff
Office of New Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Outline

- PFDD guidance series under 21st Century Cures
- Other updates
  - Performance outcome assessment (PerfO)
  - Mobile device-based endpoints
  - Recent and upcoming PFDD meetings
  - FDA's disease-specific guidance development paradigm

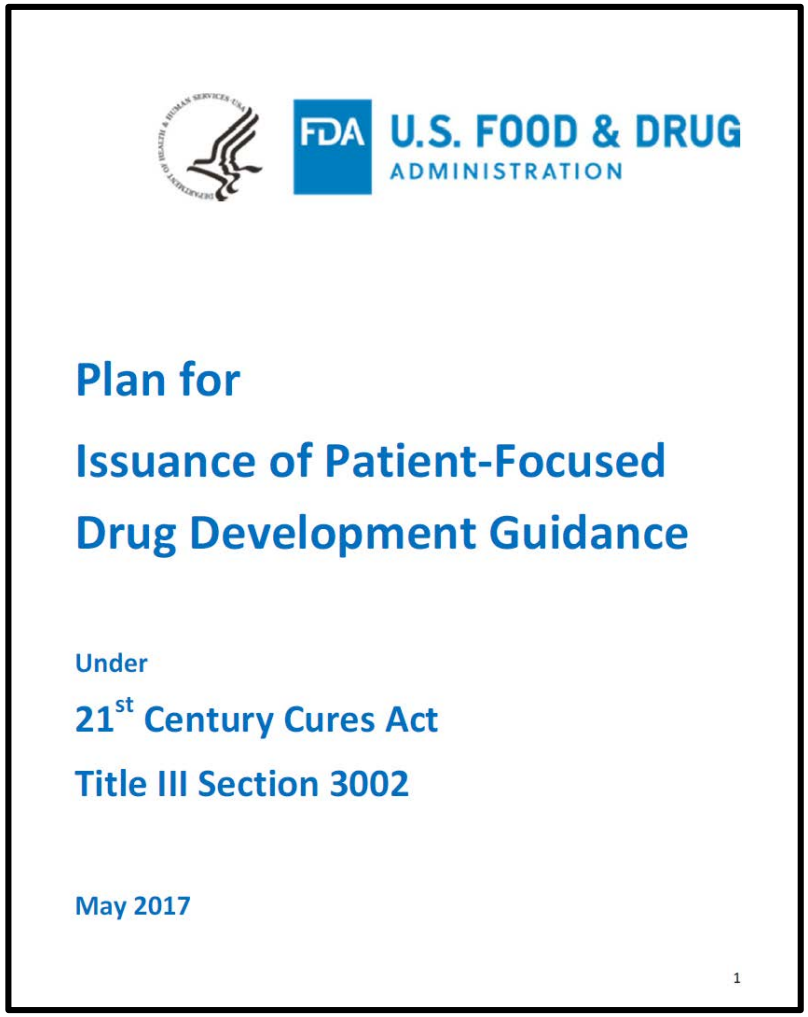
Our Ultimate Purpose: Understand Patients' Perspectives on Benefits and Risks

- Careful assessment of patients' views on benefits and risks are an important part of regulatory decision-making

- Drug development, including clinical outcome assessments, should reflect priorities of patients with a disease or condition based on what those patients have identified as mattering most to them

PFDD and 21st Century Cures

- 21st Century Cures Act of 2016 includes new statutory provisions for Patient-Focused Drug Development
- FDA developed a plan for issuance of a series of guidances on the collection and use of patient experience data (PED) as required under 21st CC
- Five-year timetable for all deliverables



https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM563618.pdf

What is patient experience data (PED)?

