U.S. FOOD & DRUG ADMINISTRATION

Public Workshop

Patient-Focused Drug Development: Workshop to Discuss Methodologic and Other Challenges Related to Patient Experience Data

December 13, 2024

Welcome

Ethan Gabbour, MS

Public Health Analyst, Patient-Focused Drug Development Program

Office of Center Director

Center for Drug Evaluation and Research

US Food and Drug Administration

Background

Prescription Drug User Fee Act VII Commitment:

FDA will issue a Request for Information (RFI) to elicit public input on methodological issues, including the submission and evaluation of patient experience data in the context of the benefit-risk assessment and product labeling, and other areas of greatest interest or concern to public stakeholders.

FDA will issue a Federal Register Notice summarizing the input to the RFI and based on the input received in response to the RFI, FDA will plan to conduct at least 2 public workshops focused on methodological issues. Based on the RFI and learnings from the workshops, FDA will produce a written summary with identified priorities for future work.

Summary: https://www.regulations.gov/document/FDA-2023-N-1506-0011

Agenda

10:00	Welcome
10:05	Opening Remarks
10:10	Overview of Patient Experience Data
10:45	Submissions of Patient Experience Data
12:00	Break
12:45	Delphi Methods- Challenges and Opportunities
2:00	Qualitative/Embedded Interviews
3:15	Break
3:30	Two Hot Topics: When to Consider Age-Normed Scores and Repurposing COAs for New Uses
4:55	Closing Remarks

PFDD

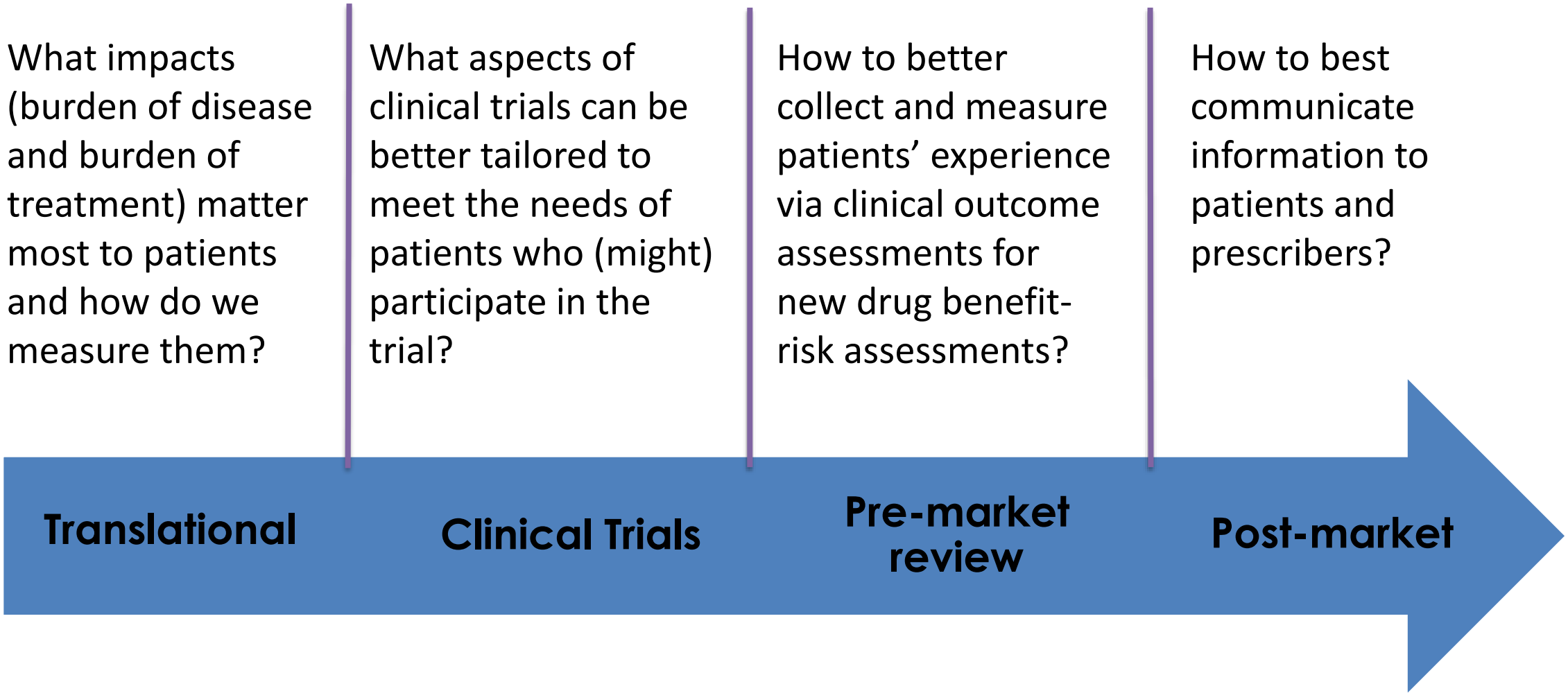
Workshop to Discuss Methodologic and Other Challenges Related to Patient Experience Data

Opening Remarks

December 13, 2024

Theresa M Mullin, PhD
Associate Center Director | Strategic Initiatives
US FDA Center for Drug Evaluation and Research

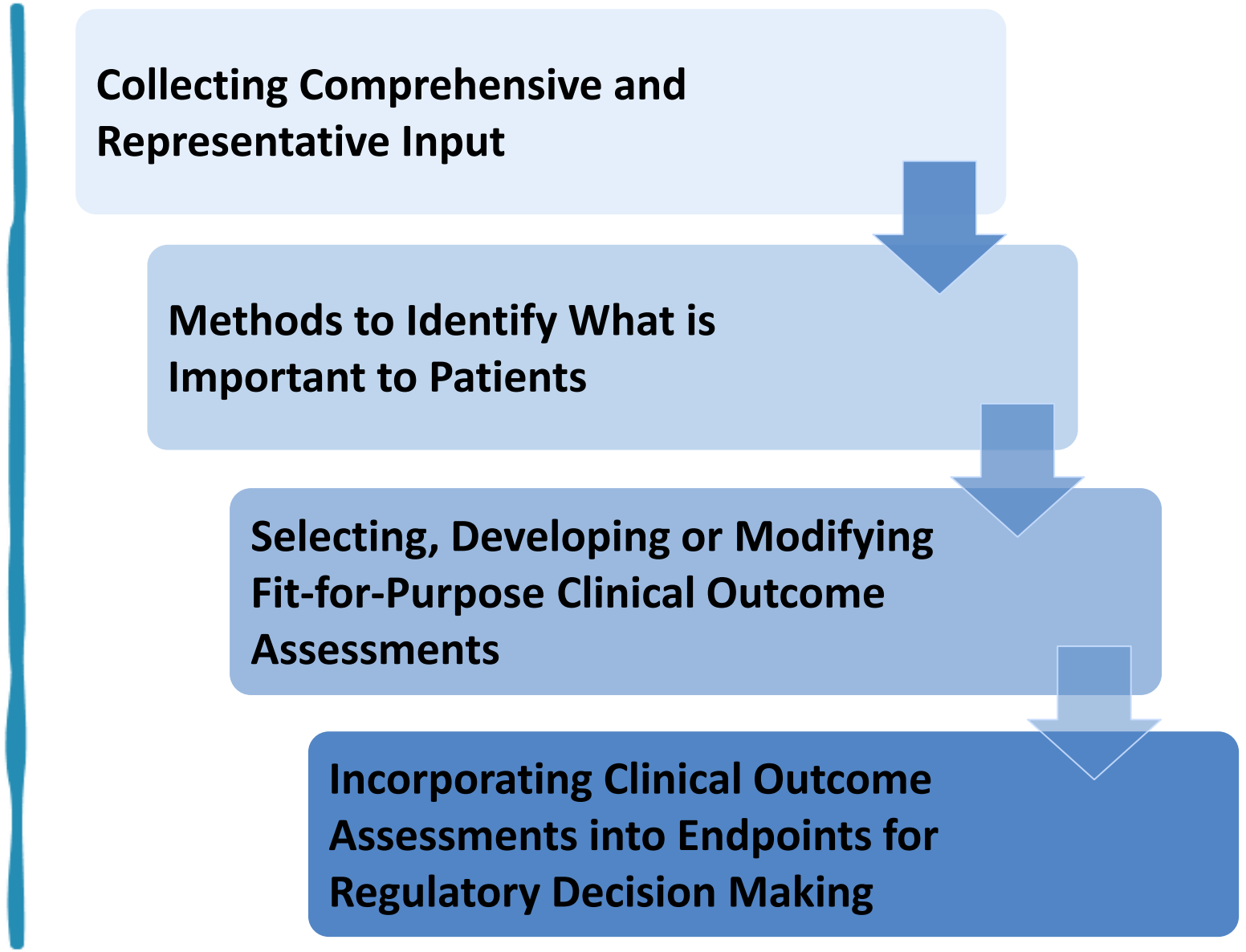
PFDD - Patient perspectives help inform medical product development and decision making



