U.S. FOOD & DRUG ADMINISTRATION

Meeting #1 in a Series of Public Meetings on Patient Focused Drug Development

Using Methods from PFDD Guidance 1 and Guidance 2 as Tools for Including Patient Experience Data in Clinical Trials: *Who to Ask and How to Ask*

June 30, 2022

#PFDD

Disclaimer

The views expressed in the following presentations are those of the individual speakers and do not necessarily represent an official FDA position.

U.S. FOOD & DRUG ADMINISTRATION

Welcome

Shannon Cole, MS
Office of the Center Director
Center for Drug Evaluation and Research

Agenda

11:00 a.m.	Welcome
11:05 a.m.	Opening Remarks
11:10 a.m.	Overview of Patient-Focused Drug Development (PFDD)
11:15 a.m.	Session I: Research Methods to Identify and Understand What Matters to Patients
12:05 p.m.	Session II: Ideas in Practice
12:35 p.m.	Clinical Regulatory Perspective
12:45 p.m.	Session III: Questions and Answers
1:00 p.m.	End

U.S. FOOD & DRUG ADMINISTRATION

Opening Remarks

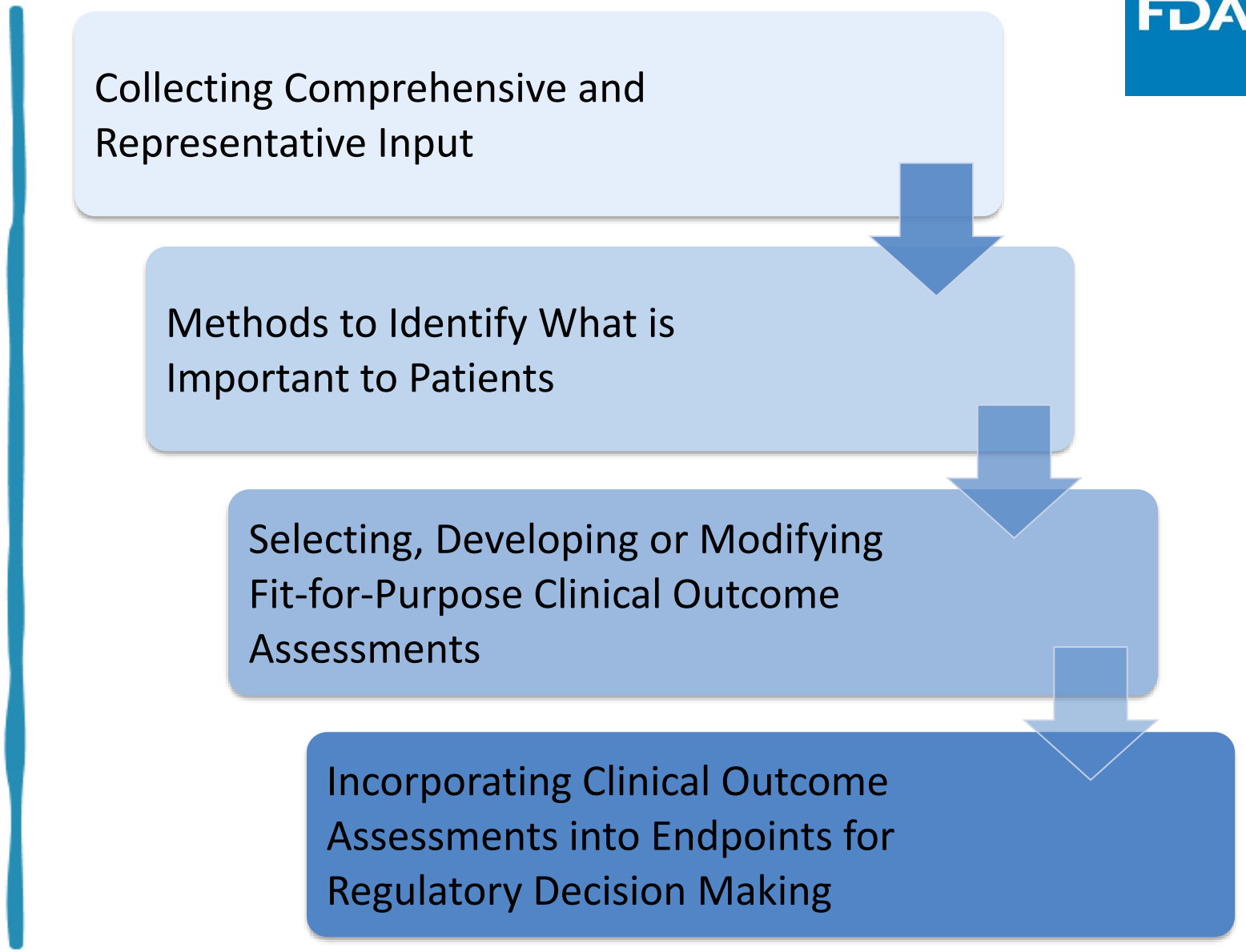
Theresa Mullin, PhD
Associate Director for Strategic Initiatives
Center for Drug Evaluation and Research

U.S. FOOD & DRUG ADMINISTRATION

Overview of Patient-Focused Drug Development (PFDD)

Robyn Bent, RN, MS
Office of the Center Director
Center for Drug Evaluation and Research

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

- 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- Issued Draft Guidance in June 2018 and Final Guidance in June 2020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

Guidance 1
Guidance 2
Guidance 3
Guidance 4

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
- Published YESTERDAY!!!

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
- Draft in progress

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

GUIDANCE DOCUMENT

Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments

JUNE 2022

Download the Draft Guidance Document

Draft

Not for implementation. Contains non-binding recommendations.

This guidance is being distributed for comment purposes only.

Share | Tweet | Linkedin | Email | Print

Submit Comments by 09/29/2022

Submit Comments Online

Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that the FDA considers your comment on a draft guidance before it begins work on the final version of the guidance, submit either online or written comments on the draft guidance before the close date.

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-selecting-developing-or-modifying-fit-purpose-clinical-outcome

Guidance Snapshot and Podcast

Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-For-Purpose Clinical Outcome Assessments—Draft Guidance (PFDD G3)

Patient-Focused Drug Development Guidance Snapshot

- Snapshot of *PFDD G3* helps readers understand the highlights of the recommendations in the guidance
- **https://www.fda.gov/media/159516/download**

First Patient-Focused Drug Development Guidance Podcast

- Subject Matter Experts talk about the importance of the document
- **https://www.fda.gov/media/159508/download**

About the Guidance Snapshot Pilot

- Leverages various communication tools to increase general public awareness and engagement for FDA guidance documents
- **https://www.fda.gov/drugs/guidances-drugs/guidance-snapshot-pilot**

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

Session 1: Research Methods to Identify and Understand What Matters to Patients

Objective

Provide an overview of research methods to identify and understand what is important to patients with an emphasis on practical implementation

APPROACHES TO COLLECTING PATIENT INPUT & SELECTION OF DATA COLLECTION METHODS

Naomi Knoble, PhD
Reviewer, Division of Clinical Outcome Assessment
Office of Drug Evaluation Science
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Selena R. Daniels, PharmD, PhD
Team Leader, Division of Clinical Outcome Assessment
Office of Drug Evaluation Science
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Approaches to Collect Patient Input

Qualitative

- Typically used to obtain a deeper understanding of the patient experience by generating in-depth information from patients in their own words

Quantitative

- Collection of quantifiable data (e.g., numerical data) and the application of statistical methods to summarize the collected patient experience data

Mixed-Methods

- Involves using both qualitative and quantitative approaches or methods in a single study or program of inquiry to understand the patient experience

Approaches to Collect Patient Input

Qualitative

- Interview-based research (one-on-one interviews, focus groups)
- Social media (content analysis)
- Group concept generation
- Delphi panel
- Surveys (open-ended questions)
- Observational ethnography
- Exit interviews/surveys

Quantitative

- Surveys (self-administered, web-based)
- Exit surveys

Mixed-Methods

- Qualitative-quantitative integration
- Group concept methodology
- Social media

Qualitative 

Example of Qualitative Methods

- Patient exit interviews from a randomized, placebo-controlled trial
  - Patients with carcinoid syndrome described that high bowel movement frequency was the most important symptom to treat
  - Patients reported that a reduction of two bowel movements per day was considered clinically meaningful
  - Patients who experienced a reduction in bowel movements described a sense of freedom from the bathroom, being better able to participate in physical and social activities

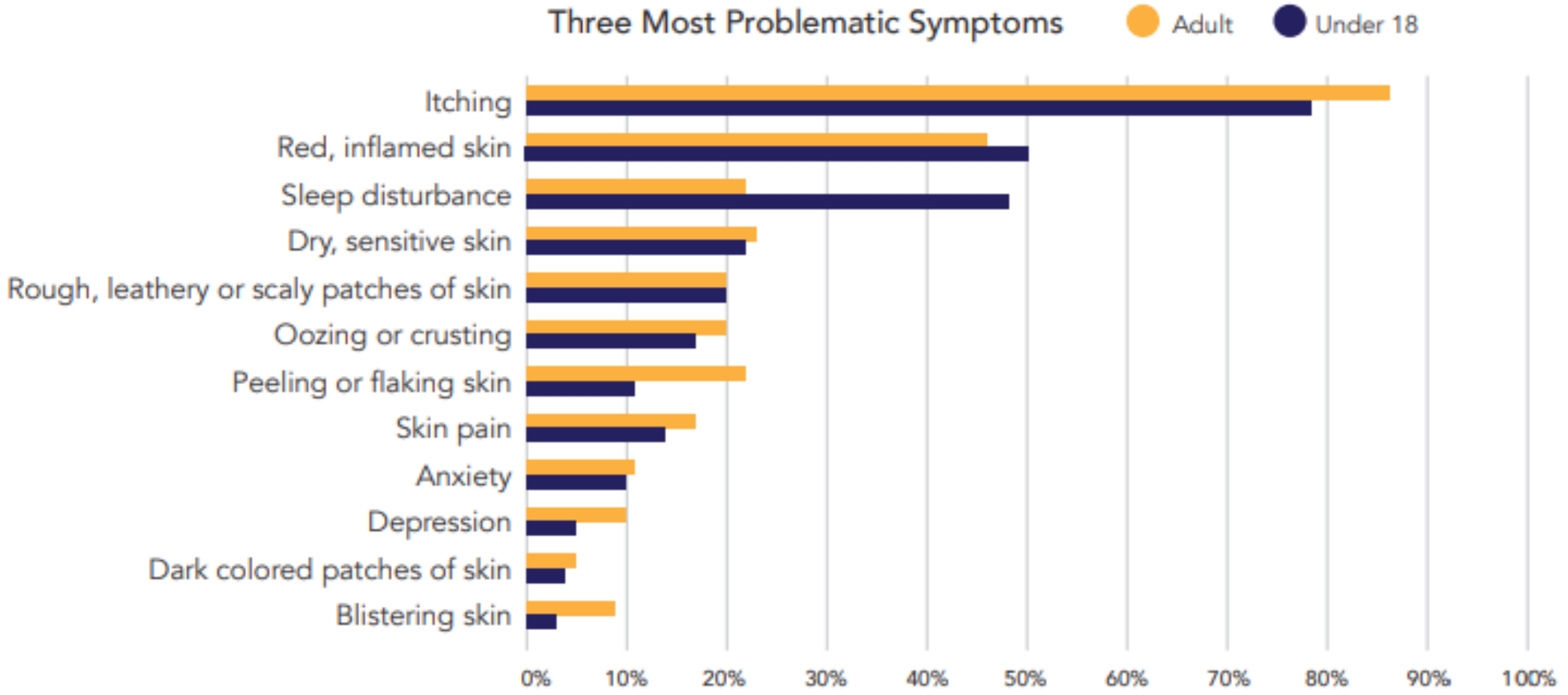
Xermelo (telotristat ethyl), approval date 28Feb2017 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208794Orig1s000TOC.cfm

Creswell, 2013; Greenbaum, 2000; Guest et al., 2013; Hennink & Levy, 2014

Quantitative

Example of Quantitative Methods

- Survey methods: Eczema Voice of the Patient Report (2020)



Voice of the Patient Report Eczema, 2020: http://www.morethanskindeep-eczema.org/report.html

Mixed-Methods

Example of Mixed-Methods Research

- **Qualitatively** driven sequential design:
  - Qualitative research followed by quantitative evidence
  - E.g., Focus groups with patients with diabetes used to identify patient experiences, followed by a diabetes-specific survey to understand prevalence

- **Quantitatively** driven sequential design:
  - Quantitative research followed by qualitative research
  - E.g., Survey data results explored in qualitative interviews to contextualize findings

- **Concurrent** (convergent) design:
  - Results of qualitative and quantitative data are merged in order to compare results
  - E.g., Qualitative exit interviews with patients and proportions of treatment responders

Christensen, 2014; Johnson & Christensen, 2017; Plano Clark & Ivankova, 2016; Teddlie & Tashakkori, 2009

Research Methods for Collecting Patient Experience Data

	Qualitative Methods	Quantitative Methods	Mixed Methods
Common Research Objectives	Description, understanding and exploration/confirmation	Numerical description, causal explanation and prediction	Multiple objectives; provide complex and fuller explanation and understanding; understand multiple perspectives
Common Study Characteristics	Understand participant views, perspectives and meanings of concepts; study groups and individuals in natural or controlled settings	Study behavior under controlled conditions; isolate the causal effect of single variables	Study multiple contexts, perspectives or conditions; study multiple factors as they operate together
Data Collection	Qualitative data (e.g., in-depth interviews, participant observations, open-ended questions)	Quantitative data generated using structured data collection instruments	Both qualitative and quantitative data

Which Research Methods to Use?

