Insight Brief

Our Perspectives on the US FDA Patient-Focused Drug Development (PFDD) Guidance 3 and 4

Integrating patient experience data into endpoints to inform a COA endpoint strategy

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Executive Summary

The FDA is currently developing a series of four Patient-Focused Drug Development (PFDD) Guidance Documents for industry. Guidance 1 and 2 focus on ensuring that sponsors obtain robust, meaningful, and interpretable patient input to understand the experience of their disease and its treatment to inform the development of endpoint measures to assess clinical outcomes of importance in medical product development. Guidance 3 and 4 address the endpoint measurement. This document presents analyses of PFDD Guidance 3 and 4 that are currently in a discussion document format.

These discussion documents reflect the FDA's current thinking on Clinical Outcome Assessment (COA) development and endpoints. Draft guidance documents will be issued with some changes reflecting recommendations from the public workshop. The timeline for issuance of the draft guidance documents has been delayed due to the current public health emergency of COVID-19.

Generating patient experience data from clinical trials for regulatory review is not a new practice. The FDA PRO Guidance (2009) outlined the rigor used by regulators to review and evaluate existing, modified, or newly created PROs to support label claims. Sponsors commonly integrate outcome assessments into clinical trials, generate conceptual disease models, and develop clinical endpoints to capture treatment effect. PFDD Guidance 1 and 2 offer an opportunity to broaden the scope (beyond endpoint development), broaden research methods (beyond qualitative work), and provide guidance for how to do this in a scientifically rigorous way by selecting the right patients from whom to collect information and choosing a suitable method for answering clear research questions. IQVIA has provided an insight brief on PFDD Guidance 1 and 2.[1]

PFDD Guidance 3 and 4 build on this robust patient experience information by integrating it into clinical development. Understanding what is important to patients, the guidance series now moves to COAs and their adequacy to measure those essential concepts in a clinical trial. And further, to endpoint development and how COA information can be used to inform regulatory decision-making.

1 https://www.iqvia.com/solutions/research-and-development/consulting/patient-centered-endpoints

BACKGROUND

Patient-Focused Drug Development (PFDD) is defined by the FDA as a systematic approach to ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation.

An essential PFDD effort to develop a series of four methodological guidance documents was initiated in December 2016 following the 21st Century Cures Act.

This act mandated that the FDA issue draft and final versions of one or more guidance documents over five years regarding collection of the patient experience data, and the use of such data and related information in drug development (Title III Section 3002). The act included strict timelines where a plan was due within 180 days of signing the act and at least one guidance final within 18 months. FDA responded by outlining the PFDD Guidance series and planned timelines as summarized in Table 1 below.

Table 1: Summary of PFDD Guidance Timelines

GUIDANCE TITLE	PUBLIC WORKSHOP DATE	DRAFT DATES	FINAL DATES
PFDD-1: Collecting Comprehensive and Representative Input	12/18/17	6/13/18	June 2020
PFDD-2: Methods to Identify What is Important to Patients	10/15/18	10/1/19	Q1 2021
PFDD-3: Selecting, Developing or Modifying Fit-for-Purpose Clinical Outcomes Assessments	10/16/18	Q2 2020*	Q4 2021
PFDD-4: Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision-making	12/6/19	Q2 2020*	Q4 2021

* Delayed due to COVID-19

Patient-Focused Drug Development (PFDD) is defined by the FDA as a systematic approach to help ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation.