Quality matters

- The quality of collected patient experience data will determine the extent to which it can be used to inform regulatory decision making
- FDA's PFDD guidance series aims to support quality

Methodologic Guidance Documents



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

Thank you for joining us for this workshop!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Overview of Patient Experience Data

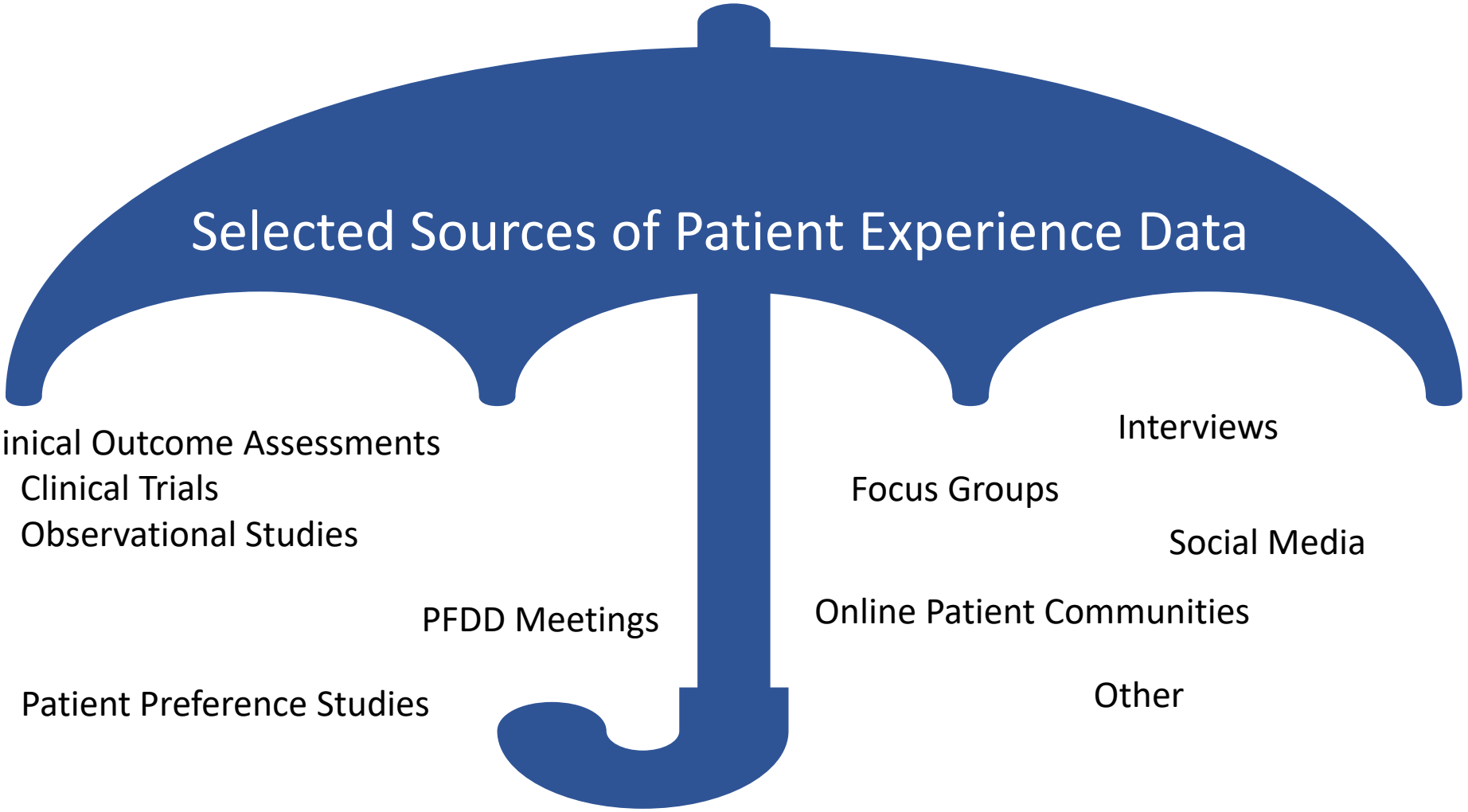
Patient Focused Drug Development: A Brief Overview

Robyn Bent
Patient Focused Drug Development
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Patient Experience

Patient Experience Data

- When and how should patient experience data be collected, and by whom?
- When and how should patient experience data be used, and by whom?
- When and how should patient experience data inform regulatory decision making?


Selected Sources of Patient Experience Data
Clinical Outcome Assessments
• Clinical Trials
• Observational Studies
PFDD Meetings
Patient Preference Studies
Interviews
Focus Groups
Social Media
Online Patient Communities
Other

Importance of Patient Experience Data

Review Process

Who typically is involved in review of patient experience data?

Clinical Reviewers

Statistical Reviewers

Division of Clinical Outcome Assessments (DCOA) Reviewers

What can be helpful?