- Data that are collected by any persons and are intended to provide information about patients' experiences with a disease or condition

- Includes the experiences, perspectives, needs and priorities of patients related to (but not limited to):

  1) Symptoms of their condition and its natural history

  2) Impact of their condition on their functioning and quality of life

  3) Experience with treatments

  4) Input on which outcomes are important to them

  5) Patient preferences for outcomes and treatments

  6) Relative importance of any issue as defined by patients

Source: Title III, Section 3002(c) of the 21st Century Cures Act

Overview of Guidances 1-4

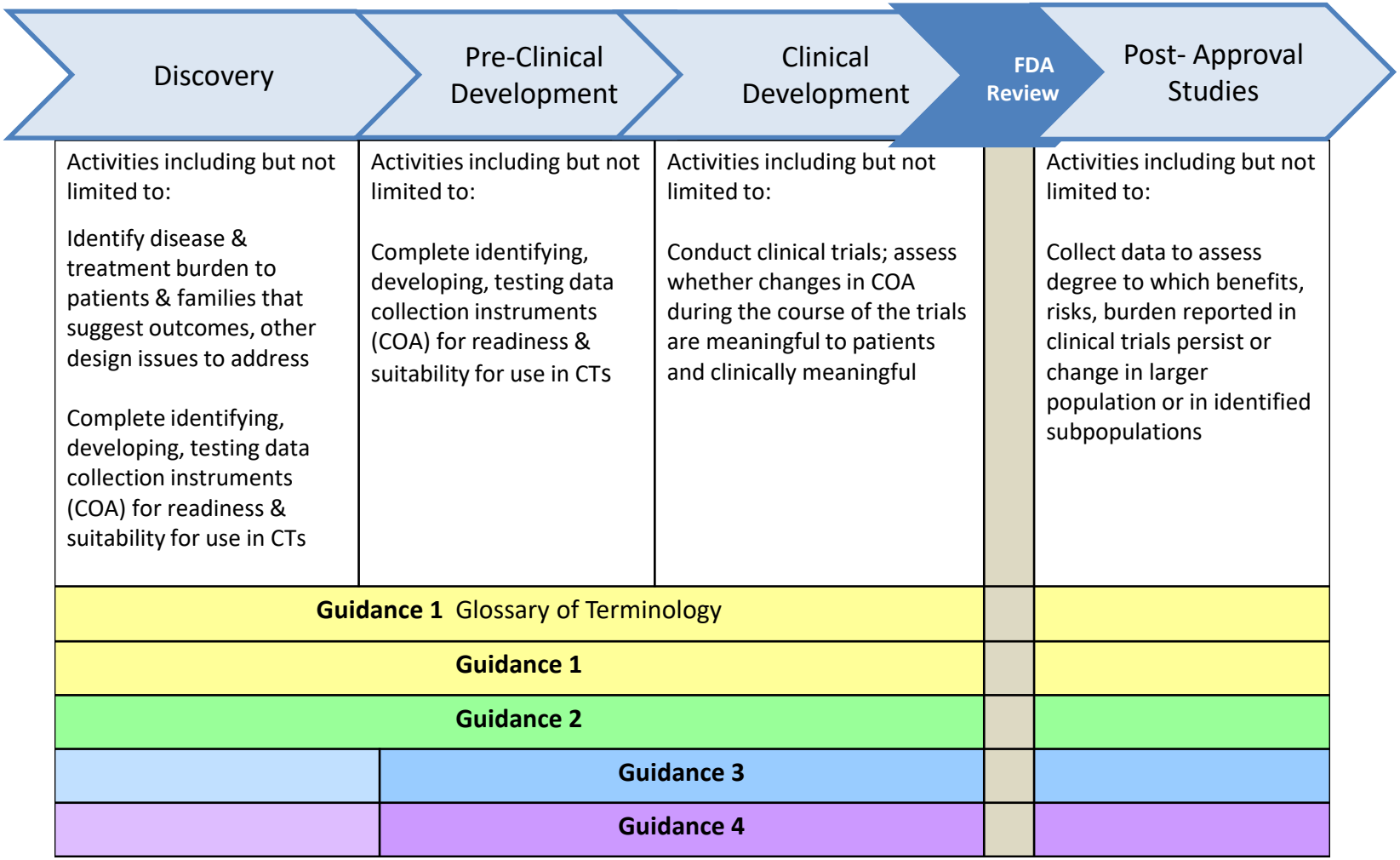
- Guidance 1: Identifying research questions and developing a sampling strategy to collect representative patient input; operationalizing data collection, management and analysis