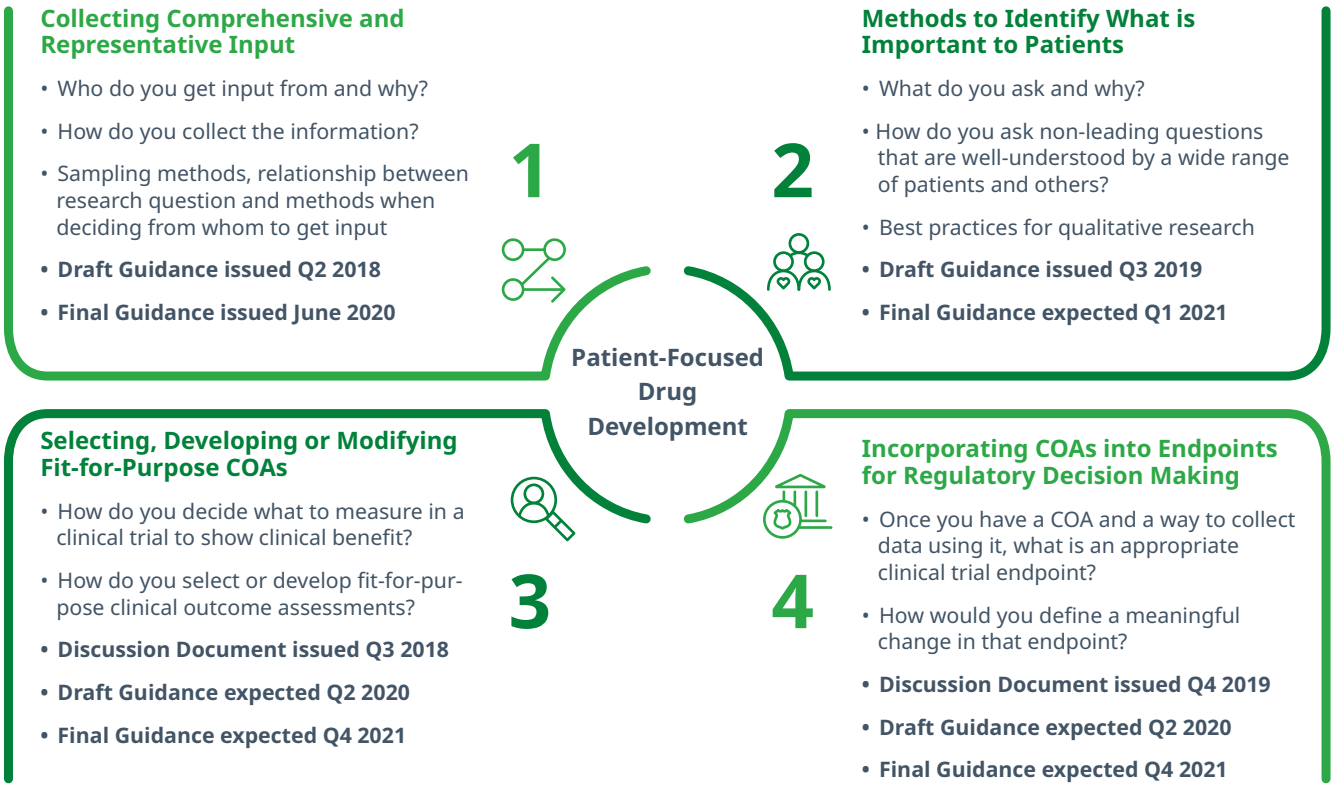
PFDD GUIDANCE SERIES OVERVIEW

The PFDD guidance series is meant to address in a stepwise manner how stakeholders can collect and submit patient experience data and other relevant information from patients and caregivers for medical product development and regulatory decision-making.

Figure 1 below briefly summarizes each guidance with the question it seeks to answer and how each question is addressed and timelines for publishing the draft and final versions. Draft guidance for PFDD-1 was released in June 2018 and finalized in June 2020. Draft guidance for PFDD-2 was released in October 2019, and draft guidance for PFDD 3 and 4 was expected Q2 2020.As mentioned above, issuance of draft PFDD-3 and -4 has been delayed due to the COVID-19 pandemic and the updated timelines are not currently available.

While the focus of this insight brief is on the recently developed PFDD Guidance Series, it's important to note that these guidance documents do not supersede the 2009 PRO Guidance (Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims). The PRO guidance is foundational and focused specifically on the use of PRO instruments to support labeling claims. This is clearly still very relevant for the industry, however the PFDD series has a broader scope of not just the strict standards for claims but a shift to patient experience data that comes from many sources and has applications in drug development, in addition to claims, specifically for the regulatory purpose of benefit-risk assessments.

Figure 1: PFDD Guidance Series Overview



PFDD Guidance 3 – Select, Develop or Modify Fit-For-Purpose Clinical Outcome Assessments

OVERVIEW AND SUMMARY OF NEW INFORMATION

The third guidance in the series is an FDA issued discussion document used for a public meeting held on October 16, 2018. The following information is based on our read of the current material with the understanding that this information may be refined or changed with the issuance of the draft guidance.

PFDD-3 builds on the prior two PFDD guidances and seeks to identify how we select, develop, or modify a fit-for-purpose COA for clinical trials. This guidance seeks to answer the questions: *How do you decide what to measure in a clinical trial to show clinical benefit?* and *How do you select or develop fit-for-purpose clinical outcome assessments?* The guidance answers these questions with methods to identify what matters most to patients regarding burden of disease and burden of treatment to guide medical product development.

Figure 2 on page 7 presents the roadmap for how to select or develop COAs for clinical trials from PFDD-3. Each concept is described in detail in the body of the guidance. The topics described in Step 1 of the roadmap in Figure 2 were covered in detail in PFDD Guidance 1 and 2, but PFDD Guidance 3 narrows the focus from patient experience data intended for a broad range of purposes to a single focus of the development of a COA measurement strategy for the purpose of clinical trial use.

PFDD-3 builds on the prior two PFDD guidances and seeks to identify how we select, develop, or modify a fit-for-purpose COA for clinical trials.

Figure 2: Roadmap to COA Selection/Development for Clinical Trials

STEP 1
Understanding the Disease or Condition

A. Natural history of the disease or condition:
- Onset/Duration/Resolution
- Diagnosis
- Pathophysiology
- Range of manifestations

B. Patient subpopulations:
- By severity
- By onset
- By comorbidities
- By phenotype

C. Current Clinical Practice(s):
- Clinical care standards
- Treatment alternatives
- Health care system (e.g. access to care)

D. Patient/caregiver/expert perspectives:
- Definition of clinical benefit
- Benefit-risk tradeoffs
- Impact of disease

STEP 2
Conceptualizing Clinical Benefit

A. Identify concept(s) of interest for meaningful clinical benefit, i.e., How a patient:
- Survives
- Feel (e.g. symptoms)
- Functions

B. Define context of use for clinical trials, for example:
- Disease/Condition entry criteria
- Clinical trial design
- Endpoint definition
- Endpoint positioning

STEP 3
Selecting/Developing/Modifying the Outcome Measure

A. Select clinical outcome assessment (COA) type:
- Patient-Reported Outcome (PRO)
- Observer-Reported Outcome (ObsRO)
- Clinician-Reported Outcome (ClinRO)
- Performance Outcome (PerfO)

B. Search for a COA measuring the concept of interest in context of use:
- COA exists and is fit-for-purpose
- COA exists but needs to be modified
- COA under development
- No COA exists (development needed)

C. Develop and Evaluate a COA:
- Content validity
- Reliability and construct validity
- Ability to detect change
- Interpretation of meaningful within-patient change

ENGAGE FDA EARLY AND THROUGHOUT MEDICAL PRODUCT DEVELOPMENT

https://www.fda.gov/media/116277/download

Key topics from the PFDD-3 discussion document and the roadmap outlined in Figure 2 on page 7 where FDA has provided new directions for industry are summarized in Table 2 below.