Early discussions

Clear rationales

Well organized dossier that tells a story

Overview of the Request for Information (RFI)

NATIONAL ARCHIVES

FEDERAL REGISTER

The Daily Journal of the United States Government

Notice

Methodological Challenges Related to Patient Experience Data; Summary of Received Comments

A Notice by the Food and Drug Administration on 12/13/2023

PUBLISHED DOCUMENT: 2023-27312 (88 FR 86343)

PDF

Document Details

Table of Contents

Public Comments

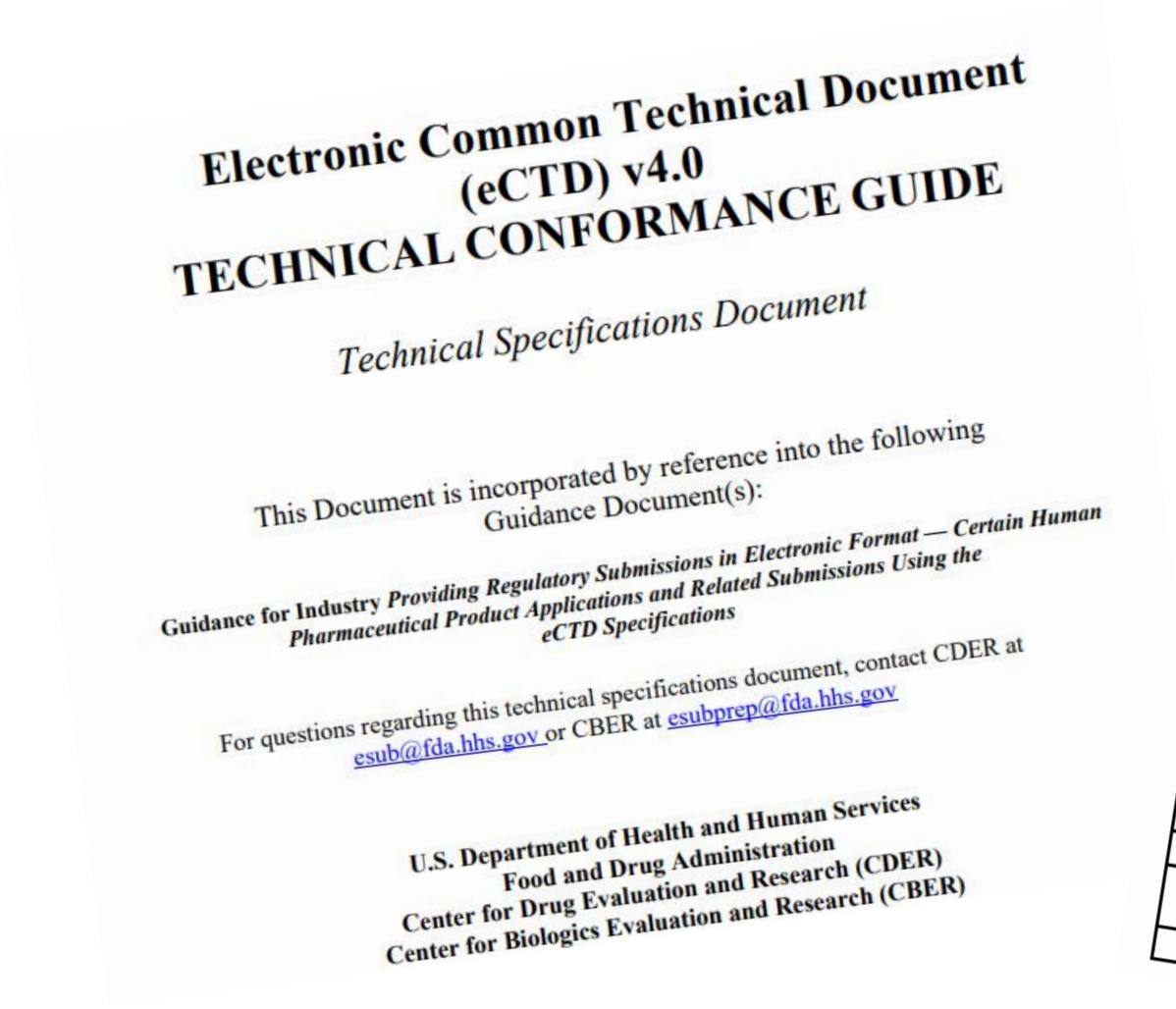
DOCUMENT HEADINGS

Department of Health and Human Services
Food and Drug Administration
[Docket No. FDA-2023-N-1506]

AGENCY:

Food and Drug Administration, HHS.

Submission of Patient Experience Data



Electronic Common Technical Document (eCTD) v4.0
TECHNICAL CONFORMANCE GUIDE

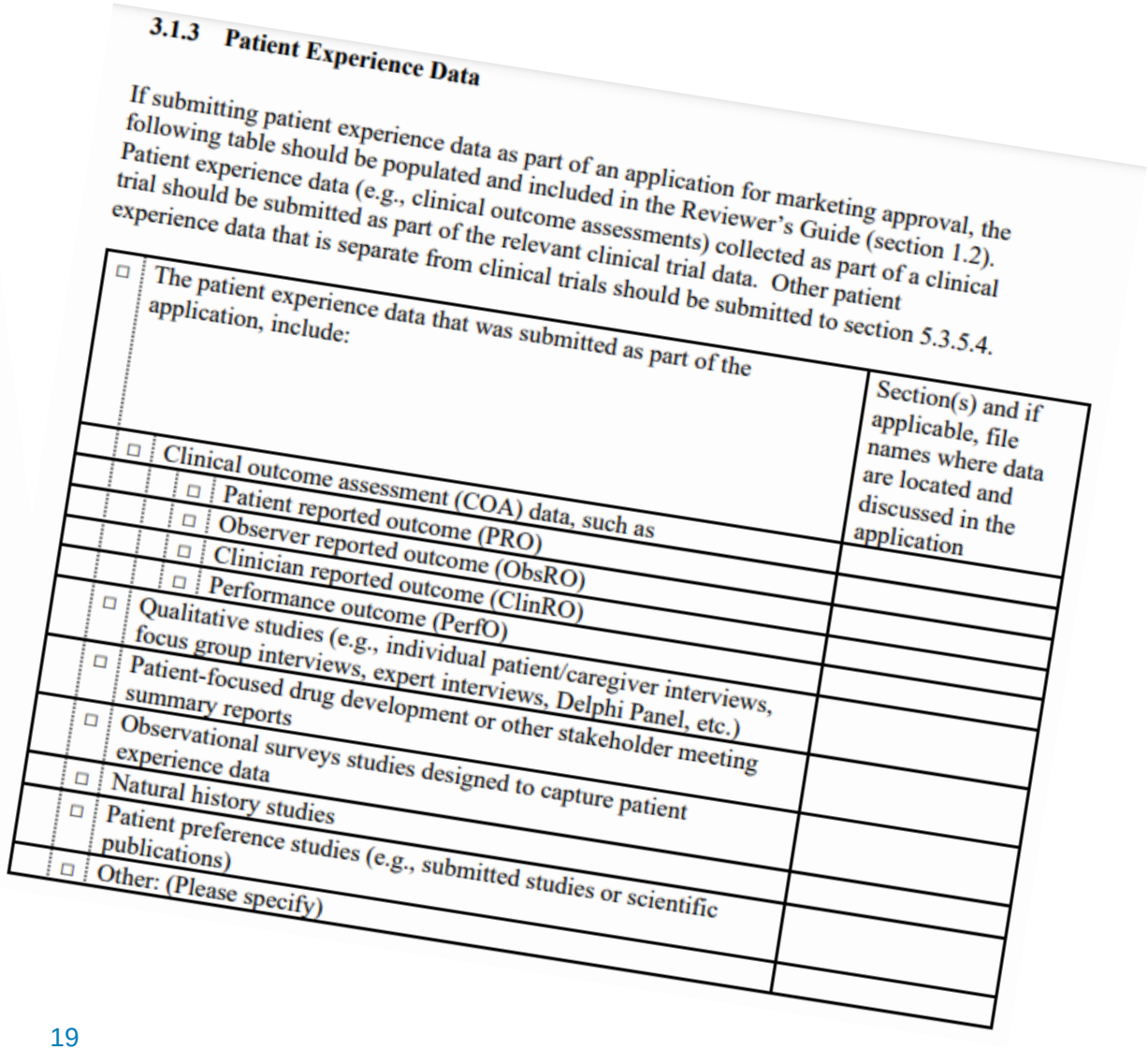
Technical Specifications Document

This Document is incorporated by reference into the following Guidance Document(s):

Guidance for Industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*

For questions regarding this technical specifications document, contact CDER at esub@fda.hhs.gov or CBER at esubprep@fda.hhs.gov

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)



3.1.3 Patient Experience Data

If submitting patient experience data as part of an application for marketing approval, the following table should be populated and included in the Reviewer's Guide (section 1.2). Patient experience data (e.g., clinical outcome assessments) collected as part of a clinical trial should be submitted as part of the relevant clinical trial data. Other patient experience data that is separate from clinical trials should be submitted to section 5.3.5.4.