QUALITATIVE

QUANTITATIVE

MIXED METHODS

General Considerations For Selecting a Research Method

- Research Objective(s) and Question(s)
- Method Characteristics
- Target Population
- Expected data
- Feasibility of leveraging existing literature and data
- Time to conduct study
- Study budget

Qualitative

Specific Considerations For Qualitative Methods

One-on-one interviews	• Patient selection and sample size
	• Interview and data collection methods
	• Interview conduct
Focus groups	• Use of a trained moderator
	• Number of focus groups
	• Sample size for each focus group
One-on-one interviews/ Focus groups	• Ask the right question

Quantitative

Specific Considerations For Quantitative Methods

Survey Instrument	• Administration method
	• Alignment of survey question(s) and response options to research question and targeted concept
	• Format
	• Assessment of response bias
	• Pilot testing
	• Use of a script (interviewer-administered)

Mixed-Methods

Specific Considerations For Mixed Methods

Qualitative and Quantitative Methods	• Sequencing of qualitative and quantitative methods • Priority (dominance) of each method

Polling Question #1

Qualitative research methods, quantitative research methods, or mixed-methods research can be used to identify what is important to patients.

a) True
b) False

Polling Question #2

Which factors are important to consider when selecting a research method to identify what is important to patients?

a) Preference for a research method

b) Research objective(s) and question(s)

c) Target population

d) b and c

U.S. FOOD & DRUG ADMINISTRATION

Who to Collect Information From: Sampling Plans and Strategies

Laura Lee Johnson, PhD
Office of Translational Sciences, Office of Biostatistics
Center for Drug Evaluation and Research

Sampling 101

- Target population: complete collection of observations we want to study
- Sample: subset of a population
  - Rarely can study the entire target population
- Every time data is collected there is a sampling strategy
  - May not think about it, but it is there

Sampling 101

- Sampling scheme
  - Selecting patient population participating in the study
  - Key to getting information relevant to addressing the research objectives
- Many approaches
  - Objectives and resource constraints
  - Online hypothetical case examples to help elucidate

Two Major Approaches

Probability Sampling

- Some version of random sampling
- Might include sample weights
- Select from a larger population
- Results more likely to reflect target population

Non-Probability Sampling

- Non-random process to select study sample
- Selected sample may not be representative of the target population

Potential Sampling Approaches

Probability	Non-Probability
• Simple random	• Convenience
• Stratified random	• Purposive
• Cluster	• Quota
• Multistage	• Snowball

Issues that Arise

Under Coverage

Non-Response & Drop-outs

Voluntary Response Bias

Generalizability and Representation

Can we generalize to the target population?

- Subgroups adequately represented in the study sample
- Various characteristics that approximate the heterogeneity of characteristics in the target population
- Weighting may used to account for the over- or under-sampling (if probability sampling was used)
  - Probabilities of selection or inclusion in the sample
  - Non-response
  - Differences between the final sample's population and the target population

Representative [of the Target Population]

- Patients in the study sample reflect the diversity and heterogeneity of patient characteristics in the target population
- Distribution of the characteristics in the sample could be different that in the population

Missing Data/Non-Response

- Impacts representativeness
  - Decline to participate
  - Stop participating (dropout)
  - Decline to answer some questions

➢ Anticipate what is likely to occur | what barriers can be removed
  - Study design features
  - Logistics
  - Specific data being collected

➢ Determine reasons for missingness

➢ Understand extent and impact

Intersection of Representativeness and Diversity (and Sampling)

- What are the attributes of interest
  - Socioeconomic and demographic background
  - Cultural background and spoken language(s)
  - Literacy and health literacy
  - Clinical characteristics
  - Others

Leverage Existing Data

- Encouraged
- Demonstrate
  - Representativeness
  - Methodological rigor of data collection methods and data integrity

Objectives, Plans, at the End What

You do not know what you do not know/hear

Considerations

FOCUS ON THE PURPOSE AND OBJECTIVES

WHAT DOES THE DECISION MAKER NEED WHAT WILL BE USEFUL

BUDGET TIME TO TALK TO DECISION-MAKERS (REGULATOR, HTA, ETC.)

Participants' Time Matters: Use methods that can answer the questions decision makers are trying to answer

PURPOSE

PRINCIPLES

SCIENCE

Session 2: Ideas in Practice

Applications of PFDD Guidance 1 and Guidance 2 as Tools for Generating Patient Experience Data to Support Medical Product Development

Who to Ask and How to Ask

Ebony Dashiell-Aje, PhD
BioMarin Pharmaceutical, Inc.
June 30, 2022

Guidance 1 and 2 are helpful for driving development of robust, meaningful, and interpretable data on patient experiences, perspectives, needs, and priorities to support medical product development

- **Guidance 1 Takeaways: Study Planning and Preparation**
  - Establish clear research questions and objectives at the onset
  - Ensure representativeness in sampling to generate insights from the appropriate target population
  - Select the right methodology to generate the right data in the right patient population

- **Guidance 2 Takeaways: Determine and Implement Appropriate Methodology**
  - Determine which method (qualitative, quantitative or mixed-methods) should be used to understand what is important to patients
  - Establish best practices to follow in order to generate reliable and valid data

APPLICATION: GUIDANCE 1 PRINCIPLE – WHO TO ASK, SAMPLING AND REPRESENTATIVENESS CONSIDERATIONS

1

Partner with Patient Advocacy Groups (PAGs) to establish rapport with the broader community

2

Partner with Investigative Sites to gather perspectives from treatment naïve and clinical trial participants

3

Innovative Recruitment strategies with Patient-centric, for-profit organizations and via Social Media

APPLICATION: GUIDANCE 2 PRINCIPLE – WHAT TYPE OF DATA AND HOW TO GENERATE IT

1

Quantitative methods to generate numeric information via a tool or survey

2

Qualitative Methods to explore the meaning and interpretation of concepts that are relevant to patients

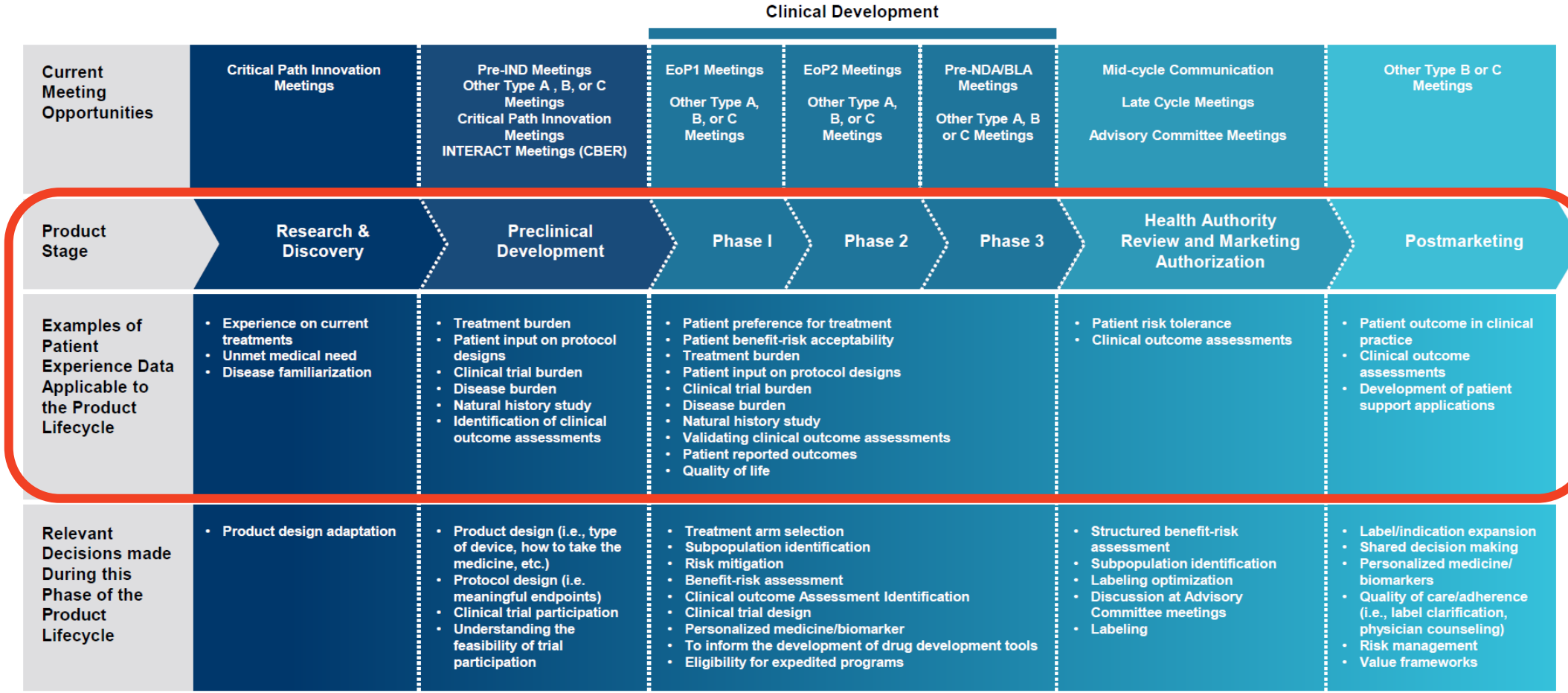
3

Mixed Methods to integrate both qualitative and quantitative approaches

APPLICATION: TRADE ORGANIZATION PARTNERSHIPS – WHEN TO GENERATE DATA

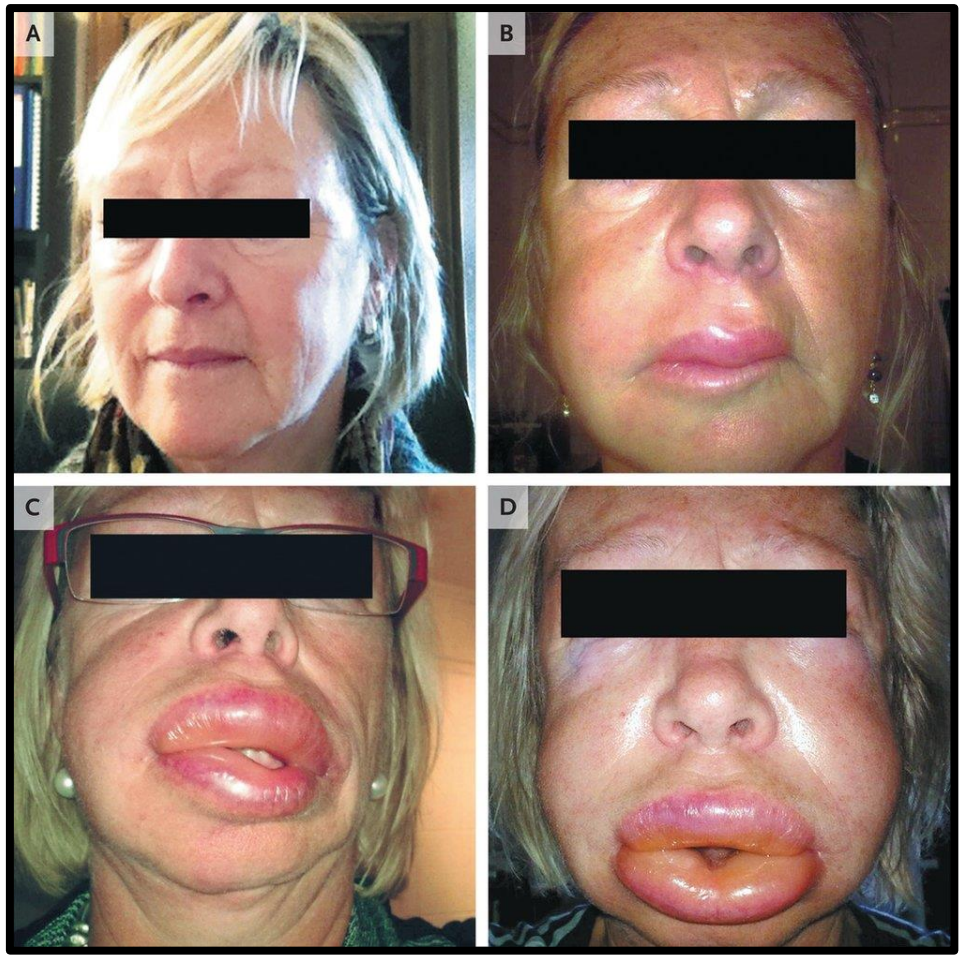
Biotechnology Innovation Organization

Framework for the Use of Patient Experience Data Throughout the Product Lifecycle