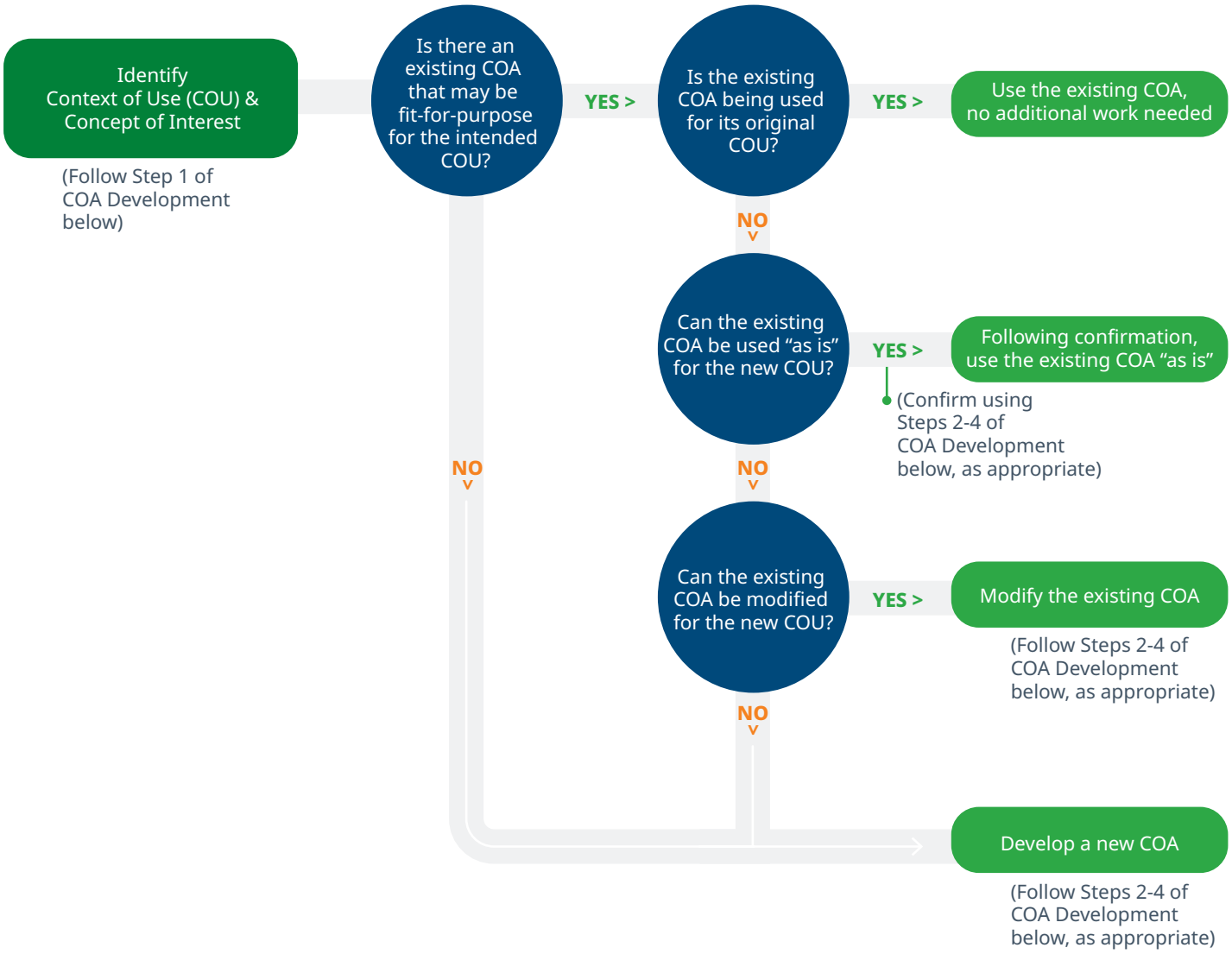
Table 2: New Directions from PFDD-3 on COA Selection/Development for Clinical Trials

TOPIC	DETAIL
General	PFDD-3 is distinct from the 2009 PRO guidance in expansion of the scope to include all COAs instead of strictly PROs. This expansion is vital to leverage emerging technologies and integrate best practices for any patient population. COAs are defined in the glossary as follows ***Clinical Outcome Assessment:*** *Assessment of a clinical outcome can be made through a report by a clinician, a patient, a non-clinician observer, or through a performance-based assessment. Types of COAs include patient-reported outcomes, clinician-reported outcome measures, observer-reported outcome, and performance outcome*
General	PFDD-3 is additionally distinct from the 2009 PRO guidance in the expansion of scope beyond labeling. FDA continues to emphasize the importance of COA data even in the absence of labeling, as evidenced in the following quote: *FDA generally reviews COA data as part of the totality of evidence to inform benefit-risk assessment, whether labeling claims are granted. Therefore, no single outcome assessment is sufficient on its own to provide the whole picture of the impact of disease and treatment on patients. (Lines 317-321)*
Understanding the Disease or Condition *Natural History*	Natural history information that is useful for the development of COA measurement strategy necessitates understanding the clinical course of the disease, including onset, duration, clinical presentation, and disease behavior, trajectory, adaptations, and subgroups
Understanding the Disease or Condition *Patient Subpopulations*	Information on patient subpopulations can be used to identify different stages that might be more measurable with a COA or taken into consideration for expected variations in experiences when selecting COAs
Understanding the Disease or Condition *Current Clinical Practice*	Clinical trial entry criteria, design, and outcome measurement can be influenced by current clinical practice and is useful to understand when developing COA strategy
Understanding the Disease or Condition *Patient/Caregiver/ Expert Perspectives*	Information from multiple streams can provide comprehensive insights into aspects of the disease and inform a COA selection. The importance of obtaining patient experience data that is representative and the methodological approaches to sampling the target population and gaining relevant, objective, and accurate perspectives are detailed in PFDD-1 and PFDD-2.