The patient experience data that was submitted as part of the application, include:	Section(s) and if applicable, file names where data are located and discussed in the application
☐ Clinical outcome assessment (COA) data, such as	
☐ Patient reported outcome (PRO)	
☐ Observer reported outcome (ObsRO)	
☐ Clinician reported outcome (ClinRO)	
☐ Performance outcome (PerfO)	
☐ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐ Patient-focused drug development or other stakeholder meeting summary reports	
☐ Observational surveys studies designed to capture patient experience data	
☐ Natural history studies	
☐ Patient preference studies (e.g., submitted studies or scientific publications)	
☐ Other: (Please specify)	

https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd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Incorporating Patient Experience Data into Regulatory Review

Teresa Buracchio, MD
Director, Office of Neuroscience
Center for Drug Evaluation and Research

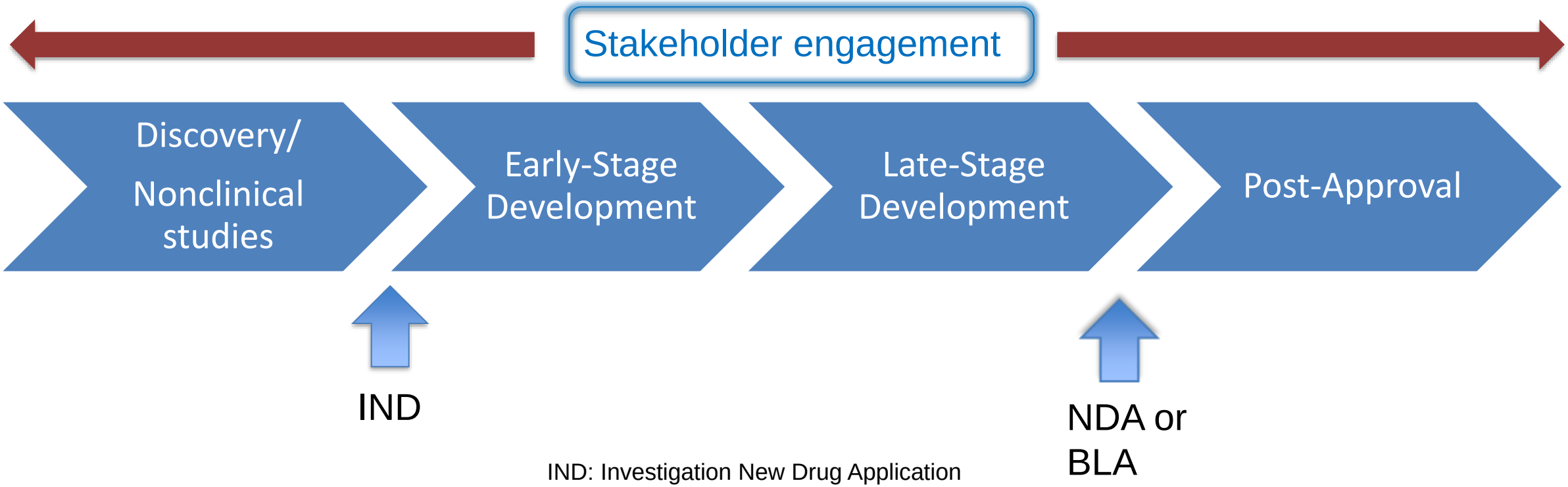
Disclosure

- This presentation is not intended to convey official US FDA policy, and no official support or endorsement by the US FDA is provided or should be inferred
- The materials presented are available in the public domain

FDA Stakeholder Engagement Activities

- Patient Listening Sessions
- Patient-focused drug development meetings
- Engagement with stakeholders
  - Scientific meetings
  - Working Groups
  - Public-Private Partnerships
  - Research Roundtables

Drug Development



IND: Investigation New Drug Application
NDA: New Drug Application
BLA: Biologics License Application

- Initial engagement with drug developers and FDA to facilitate understanding of the condition and drug development needs
- Planning activities to support drug development
  - Natural history studies and
  - Development of outcome assessments
  - Patient outreach to support anticipated clinical trials

- Continued engagement on drug development needs
- Qualitative work to support selection of trial endpoints for future studies
- Provide patient's perspective on benefit and risk
  - What does a "clinically meaningful" benefit look like
  - Tolerance of risk
  - Acceptance of uncertainty

- Provide input to on elements of trial designs
  - Selection of endpoints
  - Feasibility of the trial design
  - Burden of trial assessments

NDA/BLA Submission and Review

- Review takes into consideration input from stakeholders during the drug development process
- Advisory committee may be convened to advise on challenging issues
  - Committee includes patient and consumer representative
  - Open public hearing

- Continued engagement and input on ongoing post-marketing activities
- Voluntary reporting of adverse events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Patient Engagement

Megha Kaushal, MD, MSc
Benign Hematology Branch Chief
OCE/OTP/CBER

Patient Focused Drug Development
December 13, 2024

Patient Engagement

Activities that involve patient stakeholders sharing their experiences, perspectives, needs, and priorities that help inform FDA's public health mission.