Source: https://archive.bio.org/sites/default/files/docs/toolkit/Product-Lifecycle-Graphic.pdf

CASE STUDY: UNMET NEED AND MEASUREMENT GAPS IN HEREDITARY ANGIOEDEMA (HAE)



Source: https://www.tldrpharmacy.com/content/a-primer-on-hereditary-angioedema

- Determined the **most appropriate target population** for our trials
- **Engaged the patient community** to understand their perspective on unmet need
- Developed a **data and evidence generation plan**
  - Established need for targeted literature review, gap analysis, advisory boards, and qualitative interviews to gather relevant patient insights
- Designed and **conducted relevant studies** and executed study workstreams
- Information **used to support regulatory discussions**

CASE STUDY: ESTABLISHING CLINICAL BENEFIT IN PHENYLKETONURIA (PKU)

Adv Ther (2022) 39:971–991
https://doi.org/10.1007/s12325-021-01986-2

ORIGINAL RESEARCH

Measuring Burden of Illness in Phenylketonuria (PKU): Development of the PKU Symptom Severity and Impacts Scale as a Robust Patient-Reported Outcome

Jennifer Quinn · Alexandros Georgiadis · Hannah B. Lewis · Elaina Jurecki

Received: August 13, 2021 / Accepted: November 5, 2021 / Published online: December 18, 2021

ABSTRACT

Introduction: Phenylketonuria (PKU) is a rare, metabolic genetic disorder that can cause various neuropsychological symptoms that often affect patients' health-related quality of life, even for patients with good metabolic control. To date, no patient-reported outcomes (PRO) instrument combines the measurement of neuropsychological and dietary concepts to capture the broad impact of PKU on quality of life. This article presents the development of the PKU Symptom Severity and Impacts Scale (PKU-SSIS), a PRO instrument that is designed to evaluate neuropsychological symptoms and impacts in early-treated patients with PKU.

Methods: A draft instrument was developed based on a targeted literature review, PKU expert physician interviews, and an advisory board consisting of patients with PKU. Qualitative interviews combining concept elicitation/cognitive interviews were conducted with patients with classic PKU aged at least 15 years old. A separate sample of 20 patients with PKU completed the draft PKU-SSIS in a paper survey format, to enable preliminary assessment of any floor and ceiling effects.

Results: Patient interviews elicited four key symptom themes: neurocognitive function, emotional and behavioral, physical functioning, and physical health. Four impact themes were also identified: social function, physical health, emotions, and level of independence. No floor or ceiling effects were identified.

Conclusion: The final instrument included 22 items, covering three symptom domains (1. emotional, mood, and psychological; 2. (neuro)cognitive, executive, and intellectual function; and 3. physical health), and four impact domains (1. social relations, 2. level of independence, 3. general well-being, and 4. self-care). The PKU-SSIS will help to address an important gap in the evaluation of existing and future treatments for PKU.

Keywords: Phenylketonuria; Patient-reported outcomes; Qualitative; Interviews; Neuropsychological; Health-related quality of life

J. Quinn (✉)
BioMarin Europe Ltd, 10 Bloomsbury Way, London WC1A 2SL, UK
e-mail: jennifer.quinn@bmrn.com

Source: Measuring Burden of Illness in Phenylketonuria (PKU): Development of the PKU Symptom Severity and Impacts Scale as a Robust Patient-Reported Outcome (nih.gov)

- **Engaged the patient community** to understand their perspective on unmet need
- Identified existing **measurement gaps**
- Conducted **qualitative interviews** (clinicians, patients), and used information generated from an **advisory board** (PKU patients)
- Information **used to develop draft instrument**
- **Validation work** currently underway

CASE STUDY: EVALUATING PATIENT PREFERENCES IN HEMOPHILIA A

T06-P22

Qualitative research evaluating patient preference for haemophilia therapy

Wolfgang Miesbach[1], Leonard A Valentino[2,3], Declan Noone[4], Katherine Forsyth[5], Monika Bullinger[6], Ebony Dashiell-Aje[7], Vanessa Newman[7], Charles Hawes[7], Sara Hawley[7], Hannah B Lewis[8], Diandra Latibeaudiere-Gardner[8], Jennifer Quinn[9]

[1]Medical Clinic 2, Institute of Transfusion Medicine, University Hospital Frankfurt, Germany; [2]National Hemophilia Foundation, New York, NY, USA; [3]Rush University, Chicago, IL, USA; [4]European Haemophilia Consortium, Brussels, Belgium; [5]Barts Health NHS Trust, London, UK; [6]Department of Medical Psychology, University Medical Center Hamburg Eppendorf, Hamburg, Germany; [7]BioMarin Pharmaceutical Inc., Novato, CA, USA; [8]ICON Clinical Research Limited, London, UK; [9]BioMarin UK Ltd, London, UK

Introduction and Objectives

- In the changing haemophilia treatment landscape, it is critical to understand which impacts and outcomes of treatment are important to people with haemophilia
- Qualitative research is the first step in understanding individual treatment preference drivers and risk tolerance for new gene therapies among people with haemophilia
- Here, we present results from concept elicitation and ranking of attributes in development of a discrete choice experiment designed to identify the key drivers of individual preference when selecting one haemophilia therapy over another

Methods

- Adult participants with severe haemophilia A (factor VIII [FVIII] ≤1 IU/dL) were recruited via the National Hemophilia Foundation's community-powered registry in the US
  - Participants in gene therapy clinical trials were excluded
- Semi-structured, 60-minute concept elicitation telephone interviews were conducted with participants to collect treatment preferences
  - A combination of thematic and content analysis was used to identify themes and concepts that emerged from audio transcripts[1]
- Participants rated 15 predetermined treatment attributes on a 4-point scale from "not important (1)" to "very important (4)" and ranked attributes from most "important (1)" to "least important (15)"
- Data were analysed with descriptive statistics and mean (standard deviation [SD)] ratings and rankings were calculated
  - Mean rankings were themselves ranked to provide final attribute rankings for the sample

Results

Participant demographics and baseline characteristics

- Concept elicitation interviews were conducted with 20 participants with severe haemophilia A in the US

	N = 20
Age at enrolment, median (range), years	34.5 (20–57)
Race/ethnicity, n (%)	
White	14 (70.0)
Black	1 (5.0)
Asian	1 (5.0)
Hispanic	1 (5.0)
Other	3 (15.0)
Male sex, n (%)	20 (100)
Number of target joints, n (%)	
0	5 (25.0)
1	2 (10.0)
≥2	13 (65.0)
Other comorbidities, n (%)	
Arthritis	9 (45.0)
Depression/anxiety	4 (20.0)
Hepatitis B	1 (5.0)
Hepatitis C	5 (25.0)
Hypertension	4 (20.0)
Other	4 (20.0)
None	6 (30.0)

Treatment characteristics – the 'ideal' treatment

- Overall, 40.0% of participants spontaneously mentioned "reduction in bleeds" as an ideal treatment characteristic, increasing to 100% on probing

N = 20	Reduction in bleeds	Physical activities ability	Treatment frequency/ duration	Increase FVIII levels	Reduction in joint bleeds[a]	Mode of administration	Reduction in pain/joint pain	Reverse joint damage	Ability to have surgeries; safety of treatment; cure disease; avoid side effects; improve QOL[b]
Spontaneous, n %)	8 (40.0)	1 (5.0)	7 (35.0)	2 (10.0)	1 (5.0)	6 (30.0)	4 (20.0)	2 (10.0)	1 (5.0)
Probed, n (%)	12 (60.0)	18 (90.0)	11 (55.0)	15 (75.0)	15 (75.0)	0	0	0	0
Total[c], n (%)	20 (100.0)	19 (95.0)	18 (90.0)	17 (85.0)	16 (80.0)	6 (30.0)	4 (20.0)	2 (10.0)	1 (5.0)

[a]Some participants did not see the difference between bleeds and joint bleeds and considered them the same. [b]Participants mentioned each of these treatment characteristics spontaneously. [c]Not all treatment characteristics were probed for when discussing the "ideal" treatment. QOL, quality of life.

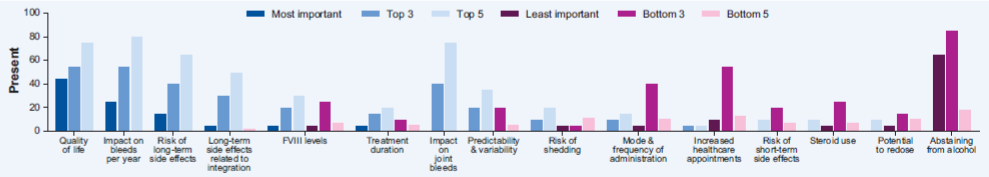
Rating and ranking

- All characteristics were considered at least somewhat important
- Annualised bleeds and health-related quality of life (HRQOL) were both rated as "very important" and overall tied for first place in the ranking
- The least important attributes by both rating and ranking were additional doctor visits and alcohol abstinence

Potential characteristics	Treatment characteristic rating task		Treatment characteristic ranking task	
	Mean (SD)[a]	Overall rating (N = 20)	Mean (SD)[a]	Overall ranking (N = 20)
Annualised bleeds	3.87 (0.52)	Very important	3.50 (2.31)	1[c]
HRQOL impact	3.78 (0.73)	Very important	3.50 (2.91)	1[c]
Annualised joint bleeds	3.93 (0.26)	Very important	4.25 (1.89)	2
Risk of long-term side effects	3.86 (0.36)	Very important	4.45 (2.76)	3
Long-term side effects related to integration	3.79 (0.42)	Very important	5.75 (3.29)	4
Predictability of treatment	3.33 (0.97)	Important	7.90 (3.82)	5
FVIII levels	3.33 (0.97)	Important	8.25 (4.46)	6[b]
Length/duration of treatment	2.89 (0.88)	Important	8.25 (3.57)	6[b]
Risk of short-term side effects	2.82 (0.88)	Important	9.05 (2.93)	7
Steroid use	2.82 (1.19)	Important	9.25 (2.23)	8
Shedding/double barrier contraception	2.95 (1.27)	Important	9.65 (3.48)	9
Potential to redose	2.76 (0.97)	Important	10.15 (2.64)	10
Treatment mode and frequency	2.39 (1.09)	Somewhat important	10.25 (3.92)	11
Additional doctor visits	2.26 (0.93)	Somewhat important	11.7 (3.10)	12
Alcohol abstinence	1.50 (0.99)	Somewhat important	14.1 (1.74)	13

[a]Attributes were rated from 1 (least important) to 4 (most important). [b]Attributes were ranked from 1 (most important) to 15 (least important). [c]The average ranks led to an overall tied ranking for these attributes.

Modal ranking of attributes



Conclusions

- Overall, participants most frequently spontaneously mentioned that the "ideal treatment" would reduce the number of bleeds, have longer treatment duration, and would have an improved mode of administration (e.g., pill)
  - When probed, participants deemed the ability to partake in physical activities, increased treatment duration, and increased FVIII levels as the most ideal treatment characteristics
- Participants ranked a reduction in annualised bleeds and an improvement in HRQOL as the most important treatment characteristics, followed by reduction in annualised joint bleeds and risk of long-term side effects
  - These attributes were also rated as "very important," as were long-term side effects related to integration
  - Additional doctor visits and alcohol abstinence were ranked as the least important treatment characteristics

Reference

1. Joffe H, Yardley L. Content and thematic analysis. In: D. Marks and L. Yardley (eds) Research Methods for Clinical and Health Psychology. London Sage. 2004: 56–68.