(continued on page 9)

TOPIC	DETAIL
Conceptualizing Clinical Benefit *Identify Concepts*	Concepts of Interest are critical for conceptualizing clinical benefit (how an individual feels, functions, or survives) • COAs should include clinically important concepts that define the disease and/or impacts of the disease • COAs can also be used to measure concepts related to treatment (safety, tolerability, or burden) • Variables that inform concepts of interest: – Patient input – Disease natural history – Aspect of the condition the treatment can modify – Targeted labeling
Concepts of Interest *Disease-related*	FDA recommends measuring at minimum the core disease-related concepts (e.g., signs and symptoms). When measuring impacts, FDA recommends targeting disease impacts that result from core disease-related concepts
Concepts of Interest *Treatment-related*	COAs may measure concepts related to treatment if the concepts represent symptoms or signs that can be reported by patients, caregivers or clinicians. When assessing treatment safety, tolerability, or burden with a PRO, FDA recommends that topics be selected in an unbiased manner, sponsors must provide a strong rationale supported by clinical and nonclinical data and capture symptomatic AEs separately from disease-related symptoms where possible
Conceptualizing Clinical Benefit *Define Context of Use*	Context of Use is critical for conceptualizing clinical benefit (how an individual feels, functions or survives) • Must be clearly defined in order to select COA • Variables that determine the context of use include: – Disease definition – Target population – Clinical practice and trial setting – Endpoint positioning
Selecting/Developing/ Modifying the Outcome Measure *COA Type*	COA type (PRO, ClinRO, ObsRO or PerfO) determination is dependent on the targeted concepts, context of use and planned trial endpoints. Additionally, the observability of the concept should be considered. Detailed information on considerations for when ObsRO and proxy reports may be considered, and evaluation strategies are provided (PFDD-3 Appendix 5)
Selecting/Developing/ Modifying the Outcome Measure *Search for COA measuring concept in context*	FDA recommends consideration of the topics in Figure 2 on page 7 of this document, starting early, and considering the following factors when searching for a COA: • Availability of existing instruments • Adequacy of COA A process flow chart outlining a decision tree for determining whether to use an existing instrument, modify an instrument or develop a new instrument as well as the iterative process of COA development is provided. This thinking is not new but the presentation is and is provided as Figure 3 on page 10 of this document
Selecting/Developing/ Modifying the Outcome Measure *Develop and Evaluate a COA*	An existing COA may be used in the following ways: • 'As is' for the intended population and context of use for which it was developed • 'As is' for a new context of use • Modified for a new context of use In all cases FDA will evaluate the measurement properties

Figure 3: Process to Select, Develop or Modify a COA



STEPS OF COA DEVELOPMENT (ITERATIVE)

STEP 1 **Identify Context of Use & Concept of Interest**	STEP 2 **Select or Draft COA & Evaluate Content Validity**	STEP 3 **Cross-Sectional Evaluation of Other Measurement Properties**	STEP 4 **Longitudinal Evaluation of Measurement Properties and Score Interpretation**
• Outline hypothesized concepts and potential claims • Determine intended population • Determine intended application/ characteristics (type of scores, mode and frequency of administration) • Perform literature/expert review • Develop hypothesized conceptual framework • Position COA within a preliminary endpoint hierarchy • Plan for multinational use and cultural adaptation, if applicable • Document context of use and concept of interest	• Obtain patient/caregiver/ expert input • Generate new forms • Select recall period, response options and format (as appropriate) • Select model/method of administration/data collection • Translatability assessment and assessment of cross-cultural relevance • Conduct cognitive interviewing • Pilot test draft COA • Finalize COA content format • Develop preliminary scoring algorithm • Document content validity	• Assess score reliability (e.g. test-retest or inter-rater) and construct validity • Confirm scoring algorithm • Establish administration procedures and training materials • Prepare user manual • Document cross-sectional evaluations	• Confirm measurement properties • Assess ability to detect change • Provide guidelines for score interpretation including meaningful within-patient change • Update user manual • Document all results

https://www.fda.gov/media/116277/download

The PFDD-3 discussion document incorporates detailed information on the evaluation of a COA and represents updated thinking on some material that is currently in the PRO guidance. The characteristics for evaluation of a COA fall into 3 general categories: (1) conceptual framework of the instrument, (2) evidence of content validity, and (3) evidence of other measurement properties. Additionally, an appendix with the information on a COA that should be provided to FDA for review is included. The differences between the topics in PFDD-3 Appendix 1 and the 2009 PRO guidance Appendix are minor:

- Replacement of targeted claims and endpoint model sections with a section specific to context of use
- Expansion on measurement properties specifically with planned psychometric analyses

PFDD-3 then moves to a discussion of clinical trial design and special populations. New directions for industry on these topics are summarized in Table 3 below.

Table 3: New Directions from PFDD-3 on Consideration for Clinical Trial Design and Special Populations

	SECTION	TOPIC	DETAIL
1	VII B	**Blinding**	FDA restates the concerns for overestimation of effect in unblinded trials but adds a recognition that it may not be feasible to blind all trials, and the limitation will need to be overcome by demonstrating substantial clinically meaningful effect. Additionally, it is noted that the size of the effect and association between the COA and other clinically meaningful measures are used when interpreting results.
2	VII F	**Electronic Administration**	Advantages to implementing eCOA over paper are detailed, examples of eCOA subtypes are presented and validation and data-related regulatory considerations are provided.
3	VII F	**Paper-electronic migration and equivalence**	Guidance on migration of paper to electronic format is provided with clarity that equivalence testing is not required in all cases but is dependent on the magnitude of changes and the extent to which it alters the interpretability of the instrument items and/or response options
4	IX	**Special Patient Population Considerations**	Specific considerations for rare disease, pediatric, and cognitively impaired or non-verbal patients are provided. Of interest for rare disease is statement that traditional COA development may not be feasible but FDA is flexible and open to other approaches.

The characteristics for evaluation of a COA fall into 3 general categories: (1) conceptual framework of the instrument, (2) evidence of content validity, and (3) evidence of other measurement properties.