Patient-Focused Drug Development Glossary | FDA

Engaging with patients…

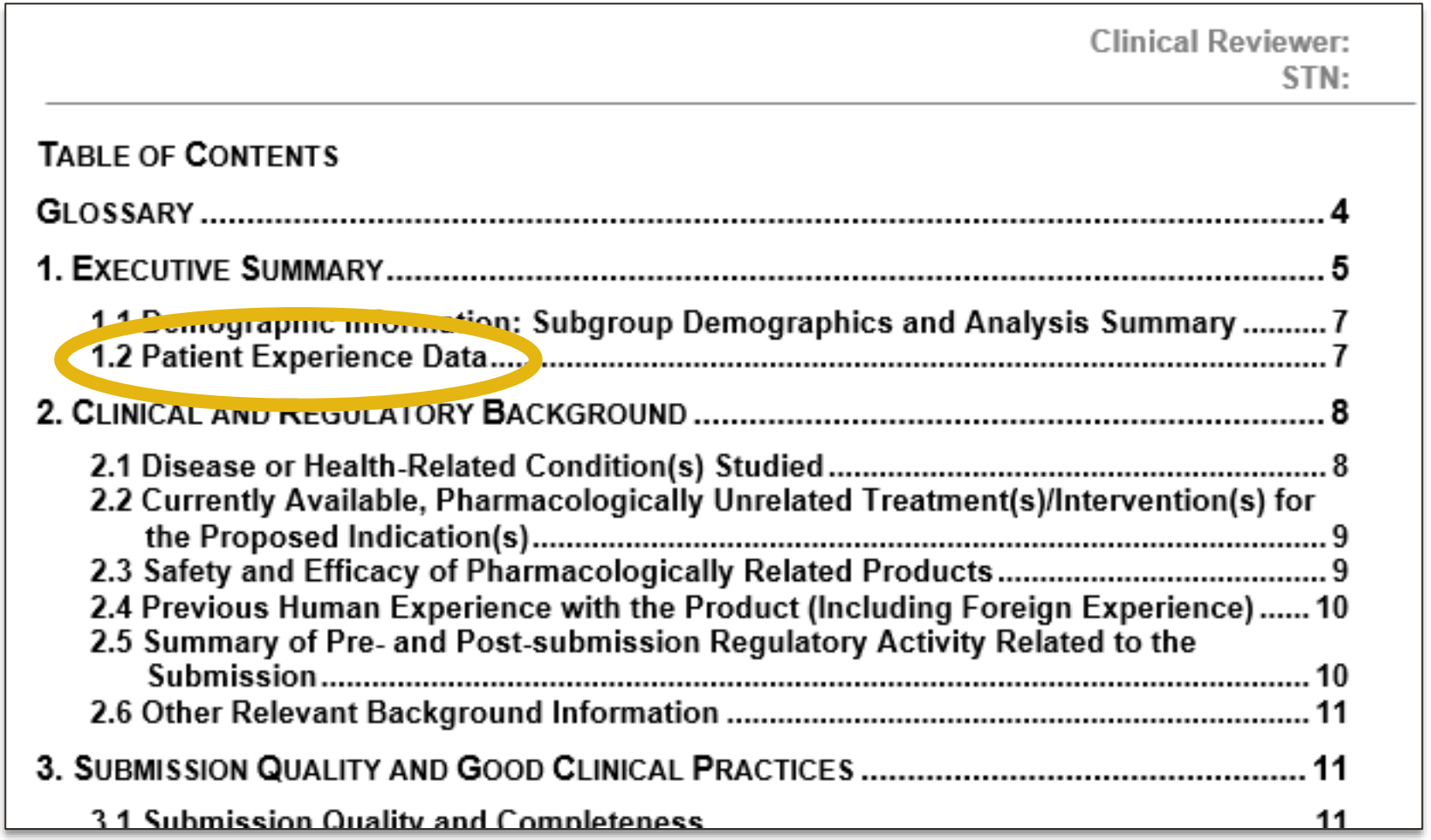
- Impact of the disease and its treatment
- Perspectives about potential and current treatments
- Views on unmet medical needs and available treatment options
- Enhance the understanding of disease natural history

When to engage with patients

Throughout the product development process

How FDA considers patient input

BLA Clinical Review Memo



Clinical Reviewer:
STN:

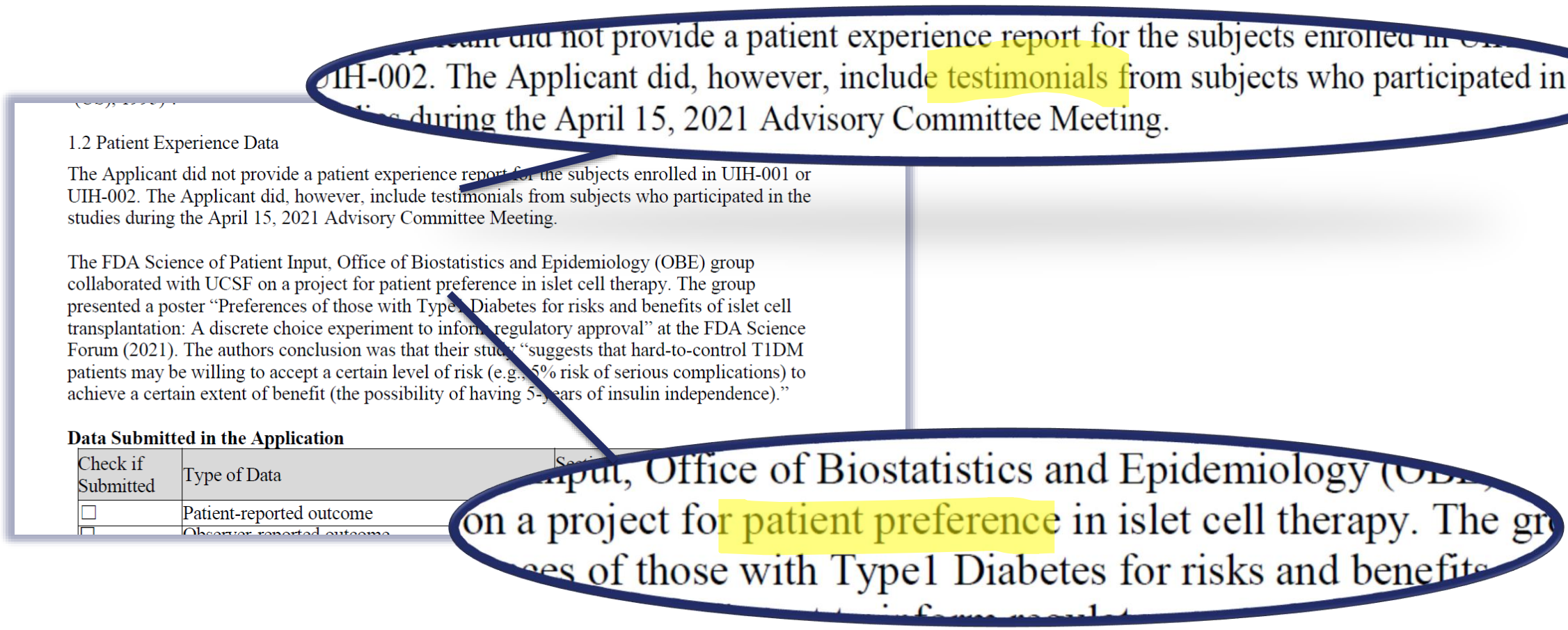
TABLE OF CONTENTS

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

Patient Engagement Case Studies

Donislecel


did not provide a patient experience report for the subjects enrolled in
IH-002. The Applicant did, however, include testimonials from subjects who participated in the
during the April 15, 2021 Advisory Committee Meeting.
1.2 Patient Experience Data
The Applicant did not provide a patient experience report for the subjects enrolled in UIH-001 or UIH-002. The Applicant did, however, include testimonials from subjects who participated in the studies during the April 15, 2021 Advisory Committee Meeting.
The FDA Science of Patient Input, Office of Biostatistics and Epidemiology (OBE) group collaborated with UCSF on a project for patient preference in islet cell therapy. The group presented a poster "Preferences of those with Type1 Diabetes for risks and benefits of islet cell transplantation: A discrete choice experiment to inform regulatory approval" at the FDA Science Forum (2021). The authors conclusion was that their study "suggests that hard-to-control T1DM patients may be willing to accept a certain level of risk (e.g., 5% risk of serious complications) to achieve a certain extent of benefit (the possibility of having 5-years of insulin independence)."
Data Submitted in the Application
Check if Submitted
Type of Data
Patient-reported outcome
Observer-reported outcome
Input, Office of Biostatistics and Epidemiology (OBE)
on a project for patient preference in islet cell therapy. The gr
ces of those with Type1 Diabetes for risks and benefits