Disclosures

Wolfgang Miesbach has received speaker honoraria and project grants from Bayer, Bioverativ/Sanofi Genzyme, CSL Behring, Chugai, Freeline, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Takeda/Shire, and uniQure. Leonard A Valentino reports nothing to declare. Declan Noone reports nothing to declare. Katherine Forsyth reports nothing to declare. Monika Bullinger has received speaker honoraria and project grants from Bayer, Bioverativ/Sanofi Genzyme, CSL Behring, Chugai, Freeline, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Takeda/Shire, and uniQure. Ebony Dashiell-Aje, Vanessa Newman, Charles Hawes, Sara Hawley, and Jennifer Quinn are employees and stockholders of BioMarin Pharmaceutical Inc. Hannah Lewis and Diandra Latibeaudiere-Gardner are employees of ICON Clinical Research Limited, which was contracted by BioMarin Pharmaceutical Inc. to conduct this study. Recently presented at the European Association for Haemophilia and Allied Disorders – 15th Annual Congress.

Presented at the 2022 Society of Thrombosis and Haemostasis Research 66th Annual Meeting: March 1–4, 2022, Leipzig, Germany

- Conducted **semi-structured, concept elicitation telephone interviews**
- Gathered insights on **ideal treatment outcomes** and perspectives on **potential risks of treatments**
- Generated **ratings and rankings of predetermined treatment attributes** ("not important" to "very important;" "most important" to "least important")

CASE STUDY: ELEVATING THE PATIENT VOICE IN FDA INTERACTIONS

Partnering with external stakeholders (patients, caregivers, advocacy leaders, clinicians, KOLs) to tell their stories via oral and written statements, videos, presentations. Also collaborating with stakeholders in COA development.

- Listening Sessions
- PFDD Meetings
- Patient Engagement Meetings
- Advisory Committee Meetings
- Panels
- COA Partnerships

GUIDANCE APPLICATION CHALLENGES STILL REMAIN

- FDA has made great progress in providing guidance to stakeholders, but we can still benefit from more progress in these areas:
  - **Greater transparency on what type of PED is considered acceptable** to support regulatory decision-making (especially when applying regulatory flexibility in rare disease drug development)
  - **Greater guidance on how more novel PED (e.g., PPI, testimonials, ethnography, video documentation) can support regulatory review** throughout the medical product lifecycle and timing of discussions with FDA
  - **Pragmatic approaches** (e.g., through publicly available examples) that help stakeholders tackle common challenges to applying regulatory guidance on PED generation (e.g., in rare disease and pediatric populations)

Acknowledgements

Thanks to the BioMarin Project Teams who have contributed to work discussed here!

Progress on the Science of Patient Input

PFDD Guidance Documents 1 and 2 and IMI PREFER EMA Qualification Procedure and Recommendations

Becky Noel, DrPH, MSPH
Executive Director, Benefit-Risk Assessment
IMI PREFER Deputy Project Leader
Eli Lilly & Co

Evolution of Patient Input: Regulatory Environment

- Individual testimony
- Patient panels

2012

- FDA CBER PFDD
- FDA CDRH Patient Preferences Initiative
- ICH update 2.5.6 Clinical Overview, references patient preferences
- EMA oncology patient preference study
- NICE melanoma patient preference project

2017

- FDA 21st Century Cures
- NICE input patient preference study

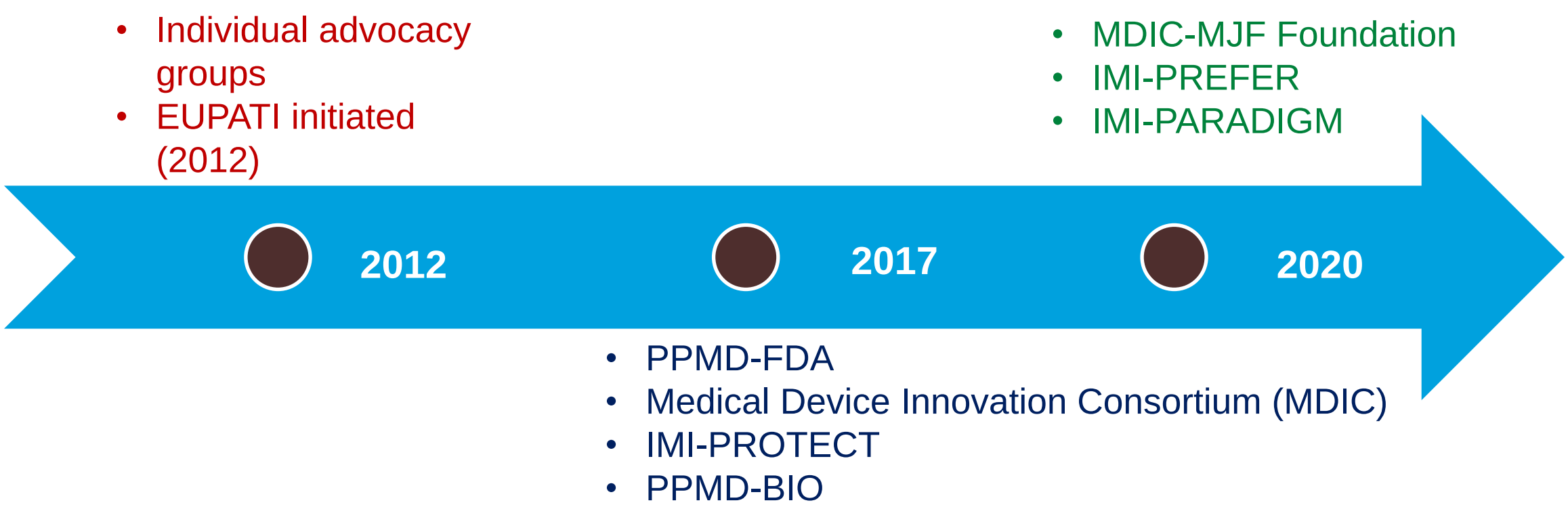
2020

- EMA 2025 – Expand benefit-risk assessment via inclusion patient preferences; Develop capability to analyze patient data for decision-making; Improve communication with HTAs/payers on therapeutic context, patient perspective

FDA PFDD Guidances 1&2

Acknowledgment: Bennett Levitan, Janssen

Evolution of Patient Input: Public-Private Partnerships



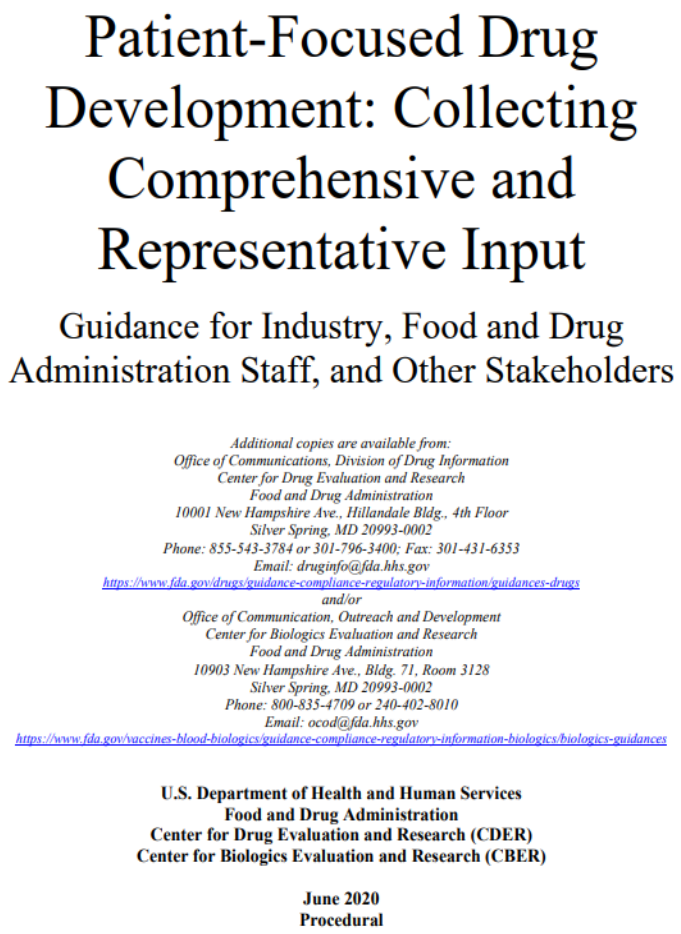
BIO - Biotechnology Innovation Organization; EUPATI – European Patients' Academy on Therapeutic Innovation; IMI – Innovative Medicines Initiative; MDIC – Medical Device Innovation Consortium; MJF – Michael J. Fox Foundation; PARADIGM - Patients Active in Research and Dialogues for an Improved Generation Medicine; PROTECT - Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium; PPMD - Parent Project Muscular Dystrophy; PREFER - Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle

Acknowledgment: Bennett Levitan, Janssen

Common Threads: Shared Perspectives on Patient Input

Patients living with a disease have a direct stake in drug development and regulatory review processes. They are uniquely positioned to relay their perspectives and preferences and thus contribute to drug development and availability.

Patient Focused Drug Development: Guidances 1 and 2



Patient-Focused Drug Development: Collecting Comprehensive and Representative Input

Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs
and/or
Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov
https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

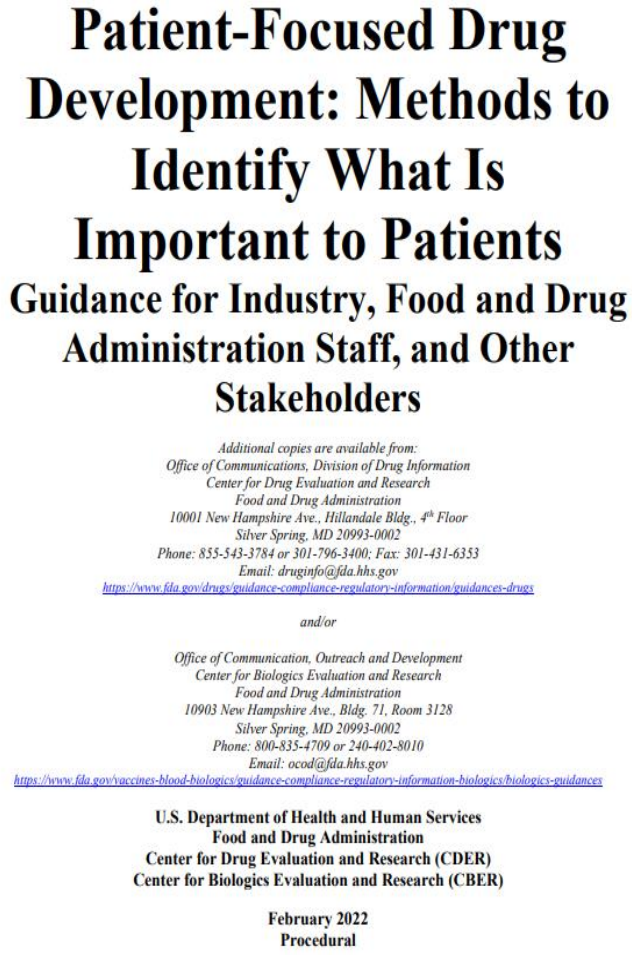
June 2020
Procedural

June 2020, FDA released the final Patient-Focused Drug Development Guidance 1

- Guidance 1 is first in a series of four guidance documents that the FDA is developing to direct stakeholders in collecting and submitting information on the patient experience in regulatory decision making and medical product development
- Guidance 1 reviews the different sampling methods that can be utilized when developing a study that uses patient input and gives a broad overview of the relationship between potential research questions and methods for deciding from whom to collect research
    - *Methods to collect accurate and representative patient experience data (PED)*

February 2022, FDA released the final Patient-Focused Drug Development Guidance 2

- The purpose of the guidance is to present a range of methods and established best research practices to *identify what is important to patients with respect to burden of disease, burden of treatment, and the benefits and risks* in the management of patients' diseases



Patient-Focused Drug Development: Methods to Identify What Is Important to Patients

Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

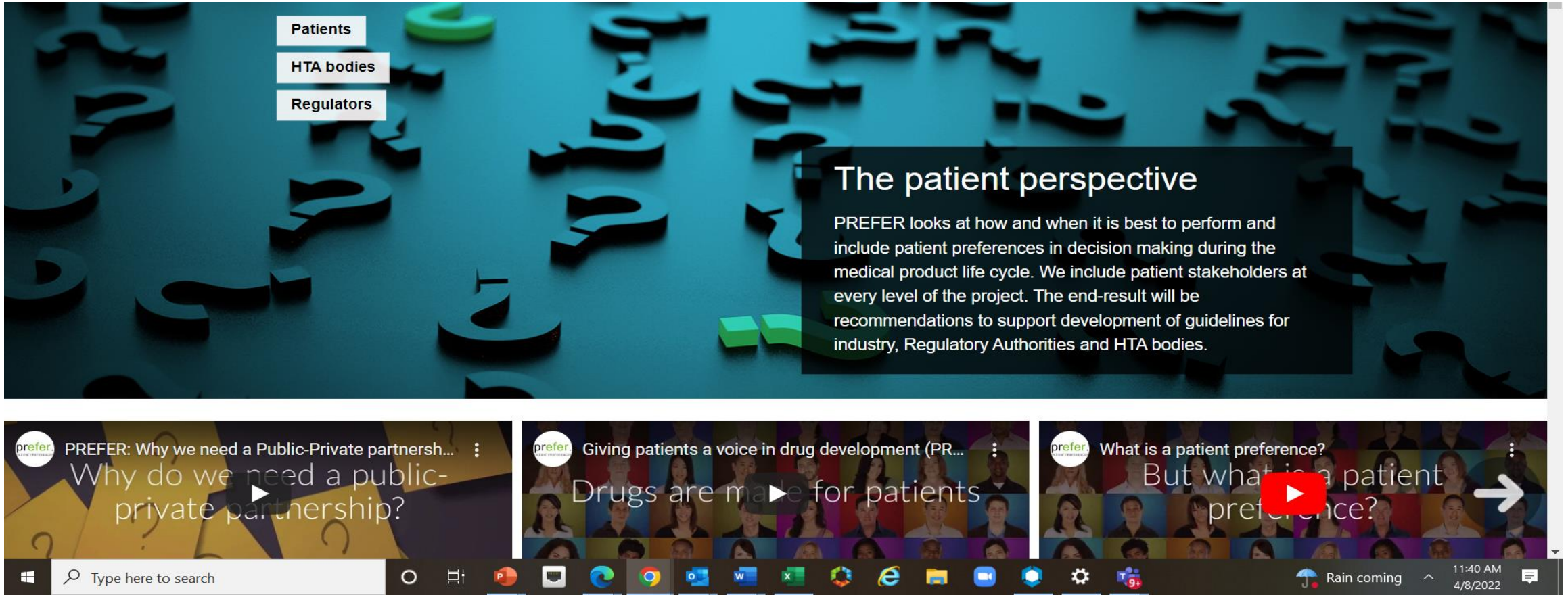
and/or

Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov
https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2022
Procedural

Innovative Medicines Initiative: PREFER



https://www.imi-prefer.eu/

So, What is Patient Preference Information?

- Patient preference information (PPI) is one type of *patient experience data*
- Patient-preference information captures the value that patients place on various aspects of the medical treatment (i.e., drug or device). PPI accounts for differing patient perspectives on the benefits and risks that come with using that device or drug to treat their condition.
  - *Note is made that the FDA PFDD Guidance 2 specifically states it doesn't address methods for collecting and analyzing PPI, but it does discuss best practices in performing qualitative research*

What is the EMA Qualification Process (QP) and the Qualification Opinion (QO)?

- The European Medicines Agency (EMA) qualification process is a new, voluntary, scientific pathway leading to either a Committee for Medicinal Products for Human Use (CHMP) opinion or a Scientific Advice on innovative methods or drug development tools:
  - (i) CHMP **Qualification Opinion** on the acceptability of a specific use of the proposed method, based on the assessment of submitted data and
  - (ii) CHMP **Qualification Advice** on future protocols and methods for further method development towards qualification, based on the evaluation of the scientific rationale and on preliminary data submitted.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

PREFER Framework: Reflection on Importance of Qualitative Research

Method Selection and Analysis

The iterative exercise of developing the PREFER Framework furthered our considerations for qualitative methods selection and analyses planning

Preference Question Development and Design

Clarified considerations for qualitative research

Enhanced details on how qualitative research informs quantitative studies

EMA/CHMP Qualification Included…

PREFER Framework for patient preference studies

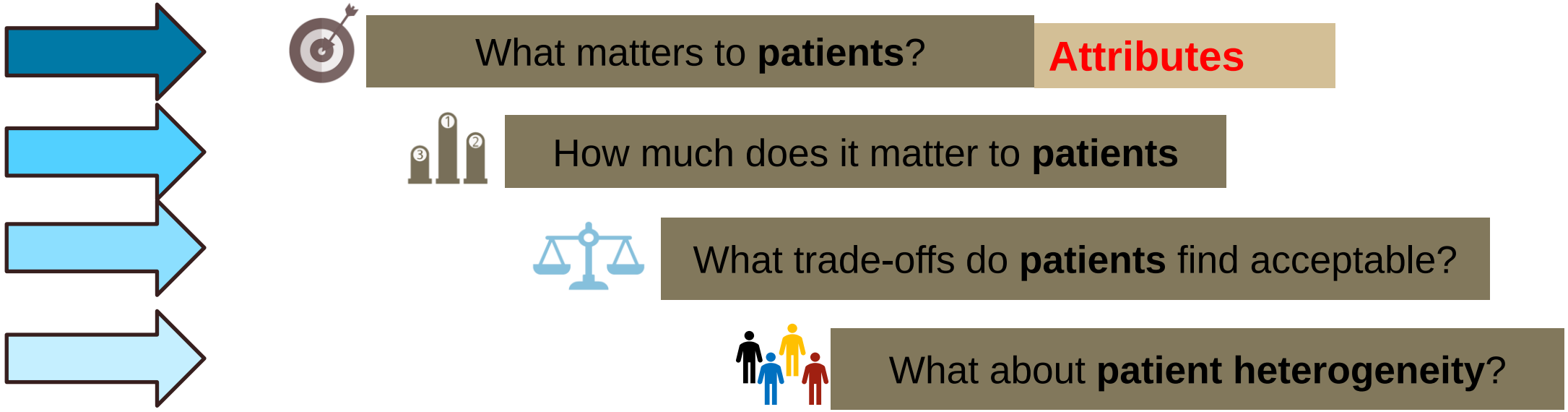
Points to consider on method selection – what preference methods is most suitable to the research question

Final CHMP Methods Qualification Opinion

PREFER Recommendations Content

SECTION 1	Introduction	
SECTION 2	Value of patient preferences	Inform stakeholders about why and when patient preference studies may benefit their decisions
SECTION 3	PREFER framework	Provide clear and step-wise insights into how to design, conduct, and evaluate patient preference studies
SECTION 4	Involvement of patients & other stakeholders	Provide insights into how patients and other stakeholders may contribute to patient preference study design and conduct to help ensure the studies provide useful information for patients and decision-makers
SECTION 5	Preference methods	Help guide preference study method selection, a crucial step for patient preference studies that require considering multiple factors
SECTION 6	Psychological constructs	Understand how participants' psychological characteristics may be assessed to understand how they may influence patients' answers in patient preference studies
SECTION 7	Educational materials	Explain which tools (e.g. survey component and multimedia) may help ensure patients' understanding in patient preference studies
SECTION 8	Areas for future research	Describe areas for future work on research questions that have been identified by PREFER but could not be addressed in the project

Qualitative Preference Study to Inform Quantitative Studies



- We know that the validity and reliability of data used in regulatory considerations must be considered, and the PREFER Qualification demonstrated how qualitative research strengthens attribute development, thereby contributing to the subsequent reliability and validity of a quantitative study component, if one is necessary...
- Aids in the interpretation of quantitative survey results
- All are themes also seen in the FDA Guidances

Human regulatory

Adaptive pathways
Advanced therapies
Clinical trials
Compassionate use
Compliance
Data on medicines (ISO IDMP standards)
Ethical use of animals

Opinions and letters of support on the qualification of novel methodologies for medicine development

Share

Table of contents

- Prognostic Covariate Adjustment (PROCOVA™)
- Use of Enroll-HD (a Huntington's disease patient registry) as a data source and infrastructure support for post-authorisation monitoring of medical products
- Islet Autoantibodies (AAs) as Enrichment Biomarkers for Type 1 Diabetes (T1D) Prevention Clinical Trials
- IMI PREFER
- Multiple sclerosis clinical outcome assessment (MSCOA)

Reflections on PREFER, PFDD Guidances 1 and 2

- Guidance 1, 2 and the PREFER recommendations all focused on ensuring robust, meaningful and interpretable patient input collected to understand patient disease experience and its treatment
  - to better inform medical product development
- PFDD 1 and PREFER both focus on preparation, understanding the research question and considerations for industry when defining approaches for collecting and evaluating patient experience/patient preference information
- PFDD 2 addresses methods to identify what matters most to patients regarding burden of disease and burden of treatment in order to guide medical product development. ***The guidance does not address methods for collecting and analyzing COA data or PPI data, rather these are methods to gain information that may inform the selection or development of COAs and the generation and use of PPI***.
- PREFER is an excellent resource and case study on the development and use of mixed methods, with complementary guidance and recommendations specific to the development and use of PPI, a type of patient experience data

Complementary Thoughts from the US and EU

- FDA's PFDD Guidances 1 and 2, along with the IMI PREFER recommendations and Qualification Opinion represent collective best practices
  - Guidances 1 & 2 fit together to outline the FDA expectations for sponsors generating a patient insight strategy. They provide clear guidance to ensure that sponsors use appropriate methodologies to obtain robust, meaningful, generalizable and interpretable patient input
- IMI PREFER Recommendations and the Qualification Opinion take a very similar approach, outlining expectations for the development of robust PPI for use in regulatory decision-making and reimbursement reviews

Further Resources

More Information about PREFER

Recommendations

See the Zenodo PREFER community

Templates

See the Zenodo PREFER community

Webinars

See the YouTube IMI-PREFER channel

Publications

See www.imi-prefer.eu

LUNGEVITY

Find it. Treat it. Live.

PATIENT FOCUSED DRUG DEVELOPMENT GUIDANCES 1 & 2: A PATIENT ADVOCACY PERSPECTIVE

Bellinda King-Kallimanis, PhD

Using Methods from PFDD Guidance 1 & 2 as Tools for Including Patient Experience Data in Clinical Trials: Who to Ask and How to Ask

June 30th, 2022

TRIAL COORDINATOR INSIGHTS INTO PRO ITEMS

"I think sometimes the questionnaires are designed by people who don't have a lot of patient contact. Sometimes you need to highlight things. Like for example, you know, this is, "We want you to complete this as how you've been feeling in the last 7 days""

I usually say ..."question number such-and-such has been missed, you haven't given a response, is that because you weren't sure how to answer it, or you didn't want to answer that question?", and they go, "Oh geez, I didn't see that one",
or, "Nausea, what does that mean?""

Mercieca-Bebber et al, 2018. Vol 9. Contemp. Clin. Trials Commun

TRIAL COORDINATOR INSIGHTS INTO PRO ITEMS

"I think sometimes the questionnaires are designed by people who don't have a lot of patient contact. Sometimes you need to highlight things. Like for example, you know, this is, "We want you to complete this as how you've been feeling in the last 7 days""

I usually say ..."question number such-and-such has been missed, you haven't given a response, is that because you weren't sure how to answer it, or you didn't want to answer that question?", and they go, "Oh geez, I didn't see that one",
or, "Nausea, what does that mean?""

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

Mercieca-Bebber et al, 2018. Vol 9. Contemp. Clin. Trials Commun

DIVERSITY AND REPRESENTATION

"Qualitative research methods, quantitative research methods, or mixed-methods research can be used to identify what is important to patients."[1]

In theory -> Our samples should look more or less like those with the disease or using the treatments researchers are trying to understand, i.e., the target population

In reality -> Our samples are convenience samples

1. Patient-Focused Drug Development: Methods to Identify What Is Important to Patients https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-methods-identify-what-important-patients

REPRESENTATION – GUIDANCE 1

Figure 2. Factors to Consider to Achieve Sufficient Representation

Socioeconomic and demographic background

- Include persons from all relevant demographics within the target population, including: age, sex, race/ethnicity, level of education, socioeconomic status to the extent possible.

Cultural background and spoken language(s)

- Include persons from all relevant cultures and languages within the target population to the extent possible
- Ensure that results from the research study apply to the entire target population. People from different cultures may describe their signs and symptoms of a disease or condition differently and/or may have different values and preferences.

Literacy and health literacy

- Include persons with all levels of reading, writing, problem solving abilities to the extent possible. Also consider person's speaking ability.