IQVIA PCE DISCUSSION

The PFDD-3 discussion document differs from PFDD Guidance 1 and 2 by presenting updated thinking on topics also described in the 2009 PRO Guidance. The scope is much broader, and the tone is flexible, open to technological innovation, and concise in incorporating of the concept of context of use. The scope is expanded in the application to all COAs (not just PROs), patient experience data utility beyond labeling and openness to integrating technologies that may include digital health technologies. PFDD-3 is intended to inform a COA measurement strategy using appropriate instruments and moves through a description of fit-for-purpose requirements to clinical study design and data analysis. The encouragement of sponsors to incorporate electronic formats for eCOA is clear and stands in stark contrast to the "Specific Concerns when using electronic PRO instruments" section of the 2009 PRO guidance. "Context of use" is not a new concept, but the updated explanation is useful when considering using or modifying existing COAs, which was not previously explored.

The development of PFDD-3 in the context of the mandate from the 21st Century Cures Act is an important difference from the 2009 PRO guidance. The prior guidance was authored primarily by the internal FDA SEALD (Study Endpoints and Labeling Development) Team (now Division of COA (DCOA)) and was purposed to provide information on how FDA should review PRO instruments used to support claims. Although the FDA Centers endorsed it there has been inconsistency in application due to differences in adoption levels by review divisions. PFDD-3 was developed using a cross-division within CDER approach and a cross-center approach with contributions from CDER, CBER, and CDRH that also have incorporated public meetings. Upon issuance of the pending draft and final guidances, IQVIA expects broad adoption that sponsors should be prepared for. Table 4 below further discusses these topics from the IQVIA PCE review of PFDD-3 with our perspective on the biopharmaceutical industry's opportunities and challenges when considering methods for selecting, modifying or developing COAs.

Table 4: PFDD-3 Opportunities and Challenges

TOPIC	OPPORTUNITY	CHALLENGE
Incorporation of the Roadmap for COA Selection / Development for Clinical Trials	The expansion of the scope of the guidance to encompass COA strategy provides clarity on FDA thinking and an opportunity to refine current strategies and guide future programs	Programs where COA selection was based on precedent may struggle to define and resource an appropriate strategy
Expansion to development of COAs which incorporates Performance Outcomes (PerfOs)	PerfOs represent an openness from FDA to accept trial information that may incorporate digital health technologies, such as wearables	Technology and data interpretation may require development lead times due to the rapidly emerging and changing nature of the field
Encouragement to incorporate eCOA	FDA's movement to encourage technology in COA development enables firms to have more efficient data collection and streamlined operational processes	No additional challenges are noted – the computer system validation requirements are unchanged and FDA is not requiring sponsors to use eCOAs
Context of Use definition as a statement that fully and clearly describes the way the COA is to be used and the medical product development related purpose of its use	The incorporation of this clarity offers opportunity to better evaluate existing COAs	Challenges may exist for programs with shifting areas of focus

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

OVERVIEW AND SUMMARY OF NEW INFORMATION

The fourth and final guidance in the series culminates to endpoint definition for a regulatory audience. This guidance seeks to answer the questions of: *How do you incorporate a given COA tool or set of measures into a defined clinical study endpoint?* and *How would you define a meaningful change in that endpoint?* The current PFDD-4 discussion guide answers the question of incorporation by laying out a framework (the "estimand framework") that aims to align the clinical study objective with the study design, endpoint, and analysis. The guide then moves to a description of methods to aid in interpretation of results to evaluate what constitutes meaningful change in the context of determining clinical benefit from the patient perspective.

Consistent with the prior guidances in the series, PFDD-4 emphasizes the fundamental importance of the COA research question but goes further to incorporate the ICH E9(R1) definition of an estimand and place it in context as depicted in Figure 4. The estimand framework is described in detail in the body of the guidance and case study examples are provided in the appendices. Table 5 on page 14 incorporates directions that are new for industry regarding the estimand framework and determination of meaningful change.