- Guidance 2: Methods to elicit detailed, unbiased, and comprehensive input from patients, patient groups, and caregivers

- Guidance 3: Using patient input to develop or identify appropriate COAs for use in clinical trials

- Guidance 4: Developing COA-related clinical trial endpoints based upon patient input; interpreting those endpoints

When would the methods addressed in these four guidances be applicable?



Guidance 1

- General Considerations for Collecting Patient Experience Data
  - Defining the research objectives and questions
  - From whom to collect information
  - Determining the study design and research setting
  - Constructing a sampling frame
  - Additional considerations to achieve sufficient representation
- Methods for Collecting & Analyzing Data
- Operationalizing and Standardizing Data Collection & Data Management
- Includes a glossary with PFDD-related terms
- Public workshop held December 18, 2017

https://www.fda.gov/Drugs/NewsEvents/ucm574725.htm

Guidance 1: Approach

- Intended for a broad audience to serve as a focus for discussion among FDA with multiple stakeholder groups
- Intended to encourage patient involvement as partners before and throughout the medical product development process
- Intended to promote a collaborative process in the collection of robust patient experience data
- Emphasizes the concept of fit-for-purpose (i.e., tools matched to the specific research questions and regulatory needs)
- Recognizes that the science of patient input is an evolving field
- Recommends a pragmatic step-wise approach to provide usable patient experience information to FDA

Questions addressed in Guidance 1 include:

- What is patient experience data?
- Why is it important to collect it?
- Where does it come from?
- How is it collected?
- When is it best collected?
- Who can collect and submit the data?
- How can external stakeholders submit the data to FDA?
- How is it used for regulatory purposes?

Who can collect and submit patient experience data?

- Anyone can collect and submit patient experience data, including
  - Patients
  - Family members and caregivers of patients
  - Patient advocacy organizations
  - Disease research foundations
  - Researchers
  - Drug manufacturers

Guidance 3:
Developing or identifying appropriate COAs

The following general concepts are expected to be reflected:

- Emphasis on the use of fit-for-purpose COAs (newly developed or existing)
  - The good measurement principles from the current 2009 PRO guidance are to be retained
- Emphasis on regulatory reflexibility as appropriate (e.g., in rare diseases)
- Will address additional COAs types (e.g., PerfO, ClinRO and ObsRO instruments) in addition to PRO instruments
- Note: The current 2009 PRO guidance, which describes good measurement principles applicable to any COA still stands

Guidance 5: 'Guidance on submitting guidance'

- Topic of guidance: developing and submitting proposed draft guidance relating to patient experience data
- Public workshop held March 19, 2018 to inform development of the guidance

https://www.fda.gov/Drugs/NewsEvents/ucm582081.htm

Key take-aways from workshop

- Various pathways for submission are needed
- Depending on the purpose and type of data, different formats may be appropriate
- **Submission of patient experience data does not always need to be in the form of proposed draft guidance**

External Resources or Information Related to Patients' Experience

Externally-led PFDD Meeting Reports or Other Stakeholder Meeting Reports

Proposed Draft Guidance Relating to Patient Experience Data

Natural History Studies or other Disease-specific Background on Condition and Discussion of Unmet Medical Need

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm579132.htm

OTHER FDA UPDATES

Upcoming Performance Outcome Assessment (PerfO) Paper

- **Developing and Implementing Performance Outcome Assessments: Evidentiary, Methodological, and Operational Considerations**
  - Accepted by Therapeutics Innovation and Regulatory Science on March 30, 2018
  - Outcome from December 2016 Duke-Margolis Meeting
  - *PerfO New Proposed Definition: A measurement based on a standardized task performed by a patient that is administered and evaluated by an appropriately trained individual or is independently completed*