Clinical characteristics

- Range of severity of disease or condition
- Range of symptoms and/or functional impacts experienced (especially for those diseases or conditions with symptom heterogeneity, such as migraines and some rare diseases)
- Range of comorbidities
- Range of physical and cognitive abilities

Patient-Focused Drug Development: Collecting Comprehensive and Representative Input https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-collecting-comprehensive-and-representative-input

PATIENT ADVOCACY SAMPLES

Tend to include patients:

- With higher socio-economic backgrounds and graduate educations
- Are younger, and healthier
- Live in cities, are predominately female and Whites are over-represented

These factors should be weighed against what the demographics look like within the specific disease area

PROBLEM

- Use a one size fits all approach in our outreach to patients to participate in our PFDD studies
- When researchers invite patients, it isn't always clear to the patient why their particular voice is important
- Don't always involve patients in development of outreach materials
- IRB requires non-coercive language, not the same language for everyone

LESSONS FROM PUBLIC HEALTH CAMPAIGNS

Market research has told advertisers that, generally speaking, women respond to emotions whereas men will respond to functionality and reputation

CASE STUDY – Smoking Cessation

Men were more likely to conduct smoking cessation searches when exposed to advertisements containing empowering content;
Women were more influenced by ads emphasizing health effects of smoking

CONCERN: how we influence health behaviors differs for different groups

TAKEAWAY: Researchers cannot rely on a one size fits all approach & should involve patients in developing outreach materials

Yom-Tov et al. *J Med Internet Res*. 2016;18(11):e306. doi:10.2196/jmir.6563

TO CONCLUDE…

"You should examine previously conducted studies and other relevant research literature and consult subject matter experts (e.g., clinicians, social scientists, patients, advocates, caregivers) to help determine the most appropriate question…"[1]

And I would add that when you include patients on your advisory group, also include them in reviewing outreach materials to ensure potential participants understand the value they bring to this work

1. Patient-Focused Drug Development: Collecting Comprehensive and Representative Input https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-collecting-comprehensive-and-representative-input

U.S. FOOD & DRUG ADMINISTRATION

Clinical Regulatory Perspective

Erica Lyons, MD, FAAP
Division of Gastroenterology, OND
Center for Drug Evaluation and Research

Implementation and Impact of PFDD: A Clinical Regulatory Perspective

Erica Lyons, MD

Associate Director for Therapeutic Review

Division of Gastroenterology (DG)

U.S. Food and Drug Administration (FDA)

Center for Drug Evaluation and Research (CDER)

Office of New Drugs (OND)

Office of Immunology and Inflammation (OII)

PFDD Meeting #1

Using Methods from PFDD Guidance 1 and Guidance 2 as Tools for Including Patient Experience Data in Clinical Trials:

Who to Ask and How to Ask

June 30, 2022

Disclosure Statement

- No conflicts of interest
- Nothing to disclose
- This talk reflects the views of the author and, unless otherwise noted, should not be construed to represent FDA's views or policies
- In this talk "drug" refers to both drugs and biologics

Thank you from the FDA and the Division of Gastroenterology

FDA Use of Patient Experience Data

- As required by the 21st Century Cures Act, FDA conducts regular assessments of its use of patient experience data in regulatory decision making

- On June 18, 2021, Eastern Research Group, Inc. published the initial report - *FDA Assessment of Use of Patient Experience Data in Regulatory Decision Making*, which included:
  - 1169 NDAs, BLAs, and efficacy supplements from June 2017 to June 2020
  - 176 applications for NMEs (68% described patient experience data)

Assessment of the Use of Patient Experience Data in Regulatory Decision-Making | FDA

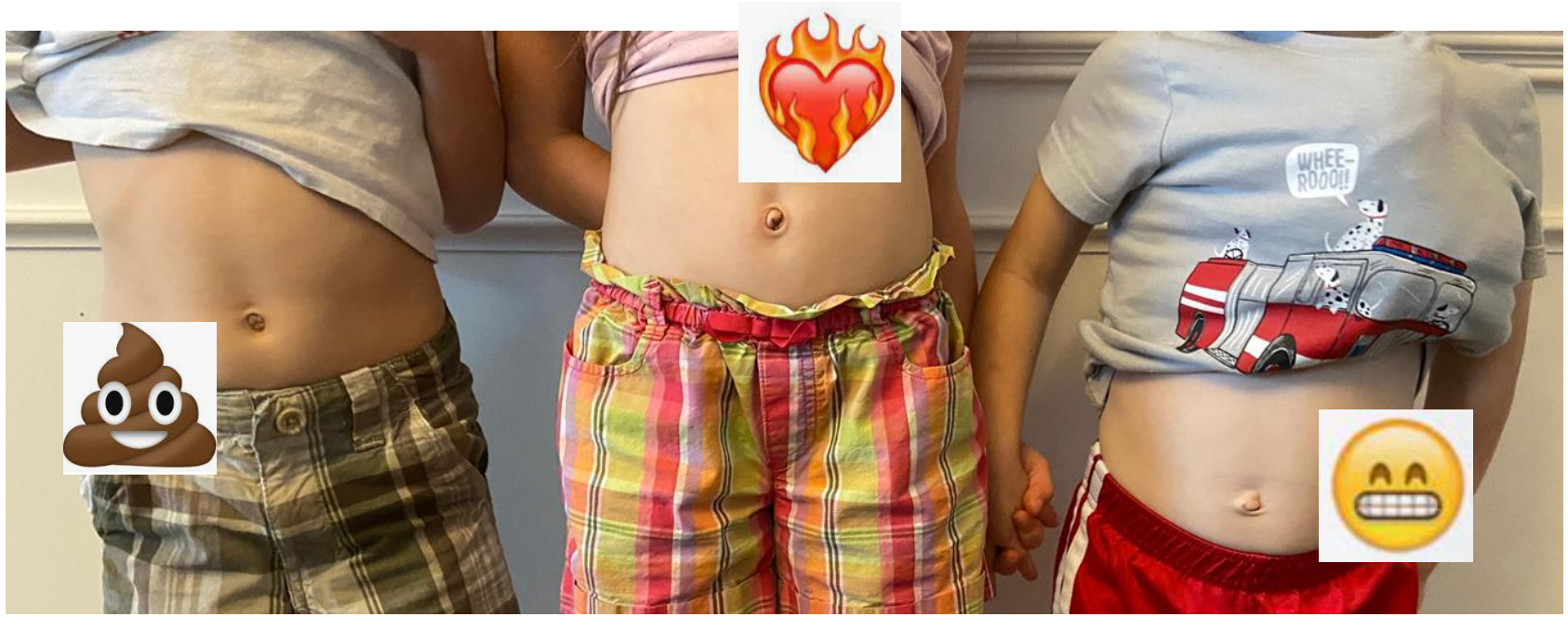
Types of Patient Experience Data in FDA Reviews

Metric	FDA Reviews that Contain PED for Approved NME NDAs and BLAs (n=120)
Of FDA reviews that mention patient experience data, percent that mention data from **applicants**	97%
• PRO	84%
• ClinRO	33%
• PerfO	9%
• ObsRO	7%
• Patient preference study	3%
Of FDA reviews that mention patient experience data, percent that mention data from **other sources**	11%
• PFDD meetings	4%
• Natural history study	3%

PED = Patient Experience Data. PRO = Patient-Reported Outcome. ClinRO = Clinician-Reported Outcome. PerfO = Performance Outcome. ObsRO = Observer-Reported Outcome.

[Assessment of the Use of Patient Experience Data in Regulatory Decision-Making | FDA]

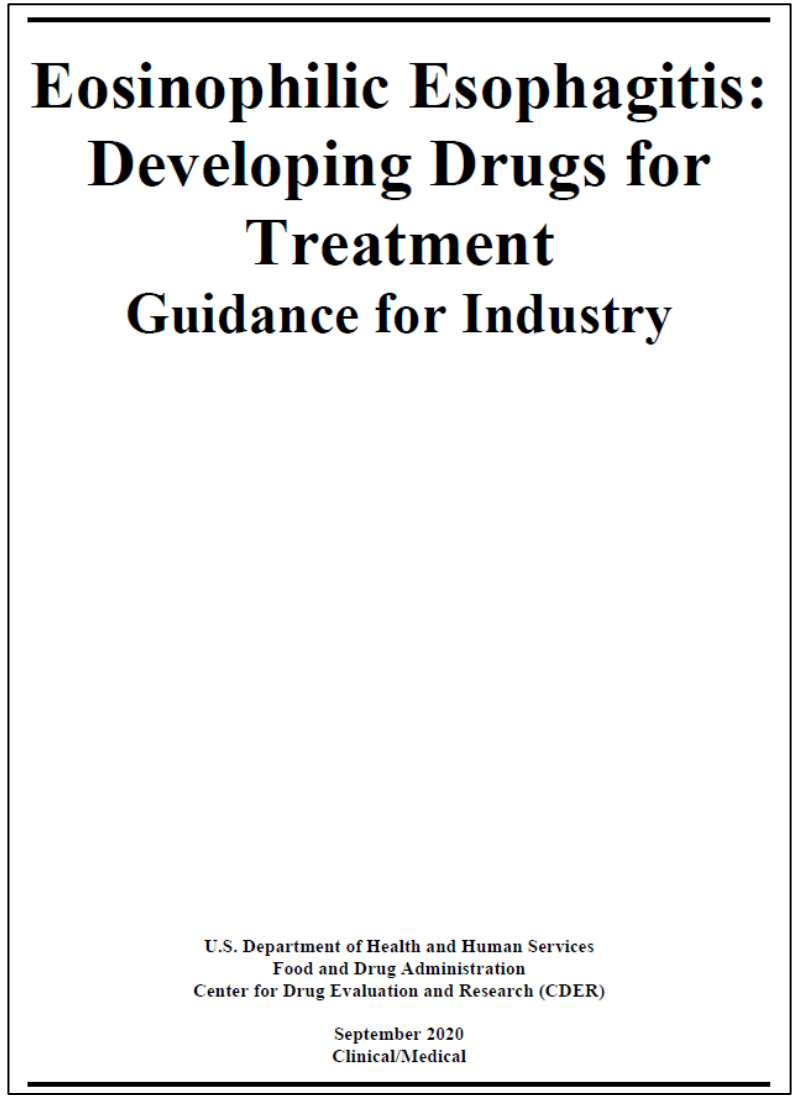
Why are PROs Commonly Used in GI?



- In many GI disorders, patients commonly experience symptoms that have substantial impact
- Outcomes such as irreversible morbidity or mortality occur infrequently and are not practical to assess

Additional Disclosure: Patient models for common GI symptoms were compensated with M&Ms for their participation and contribution.