Figure 4: Estimand Framework

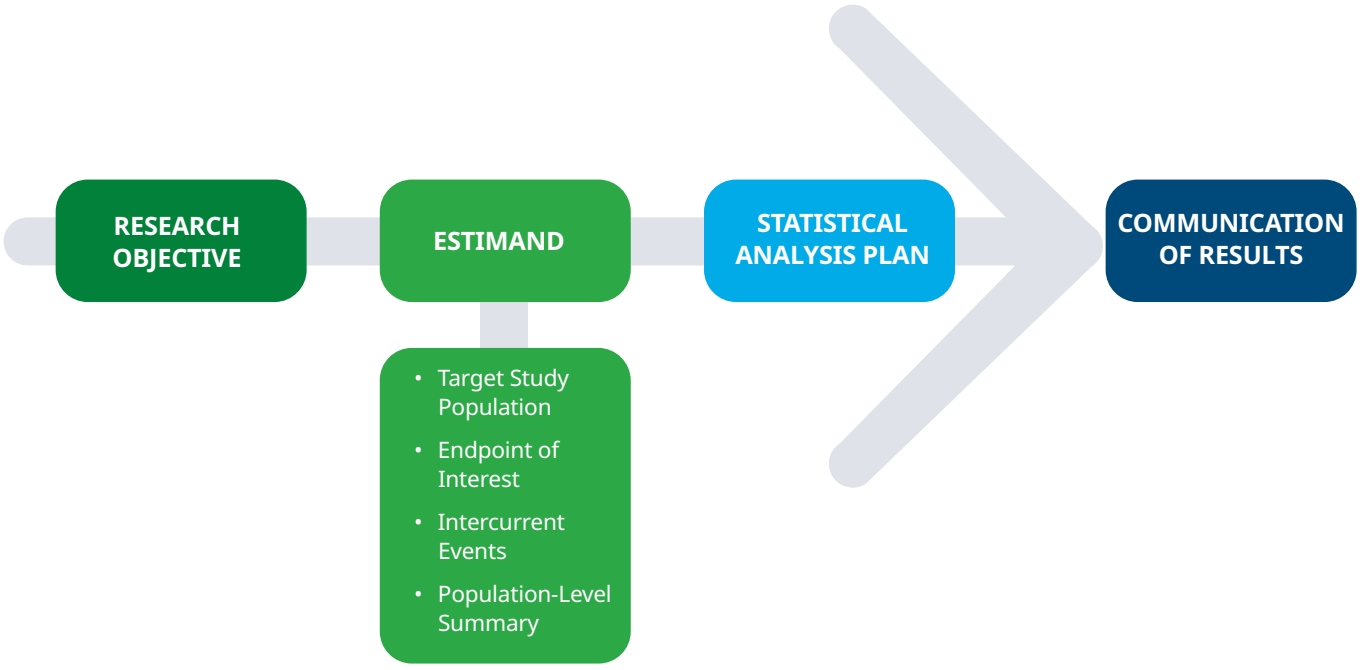


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Table 5: New Directions from PFDD-4 on Incorporation of COAs into Endpoints

	TOPIC	DETAIL
1	**Estimand Framework**	The attributes of the estimand – Target Study Population, Endpoint of Interest, Intercurrent Events and Population Level Summary – are recommended to be clearly defined **before** the protocol and included in both the protocol and SAP
2	**Estimand Framework** *COA Research Objective*	FDA recommends setting a research objective specific to COA data from clinical trials taking into account both the natural history of the disease and the treatment goal for the intended product
3	**Estimand Framework** *Target Study Population*	FDA clarifies that multiple COA analysis populations in a single trial are common and should be identified a priori in the protocol and SAP with a justification
4	**Estimand Framework** *Endpoint of Interest*	Pooling Tools and/or Concepts: FDA provides detailed guidance on construction of multicomponent, multidomain responder index (MDRI), and personalized endpoints. Considerations for pooling across reporters and delivery modes is also provided
5	**Estimand Framework** *Endpoint of Interest*	Timing of Assessments: The criticality of the timing of assessments is highlighted as vital for gaining reliable and meaningful information. FDA provides guidance to consider recall period, anticipated rate of change of the construct, administration burden, schedule with other endpoints, baseline data, anchor administration timing, consistency in order of administration and treatment administration
6	**Estimand Framework** *Intercurrent Events*	Identification and management of events that may affect the interpretation of the COA measurement are highlighted and discussed at length. FDA outlines an expectation for researchers to anticipate and put in place measures to mitigate the impact of intercurrent events but also to account for them in statistical planning. Specific examples of FDA's current thinking are provided for sample intercurrent events of: use of assistive devices, concomitant medications and other therapies, impact of disease progression and impact of treatment, practice effects, participant burden, mode of administration, missing data and event-driven COA reporting, and missing scale-level data
7	**Estimand Framework** *Population-Level Summary*	Statistical considerations for COA-based endpoints that commonly arise are briefly discussed for the topics of: landmark analysis, analysis of ordinal data, time to event analysis, responder and percent change from baseline
8	**Meaningful Within-Patient Change**	FDA is interested in interpreting study results with an understanding of what constitutes improvement or deterioration from the patient's perspective in concepts assessed by COAs. The guidance highlights that between-group differences do not address the individual within-patient change and therefore MCID and MID (which represent between-group differences) should be avoided for regulatory decisions
9	**Meaningful Within-Patient Change**	Sponsors are expected to propose appropriate thresholds that constitute clinically meaningful within-patient change for FDA review with inclusion of score interpretability for transformed scores
10	**Meaningful Within-Patient Change**	FDA recommends the use of anchor-based methods supplemented by both eCDF and PDF curves to establish a threshold for meaningful within-patient change and provides considerations for anchor measures
11	**Meaningful Within-Patient Change**	Other methods discussed by FDA for evaluating or supporting meaningfulness are emerging methods, distribution-based methods and Receiver Operator Characteristic Curve analysis
12	**Meaningful Within-Patient Change**	Additional considerations that include recommendations for COAs when planning a study and a short list of formatting and submission considerations applicable to COA data is also provided

IQVIA PCE DISCUSSION

PFDD-4 narrows the focus from collecting patient experience data for the purpose of integration of the patient voice in drug development broadly to integration of COA data from clinical trials into endpoints for the specific purpose of regulatory decision-making. This focus assumes that the COA data has been collected using fit-for-purpose COAs and that an anchor instrument has also been deployed in the clinical trial. That said, the decision-making scope is not limited to label claims as it was in the 2009 PRO Guidance but is clearly outlined as also being useful for informing the FDA's benefit-risk decisions.

The introduction of the estimand framework and emphasis on intercurrent events represent a change in regulatory expectations for sponsors. This change is specifically directed at integrating COA development and research objectives into clinical development much earlier than is typical. The expectation is to outline not only the COA endpoint but also frame it in the context of an estimand and identify issues that may impact the interpretability of COA data and the plans for management of these intercurrent events prior to clinical protocol and SAP development.

The information presented on meaningful within-patient change is additionally critical for drug developers to understand in the current environment. The 21st Century Cures Act requires the Agency to issue guidance describing how FDA anticipates incorporating relevant patient experience data and related information into the structured benefit risk assessment framework presented in Figure 5 below. This framework was developed to be flexible in supporting FDA's decision-making throughout the drug lifecycle and FDA is currently identifying strategies for incorporating patient input into this structured benefit-risk assessment. The connection to this work with understanding the patient's perspective on meaningful change is made quite clear in the following statement from the PFDD-4 discussion document: "To holistically determine what is a meaningful change, both benefit and risk, improvement and deterioration, may need to be accounted for. This document is not directly addressing this integration of benefit and risk, but the methods described can be used to help interpret benefit or risk." (Lines 600-603)

Figure 5: FDA's Benefit-Risk Framework[2]

Benefit-Risk Integrated Assessment

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk and Risk Management		

2 Benefit-Risk Assessment in Drug Regulatory Decision-Making, Draft PDUFA VI Implementation Plan (FY 2018-2022), March 30, 2018 https://www.fda.gov/files/about%20fda/published/Benefit-Risk-Assessment-in-Drug-Regulatory-Decision-Making.pdf

Table 6 discusses these expectations along with other topics from the IQVIA PCE review of PFDD-4 including our perspective on the opportunities and challenges for the biopharmaceutical industry on endpoint development using COAs.