Increased interest use of mobile device-based endpoints

- Two letters of intent for activity monitors to the COA Qualification Program since beginning of 2018

- Increased consults to COA Staff on activity monitors in the IND arena

- *"Today we have many more tools to measure these patient benefits – including wearable devices, medical apps and even machine-learning programs. These tools can bring us a better understanding of how patients experience their illness…"*

  -FDA Commissioner Scott Gottlieb, M.D. (3/30/2018)

digital biomarkers

Digit Biomark 2018;2:11–30

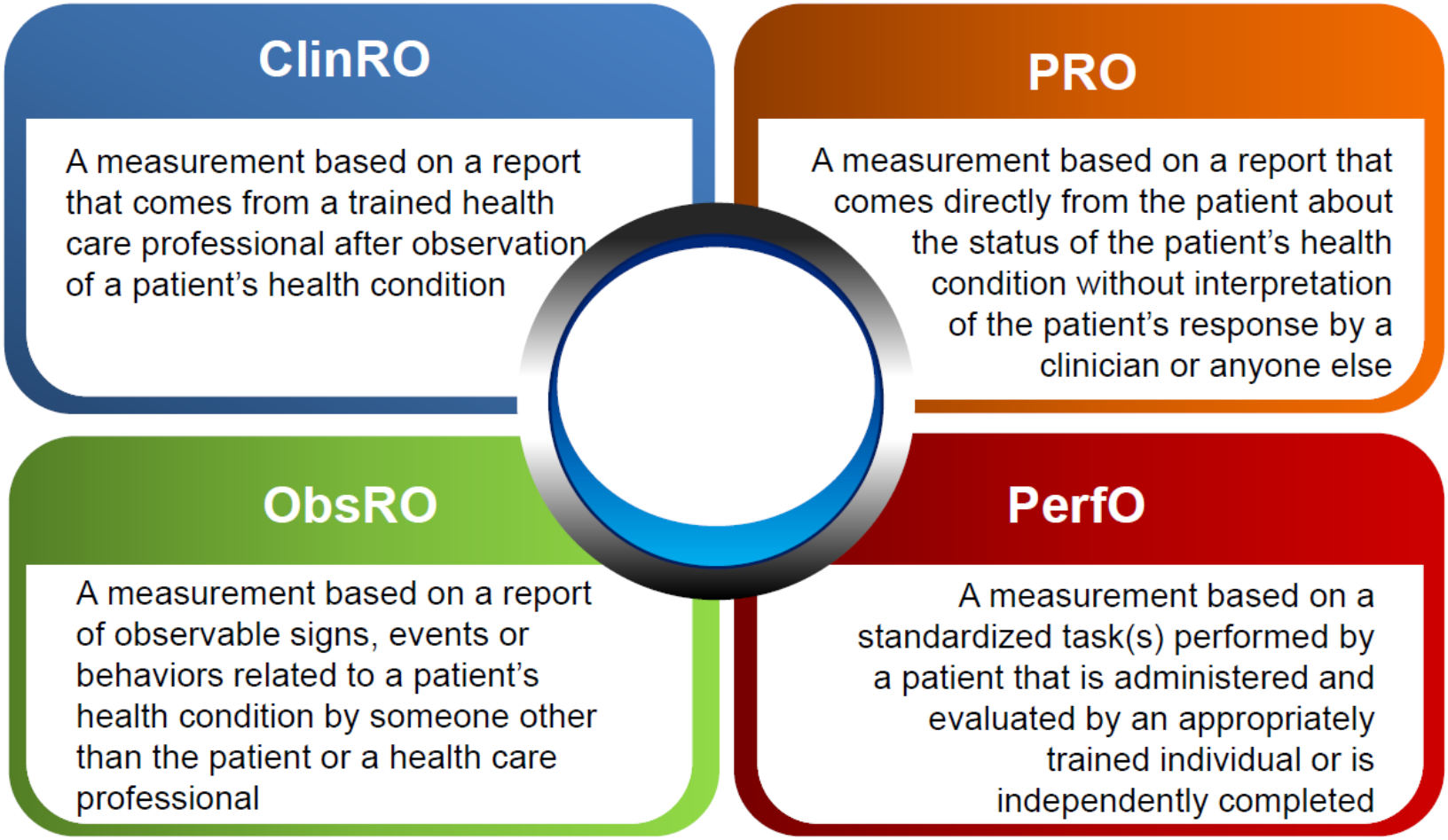
DOI: 10.1159/000486347
Received: August 18, 2017
Accepted: December 13, 2017
Published online: January 31, 2018