Recent FDA Guidance from Gastroenterology

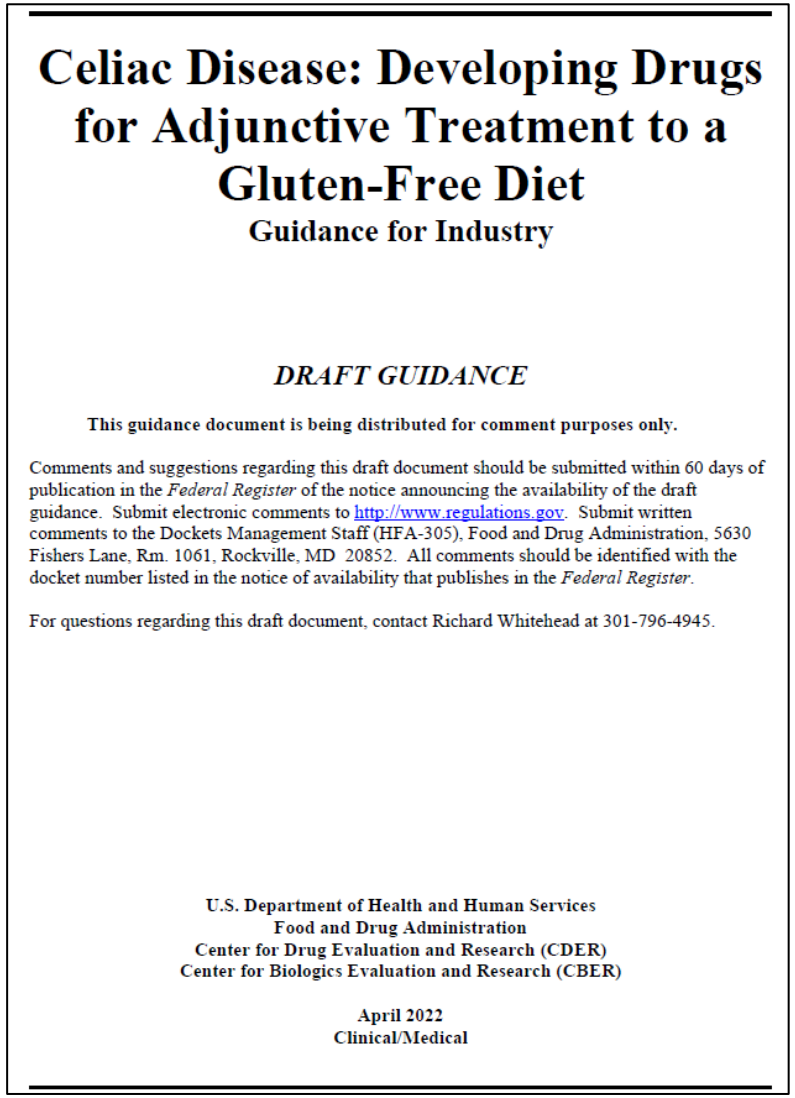


Eosinophilic Esophagitis: Developing Drugs for Treatment

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

September 2020
Clinical/Medical



Celiac Disease: Developing Drugs for Adjunctive Treatment to a Gluten-Free Diet

Guidance for Industry

DRAFT GUIDANCE

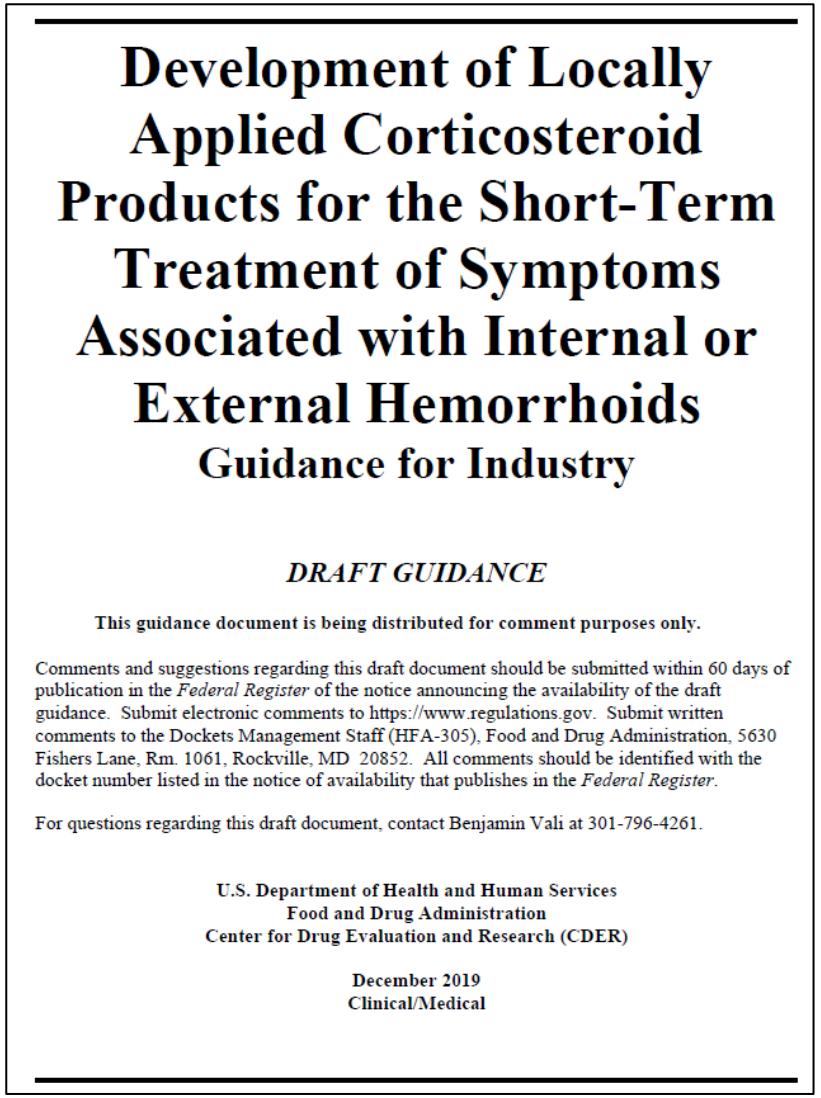
This guidance document is being distributed for comment purposes only.

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 http://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 Richard Whitehead at 301-796-4945.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2022
Clinical/Medical



Development of Locally Applied Corticosteroid Products for the Short-Term Treatment of Symptoms Associated with Internal or External Hemorrhoids

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*.

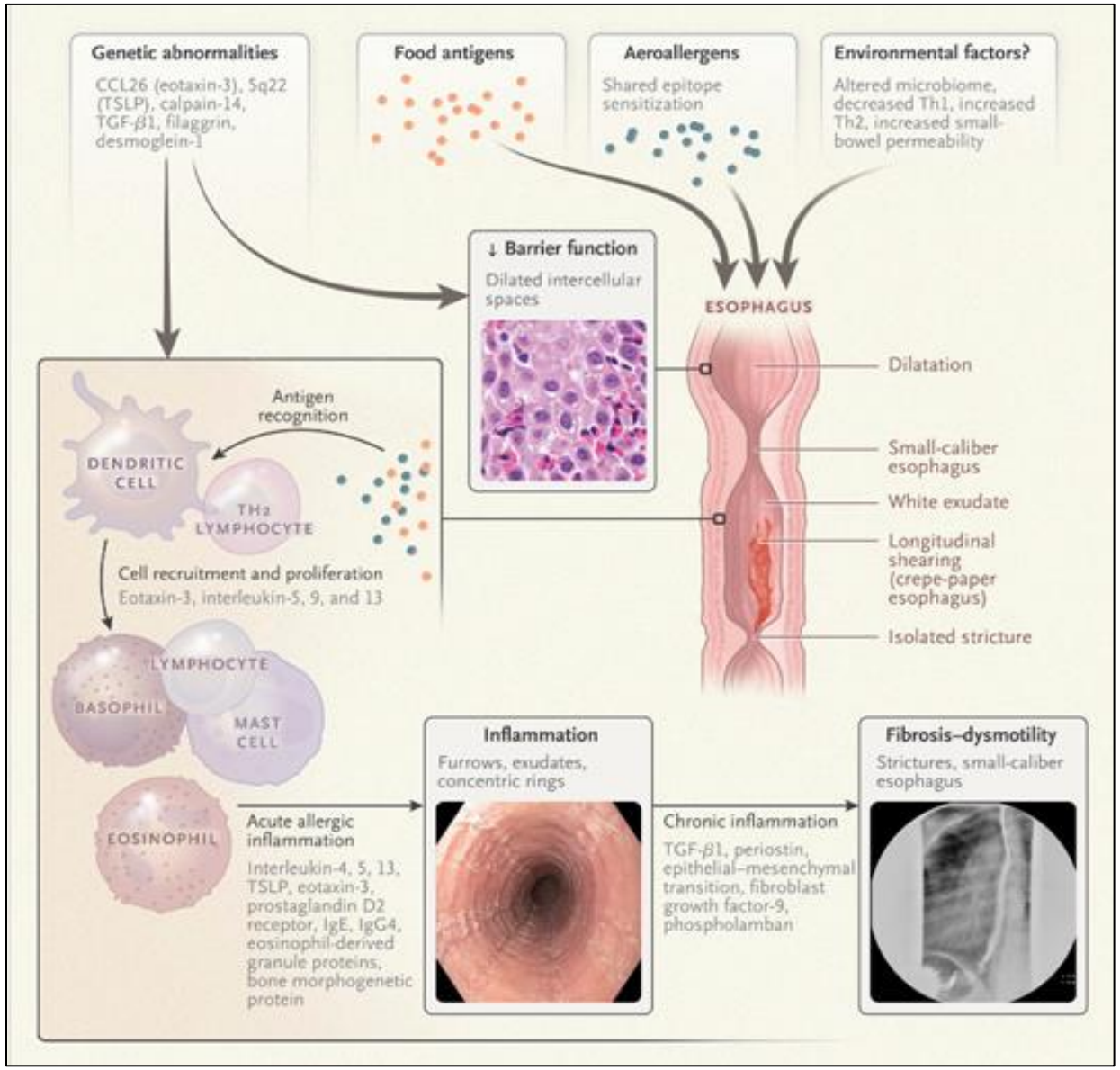
For questions regarding this draft document, contact Benjamin Vali at 301-796-4261.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2019
Clinical/Medical

We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

Background: Eosinophilic Esophagitis (EoE)

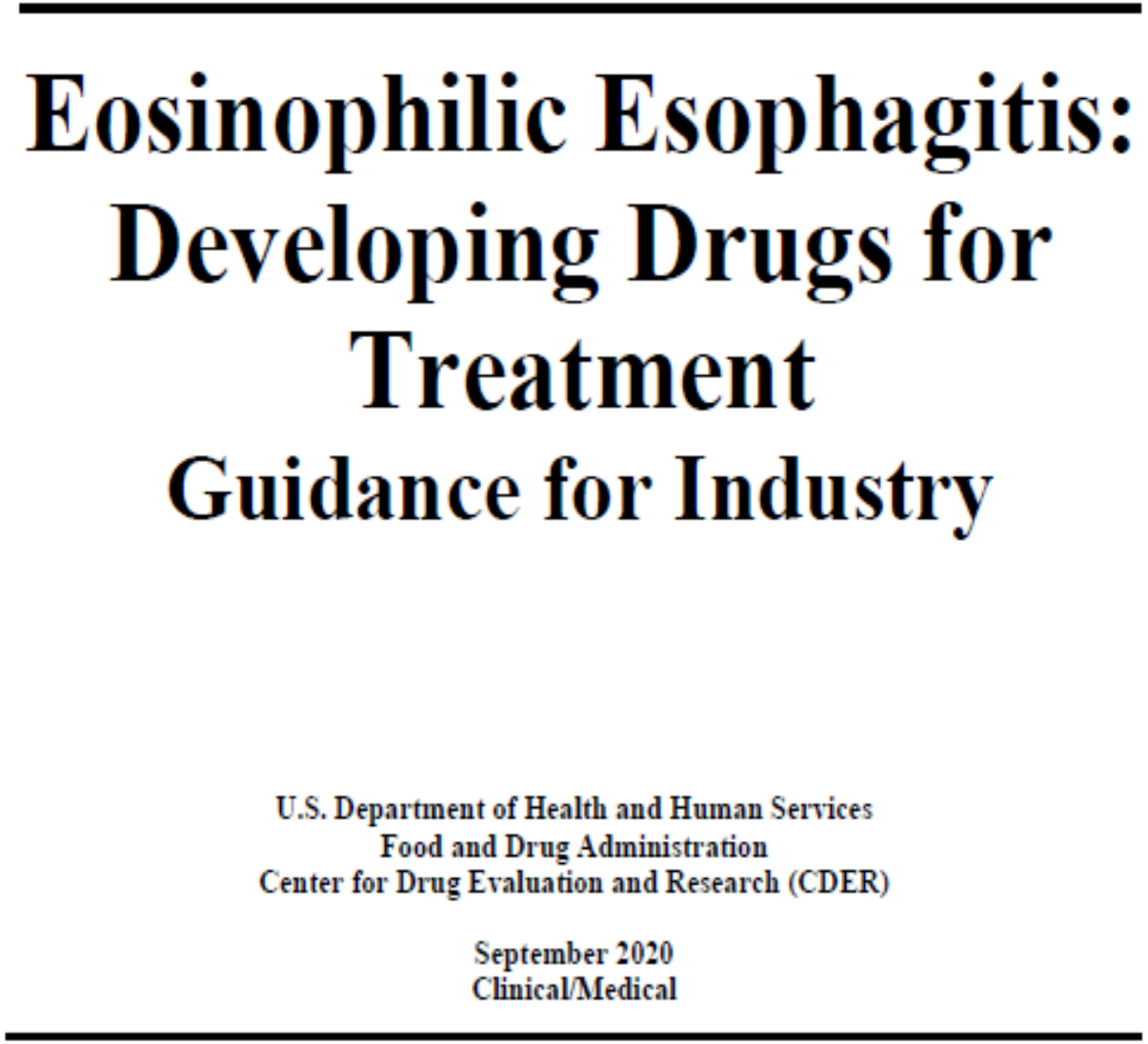


Furuta, G and Katzka, D . Eosinophilic Esophagitis. N Engl J Med 2015; 373:1640-1648, October 22, 2015. DOI: 10.1056/NEJMra1502863

- By current estimates, EoE affects somewhere between 1-2/2000 people
  - (prevalence of 0.5-1 cases per 1000 persons[1])
- ~166,000 – 332,000 children and adults in the US with EoE[2]

1- Dellon ES, Jensen ET, Martin CF, Shaheen NJ, Kappelman MD. Prevalence of eosinophilic esophagitis in the United States. Clin Gastroenterol Hepatol. 2014 Apr;12(4):589-96.e1. doi: 10.1016/j.cgh.2013.09.008. Epub 2013 Sep 11. PMID: 24035773; PMCID: PMC3952040.

2- United States Census Bureau, Population Clock. The US population was 332,825,548 on June 27, 2022.