Table 6: PFDD-4 Opportunities and Challenges

TOPIC	OPPORTUNITY	CHALLENGE
Integration of the estimand framework into clinical protocols and SAPs	Prioritization and planning of COA endpoints provides opportunity to engage thoughtfully with FDA earlier and lead to improved integration of the patient voice	Estimand development is a new way of thinking for many researchers and the early development requires sponsors to integrate cross-functional expertise that may not currently be accounted for. Additionally, changes in strategy may be more challenging to manage
Pre-definition and justification of improvement and worsening in endpoint construction	This work being pre-defined provides an opportunity for improved clarity in communication of endpoints	Limitations in number of trials and experience with new or modified COAs may limit the ability to pre-define these thresholds
Intercurrent events and missing data	The emphasis on identification and planning may lead to improved data quality and provide opportunity for FDA agreement on statistical plans for management of missing data as a part of clinical trial design	Requirement for investment of time and expertise prior to study start is typically not accounted for in clinical development programs and budgets. Additionally, routine collection of intercurrent event information may increase burden on sites and patients. (e.g., trials with a physical function endpoint would need to measure other things that could influence it positively or negatively)
Meaningful within-patient change	Opportunity to provide succinct data that supports the benefit of the product from the patient perspective	Programs with small sample sizes may have challenges with interpretation that are not well addressed in the guidance

Conclusion

INTEGRATING PATIENT EXPERIENCE DATA INTO ENDPOINTS: PFDD GUIDANCE 3 AND 4 FIT TOGETHER TO INFORM A COA ENDPOINT STRATEGY

The information provided in the PFDD series represents the current thinking of US regulators and requires sponsors to identify strategies for integration of the patient voice into their drug development programs. PFDD Guidance 3 and 4 are focused on ensuring that sponsors use the robust, meaningful, and interpretable patient experience data from PFDD Guidance 1 and 2 to inform COA selection and endpoint development. A practical COA instrument development process that incorporates PFDD-3 is provided in Figure 6 below. Similarly, Figure 7 on page 18 represents COA endpoint development and evaluation according to PFDD-4 where meaningful clinical benefit can be established and communicated to regulators.