Review Article

Use of Mobile Devices to Measure Outcomes in Clinical Research, 2010–2016: A Systematic Literature Review

Brian Perry[a, b] Will Herrington[c] Jennifer C. Goldsack[b, d]
Cheryl A. Grandinetti[e] Kaveeta P. Vasisht[e] Martin J. Landray[c]
Lauren Bataille[f] Robert A. DiCicco[g] Corey Bradley[h] Ashish Narayan[i]
Elektra J. Papadopoulos[e] Nirav Sheth[j] Ken Skodacek[k] Komathi Stem[l]
Theresa V. Strong[m] Marc K. Walton[n] Amy Corneli[a, b]

Activity monitors: A 5th COA Type?



FDA will be hosting its 26th Patient-Focused Drug Development meeting on July 9th for Chronic Pain

Fiscal Year 2013	Fiscal Year 2014	Fiscal Year 2015	Fiscal Year 2016	Fiscal Year 2017	Fiscal Year 2018
• Chronic fatigue syndrome/ myalgic encephalomyelitis • HIV • Lung cancer • Narcolepsy	• Sickle cell disease • Fibromyalgia • Pulmonary arterial hypertension • Inborn errors of metabolism • Hemophilia A, B, and other heritable bleeding disorders • Idiopathic pulmonary fibrosis	• Female sexual dysfunction • Breast cancer • Chagas disease • Functional gastrointestinal disorders • Parkinson's disease and Huntington's disease • Alpha-1 antitrypsin deficiency	• Non-tuberculous mycobacterial lung infections • Psoriasis • Neuropathic pain associated with peripheral neuropathy • Patients who have received an organ transplant	• Sarcopenia • Autism • Alopecia Areata • Hereditary angioedema	• Opioid Use Disorder • **Chronic Pain – July 9th**

FDA announced the opportunity for externally-led PFDD meetings in December 2015

- Since then, **10 externally-led PFDD meetings*** have been hosted by patient organizations following the process outlined on FDA's externally-led PFDD webpage.
  - Acute Porphyrias
  - C3 Glomerulopathy
  - Friedreich's Ataxia
  - Hyperhidrosis
  - Lupus
  - Myotonic Dystrophy
  - Osteoarthritis
  - Spinal Muscular Atrophy
  - Thalassemia
  - Tuberous Sclerosis Complex
- Upcoming EL-PFDD Meetings: Externally-led PFDD meetings are hosted by external organizations, and it is considered that those organizations will determine whether and when to publicly announce their meeting.

*As of March 1, 2018

From PFDD to Implementation: Streamline Guidance on Specific Diseases

- An important part of the science of patient input is how the information is ultimately used
- FDA is aiming to sharply increase the number of disease-focused guidance –many of these will include advice on COAs or concepts such as symptoms and impacts based on patient input
- These guidances will outline clear, concise and up-to-date development guidelines

Source: Remarks from FDA Commissioner Scott Gottlieb, M.D. on Fiscal Year 2019 budget request for FDA (April 17, 2018):
https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm604826.htm

In Closing

- The COA DDT Qualification Program continues to expand and evolve under new legislation
- FDA continues to encourage and support precompetitive efforts to better capture patient voice and address unmet public health needs in drug development

U.S. FOOD & DRUG ADMINISTRATION

Thank you!

Presenters/Panelists

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