Coprimary Endpoints

- Assess significant improvement from baseline in signs and symptoms, compared to placebo, using a well-defined and reliable clinical outcome assessment (COA) instrument
  - Clinically meaningful effect that is considered a treatment benefit by patients
- Document a histologic response of peak eosinophil per HPF of ≤ 6 across all available esophageal levels

Patient-Focused Drug Development: Collecting Comprehensive and Representative Input

Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2020
Procedural

Patient-Focused Drug Development: Methods to Identify What Is Important to Patients

Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

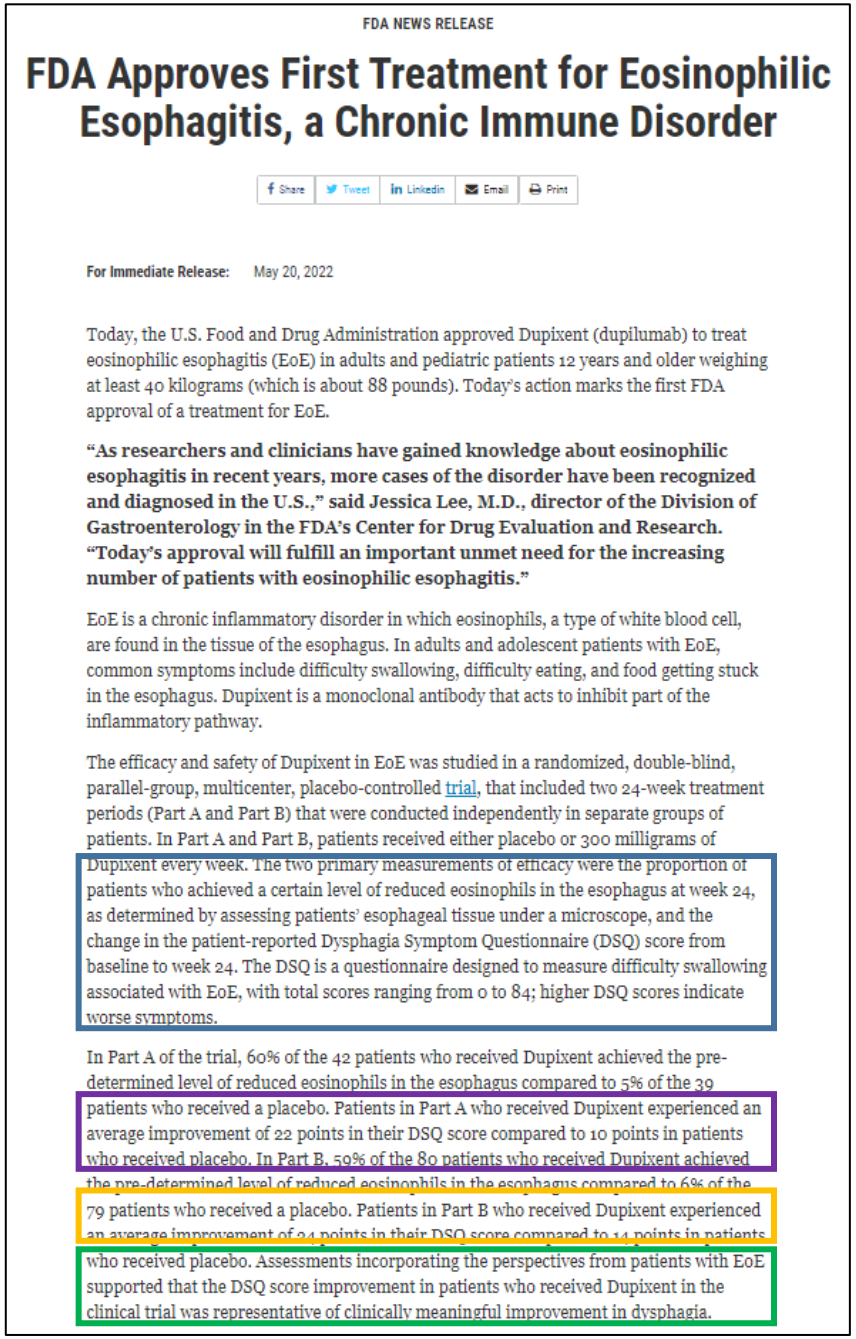
February 2022
Procedural

The two primary measurements of efficacy were the proportion of patients who achieved a certain level of reduced eosinophils in the esophagus at week 24, as determined by assessing patients' esophageal tissue under a microscope, and the change in the patient-reported Dysphagia Symptom Questionnaire (DSQ) score from baseline to week 24. The DSQ is a questionnaire designed to measure difficulty swallowing associated with EoE, with total scores ranging from 0 to 84; higher DSQ scores indicate worse symptoms.

Patients in Part A who received Dupixent experienced an average improvement of 22 points in their DSQ score compared to 10 points in patients who received placebo.

Patients in Part B who received Dupixent experienced an average improvement of 24 points in their DSQ score compared to 14 points in patients who received placebo.

Assessments incorporating the perspectives from patients with EoE supported that the DSQ score improvement in patients who received Dupixent in the clinical trial was representative of clinically meaningful improvement in dysphagia.



FDA NEWS RELEASE

FDA Approves First Treatment for Eosinophilic Esophagitis, a Chronic Immune Disorder

Share Tweet LinkedIn Email Print

For Immediate Release: May 20, 2022

Today, the U.S. Food and Drug Administration approved Dupixent (dupilumab) to treat eosinophilic esophagitis (EoE) in adults and pediatric patients 12 years and older weighing at least 40 kilograms (which is about 88 pounds). Today's action marks the first FDA approval of a treatment for EoE.

"As researchers and clinicians have gained knowledge about eosinophilic esophagitis in recent years, more cases of the disorder have been recognized and diagnosed in the U.S.," said Jessica Lee, M.D., director of the Division of Gastroenterology in the FDA's Center for Drug Evaluation and Research. "Today's approval will fulfill an important unmet need for the increasing number of patients with eosinophilic esophagitis."

EoE is a chronic inflammatory disorder in which eosinophils, a type of white blood cell, are found in the tissue of the esophagus. In adults and adolescent patients with EoE, common symptoms include difficulty swallowing, difficulty eating, and food getting stuck in the esophagus. Dupixent is a monoclonal antibody that acts to inhibit part of the inflammatory pathway.

The efficacy and safety of Dupixent in EoE was studied in a randomized, double-blind, parallel-group, multicenter, placebo-controlled trial, that included two 24-week treatment periods (Part A and Part B) that were conducted independently in separate groups of patients. In Part A and Part B, patients received either placebo or 300 milligrams of Dupixent every week. The two primary measurements of efficacy were the proportion of patients who achieved a certain level of reduced eosinophils in the esophagus at week 24, as determined by assessing patients' esophageal tissue under a microscope, and the change in the patient-reported Dysphagia Symptom Questionnaire (DSQ) score from baseline to week 24. The DSQ is a questionnaire designed to measure difficulty swallowing associated with EoE, with total scores ranging from 0 to 84; higher DSQ scores indicate worse symptoms.

In Part A of the trial, 60% of the 42 patients who received Dupixent achieved the pre-determined level of reduced eosinophils in the esophagus compared to 5% of the 39 patients who received a placebo. Patients in Part A who received Dupixent experienced an average improvement of 22 points in their DSQ score compared to 10 points in patients who received placebo. In Part B, 59% of the 80 patients who received Dupixent achieved the pre-determined level of reduced eosinophils in the esophagus compared to 6% of the 79 patients who received a placebo. Patients in Part B who received Dupixent experienced an average improvement of 24 points in their DSQ score compared to 14 points in patients who received placebo. Assessments incorporating the perspectives from patients with EoE supported that the DSQ score improvement in patients who received Dupixent in the clinical trial was representative of clinically meaningful improvement in dysphagia.

FDA News Release May 20, 2022. Available: FDA Approves First Treatment for Eosinophilic Esophagitis, a Chronic Immune Disorder | FDA

In Closing

- The implementation of Patient-Focused Drug Development has had broad impacts on the evaluation of new drugs across the FDA
- Capturing the patient voice and ensuring robust, meaningful, and representative input is a key element in clinical trial design and conduct
- Applying the principles and best practices outlined in PFDD Guidances 1 and 2 can support the identification and development of endpoints that are both clinically meaningful and feasible to assess in clinical trials


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Session 3: Question and Answer

Topics for Discussion at Meeting #2 (July 25, 2022)

The second in this series of two public meetings will take place virtually on July 25, 2022 11am-1pm ET.

Speakers and participants will discuss a range of issues data collection and analysis, focusing on lessons learned and on areas identified as particularly challenging for stakeholders.

Registration: To register for this meeting, visit: https://www.eventbrite.com/e/patient-experience-data-in-clinical-trials-lessons-learned-tickets-363026190107

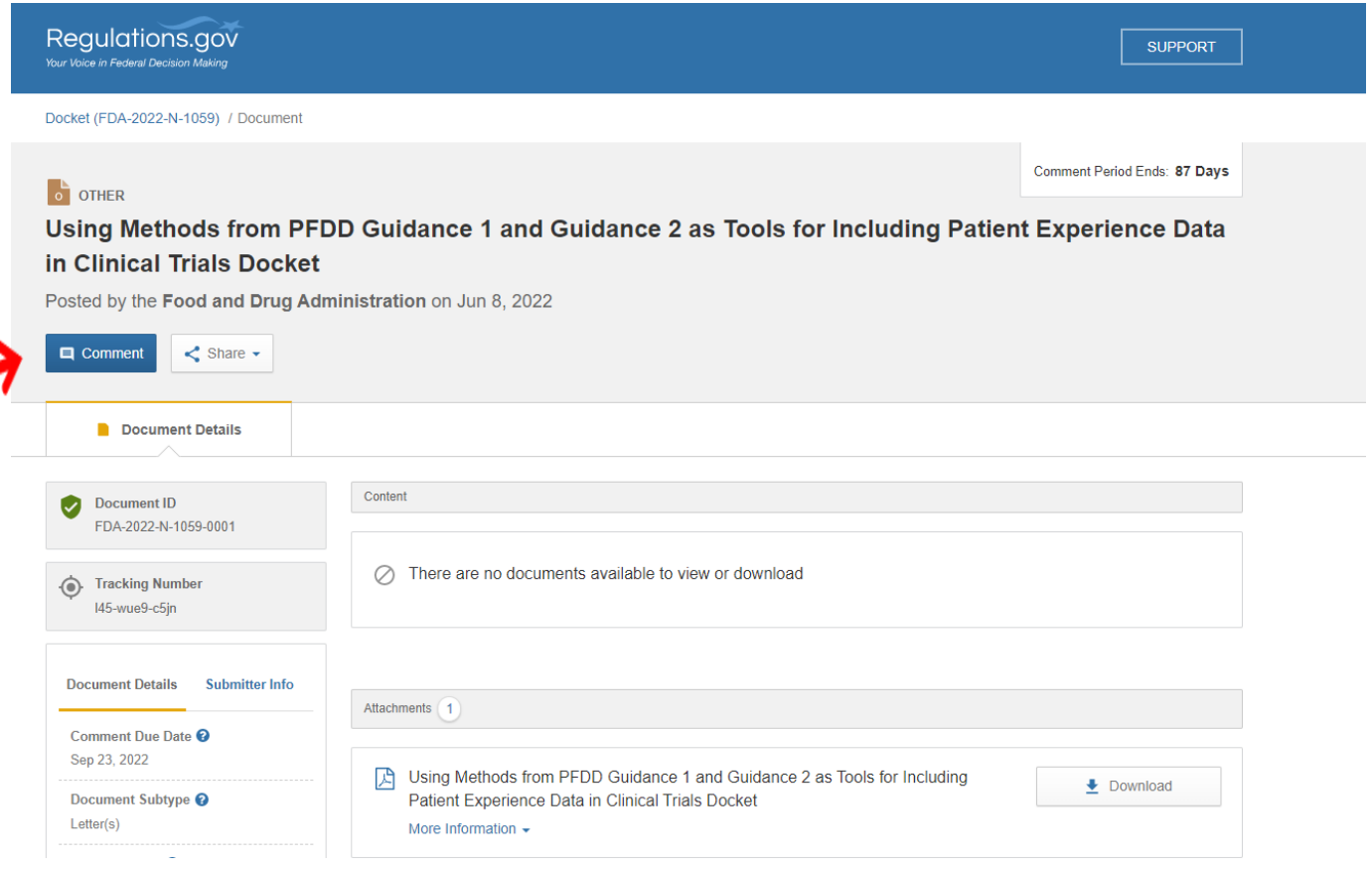
Send us your comments!

If you have examples of how you have used the PFDD Methodologic Guidance Series to advance the inclusion of the patient voice in the drug development process, please submit to the public docket for this series of meetings.

The docket will close on September 23, 2022.

How do you submit a comment?

- Please visit: https://www.regulations.gov/document/FDA-2022-N-1059-0001
- And **Click Comment**



U.S. FOOD & DRUG ADMINISTRATION

Thank you!