Figure 6: COA Instrument Development Process

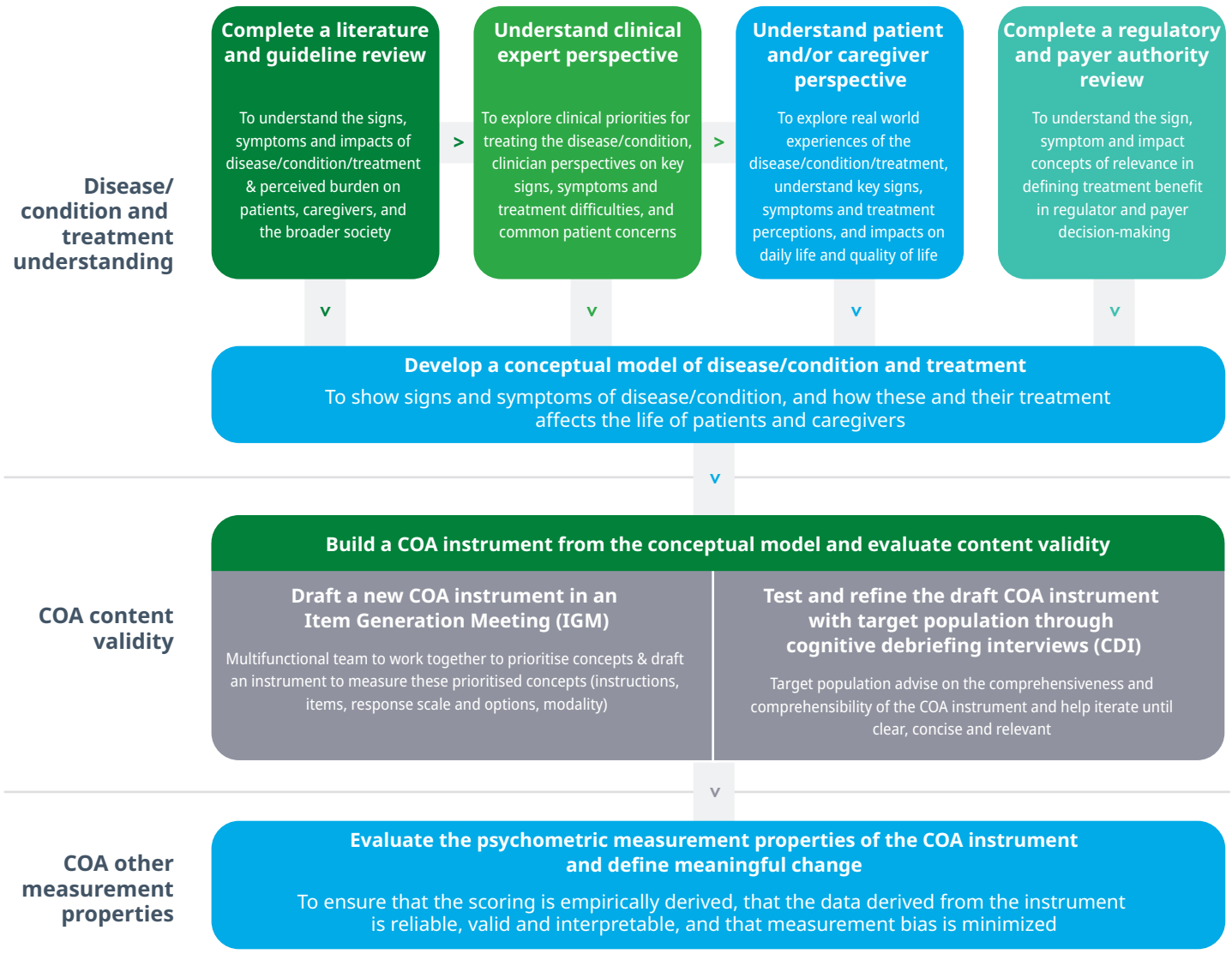
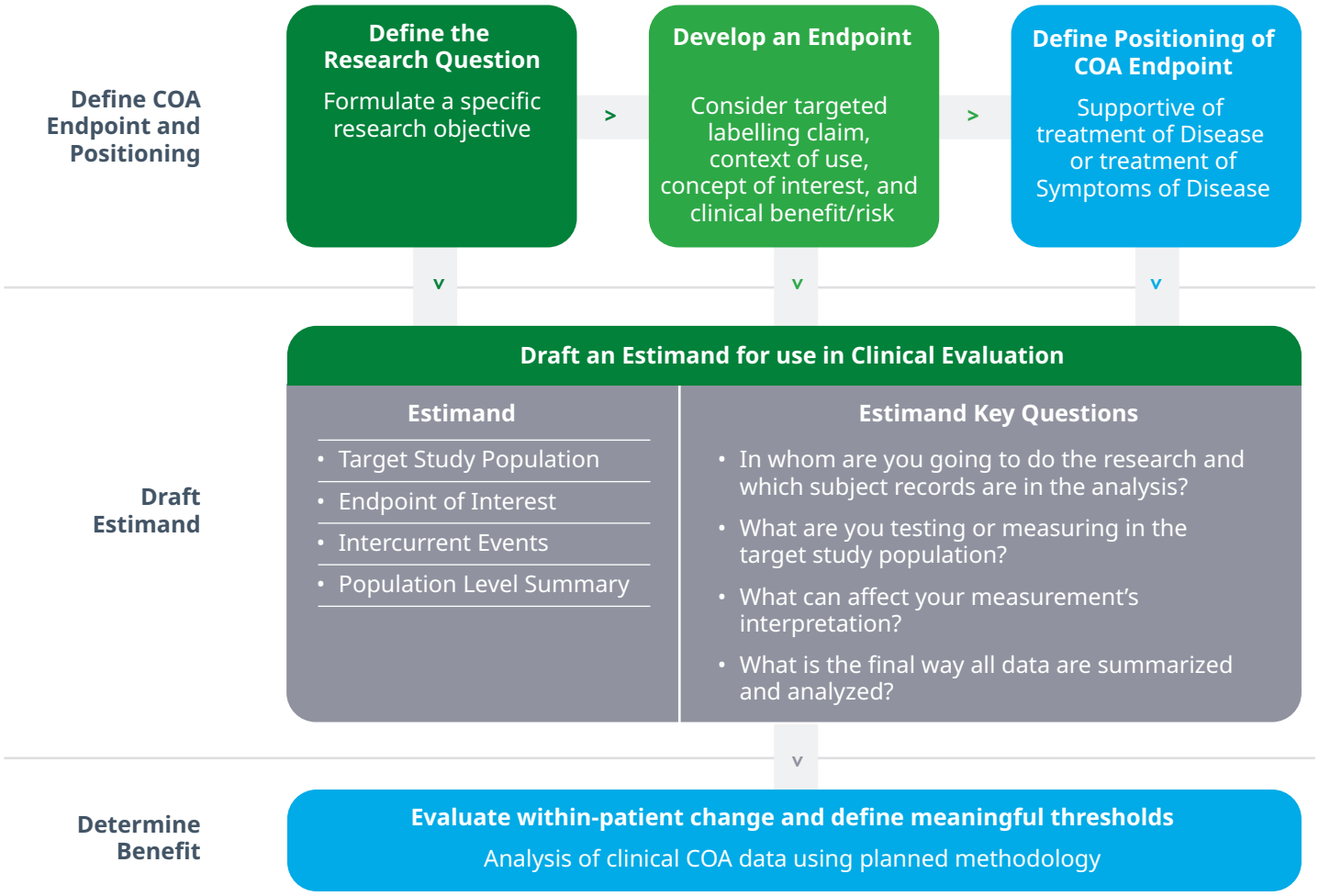


Figure 7: COA Endpoint Development and Evaluation



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As senior principal and head of Scientific and Analytic Research for the Patient Centered Sciences team at IQVIA, Matt provides scientific oversight and support to PCE consulting projects, and other PCE services that require scientific participation, with a focus on patient insight generation and COA.

Matt has extensive experience in COA development, implementation, analysis and interpretation.

He has worked across academic, consulting, clinical and industry settings and is an active leader in the COA science industry. Matt joined IQVIA in 2019.

Matt has a BS in Psychology, and an MS in Health Psychology. He is a Chartered Practitioner Health Psychologist and a Chartered Scientist. Matt has been awarded Fellowships by the Royal Society of Medicine and the Royal Society of Public Health and an Associate Fellowship by the British Psychological Society.

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As an associate principal and senior regulatory advisor for the Patient Centered Sciences team at IQVIA, Joy provides leadership in integration of the patient voice into effective data-driven regulatory strategies.

Joy has a broad industry background as a regulatory and quality professional. She has held leadership positions in multiple drug development programs with a consistent focus on the patient in all aspects, including heading up regulatory programs with patient experience data as a primary measure of effectiveness, establishment of quality systems in drug product manufacturing and oversight of clinical compliance for late-stage trials. Joy joined IQVIA in 2019.

Joy has a BS in General Biology from the University of California at San Diego.

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