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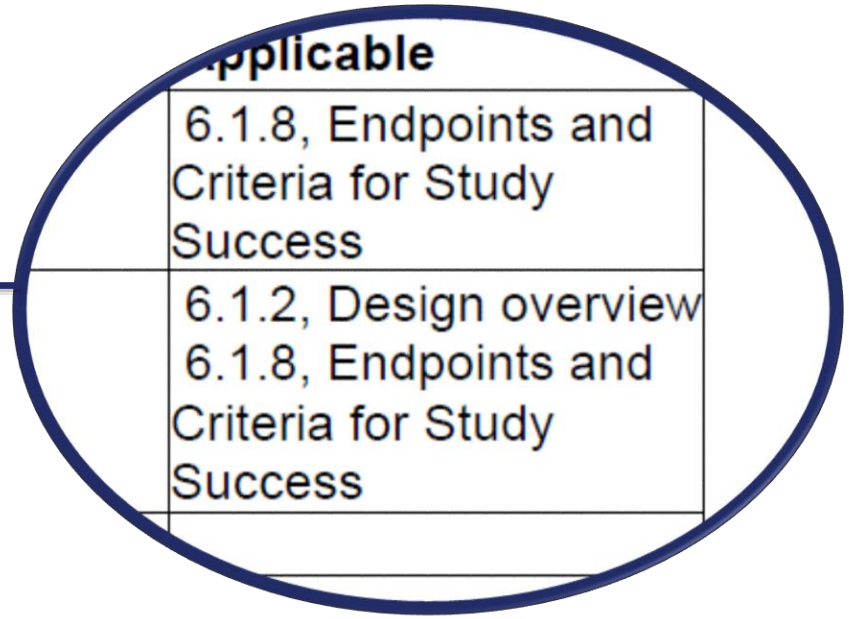
1.2 Patient Experience Data

Patient experience data relevant to this submission are summarized in Table 2.

Table 2. Patient Experience Data Relevant to This Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☒	Patient-reported outcome	6.1.8, Endpoints and Criteria for Study Success
☒	Observer-reported outcome	6.1.2, Design overview 6.1.8, Endpoints and Criteria for Study Success
☐	Clinician-reported outcome	
☐	Performance outcome	
☐	FDA Patient Listening Session	
☒	Other stakeholder meeting summary report	2.1, Disease or Health-Related Condition(s) Studied
☐	Observational survey studies	
☐	Other: (please specify)	



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1.2 Patient Experience Data

Patient experience data relevant to this submission are summarized in T

Table 2. Patient Experience Data Relevant to This A

Check if Submitted	Type of Data	
☒	Patient-reported outc	
☒	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
☐	FDA Patient Listening Session	
☒	Other stakeholder meeting summary report	2.1, Disease or Health-Related Condition(s) Studied
☐	Observational survey studies	
☐	Other: (please	

art of the FDA Externally Led Patient-Focused Drug Development initiative, on April 6, 2018, a joint public meeting led by Pachyonychia Congenita (PC) Project and the Dystrophic Epidermolysis Bullosa Research Association of America (DEBRA) (Pachyonychia Congenita Project 2018) was held.

The following pertinent questions were asked during the meeting with the responses gathered e attendants (in person and online):

participating in a clinical trial?

not totally relieve, symptoms with few

On June 15, 2022, DEBRA held a listening session with FDA. Patients with DEB and their caregivers shared their perspectives of the disease that mattered most to them. The representatives from DEBRA stated that any wound area reduction or pain reduction would be red important to them.

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STN: 125758

Reviewer comments on patient experience data

In addition to the clinician-reported outcome (ClinRO) and performance-based outcome (PerfO) evidence submitted, this reviewer also considered the following sources of PED:

1. Externally-led Patient-Focused Drug Development Voice of the Patient reports:
   a. Cure MLD (2022). Metachromatic Leukodystrophy (MLD) Voice of the Patient Report, October 21, 2022 and November 18, 2022. Accessed from:
2. Patient-Cent
   a. Harrington, M., Whalley, D., Twiss, of metachromatic leukodystrophy from interviews with caregivers. Orphanet J Rare Dis 14, 89 (2019).

These additional PED helped confirm the importance of preserving cognitive functioning for all MLD patients but, in particular, for juvenile patients for whom cognitive symptoms may be an early emerging symptom. In the MLD Voice of the Patient report, caregivers indicated a top concern was decreased communication/responsiveness for MLD patients and the report described patients as "locked in" which is assumed to mean complete dependence on caregivers and no communication abilities, even minimally (e.g., blinking yes/no). Slowing disease progression and increasing responsiveness for patients were reported as valued aspects of a treatment for MLD. These PED further emphasize the substantial unmet treatment need and the importance of neurocognitive preservation as a treatment outcome for patients of all MLD subtypes.

blinking yes/no). Slowing disease progression and increasing responsiveness for patients were reported as valued aspects of a treatment for MLD. These PED further emphasize the substantial unmet treatment need and the importance of neurocognitive preservation as a treatment outcome for patients of all MLD subtypes.

Hemophilia

"This valuable input has already been used in ways that help advance overall development of gene therapy products for hemophilia."

How FDA is Putting the Patient Voice at the Forefront of Gene Therapy Clinical Trials for Hemophilia | FDA

Following the listening session:

- Agenda for "Product Development in Hemophilia" public workshop
- Public summary is a resource
- Reinforced public comments on the "Human Gene Therapy for Hemophilia" draft guidance

Summary

- Patients are the experts in what it is like to live with their disease.
- Patient engagement is the first step in a patient-focused drug development program.


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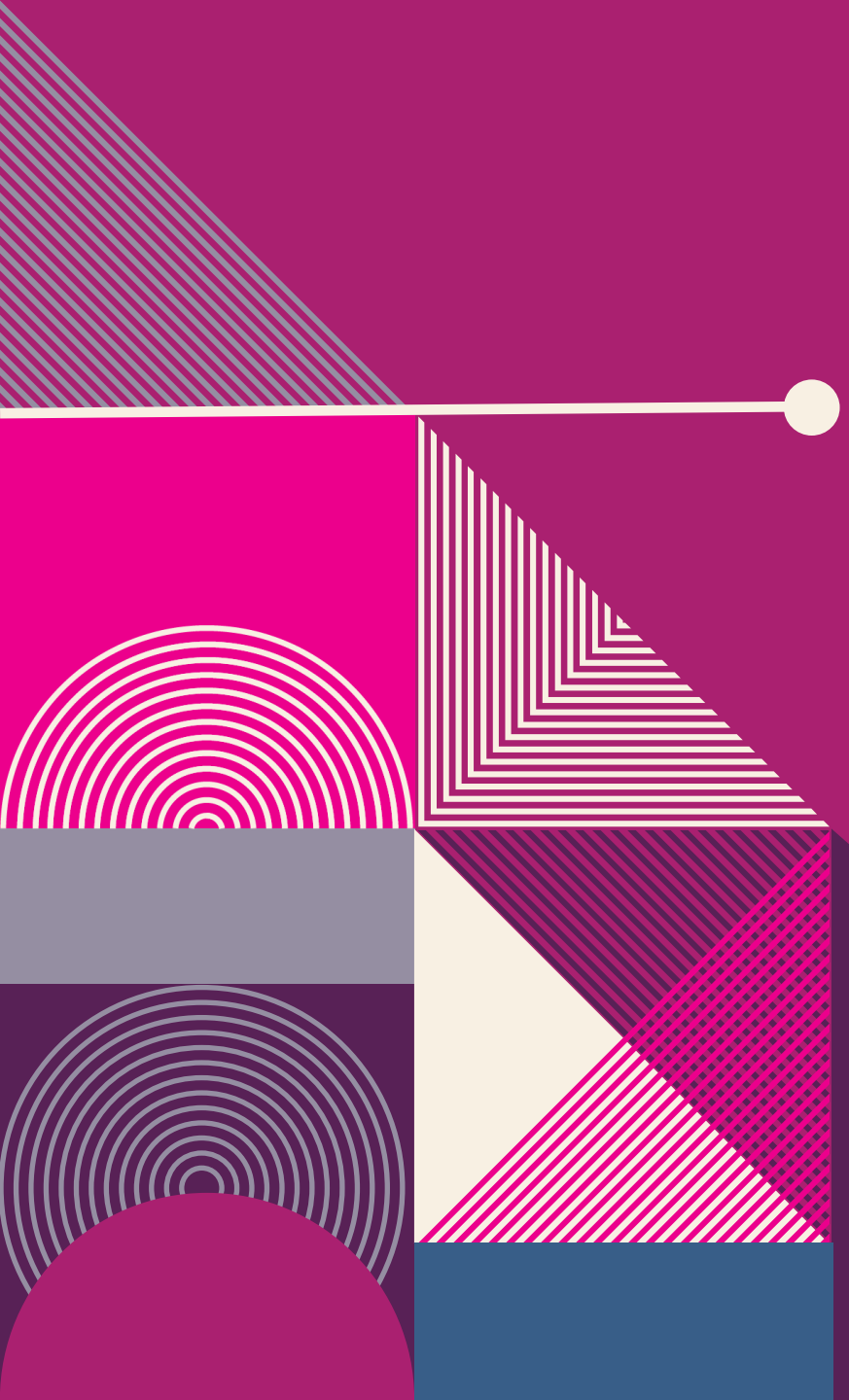
Submissions of Patient Experience Data


Panel Discussion
followed by
Q+A

Lunch Break

Please return at 12:45 p.m. EST

Delphi Methods- Challenges and Opportunities



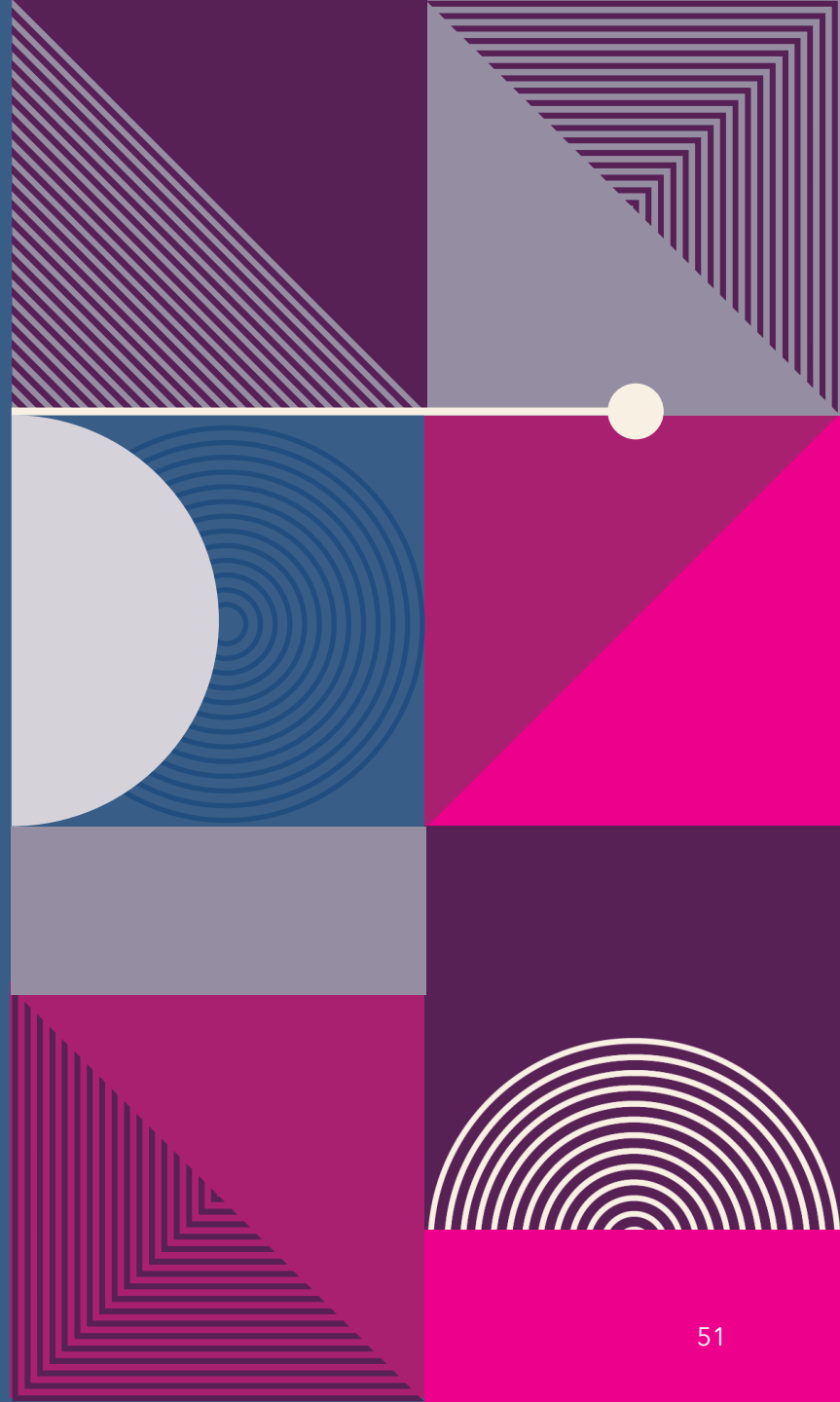
DELPHI METHODOLOGY: HISTORICAL CONTEXT, ADVANTAGES, AND LIMITATIONS

Understanding the Established Research Technique and Opportunities in Medical Product Development

Ebony Dashiell-Aje, PhD
Executive Director & Head, Patient Centered Outcomes Science
BioMarin Pharmaceutical, Inc.

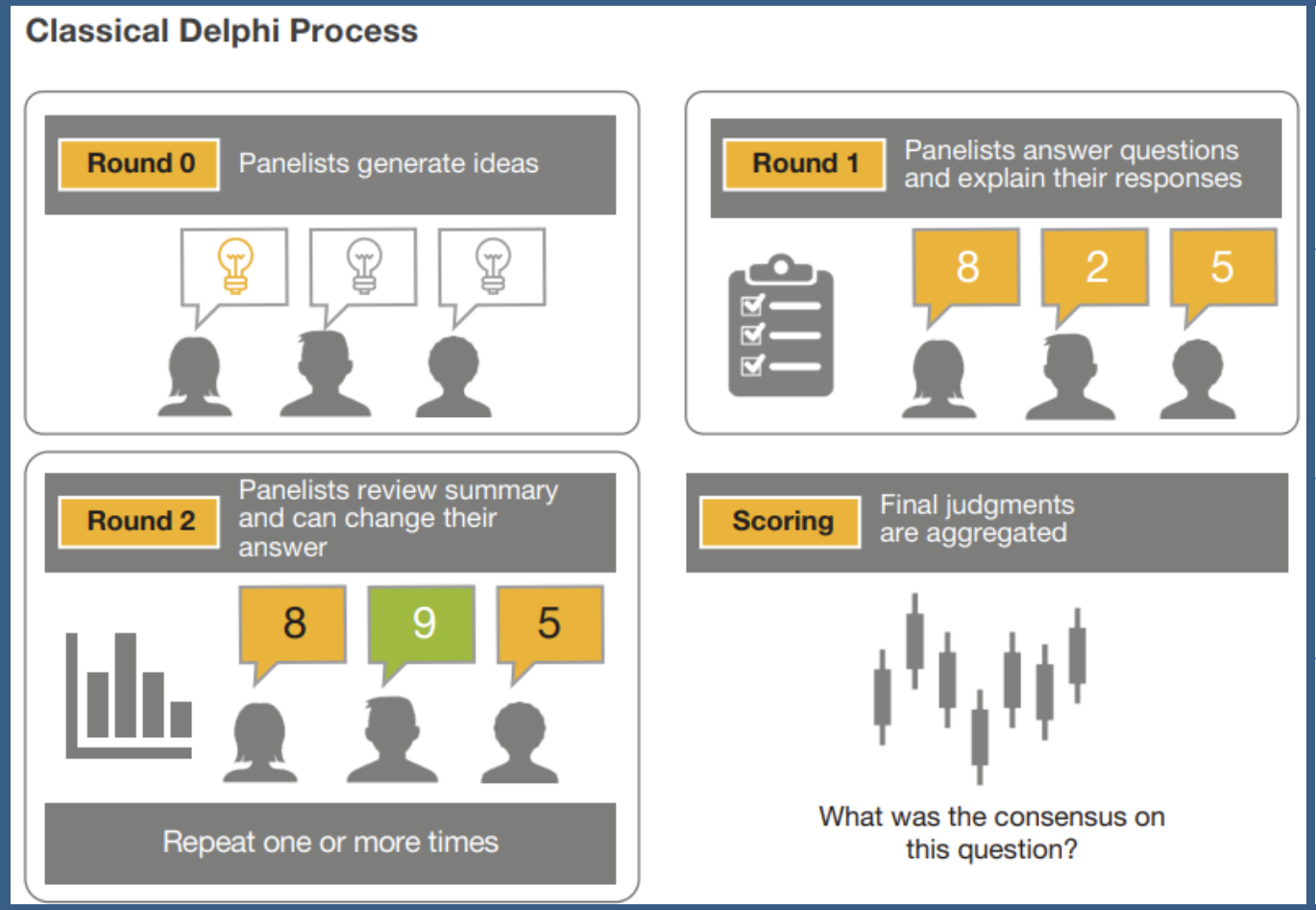
OVERVIEW

- Historical Context & Evolution of Delphi Methodology
- What Delphi Methodology Is and What It's Not
- Utility of Delphi Methodology in Patient Experience Data Generation
- Advantages & Limitations

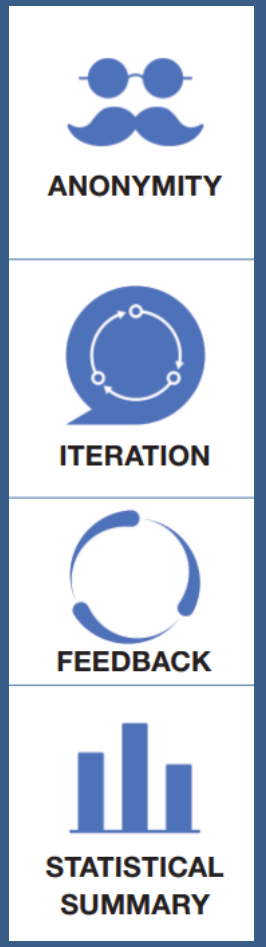


HISTORICAL CONTEXT

PROCESS



FEATURES



- Delphi methodology is a research technique used to gather opinions and achieve consensus
- Developed by RAND in the 1950s to forecast the effect of technology on warfare. It has since been applied to healthcare, education, management, and environmental science fields, to name a few.
- New, modified methods are now commonly used across disciplines.

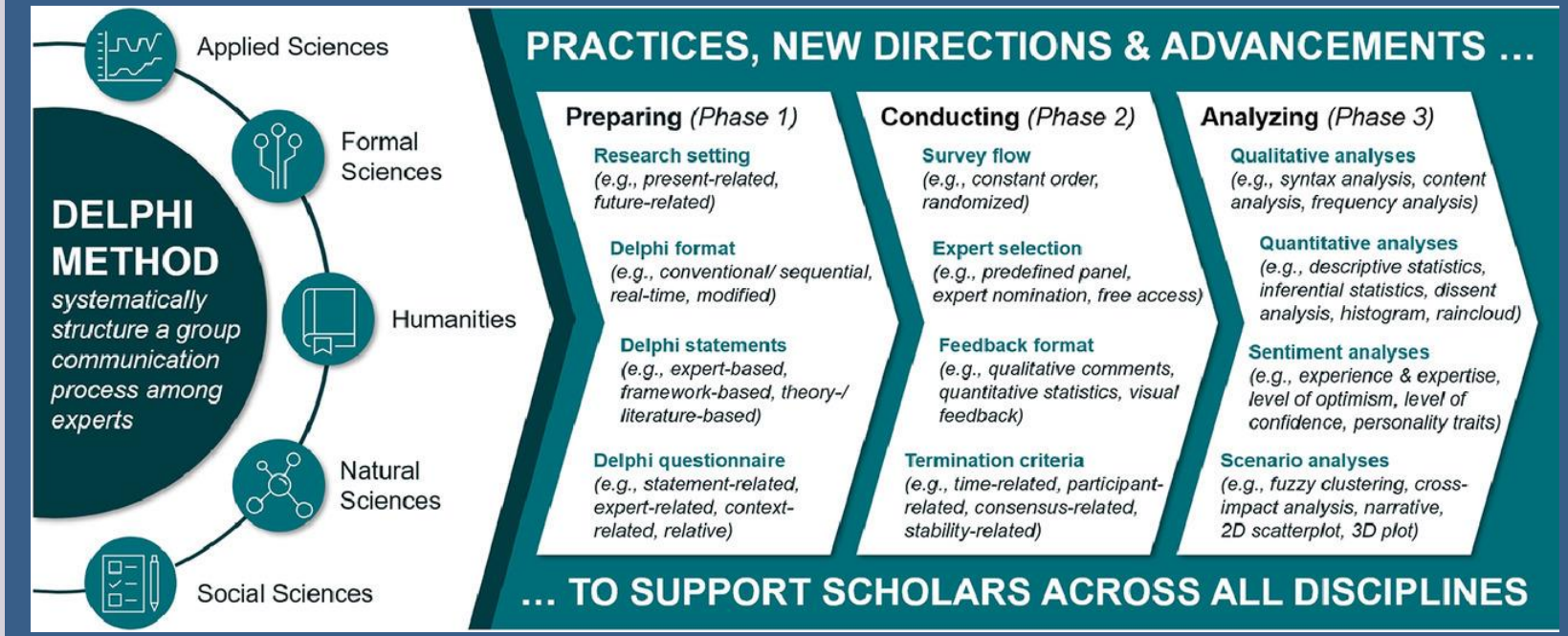
Source: Khodyakov, Dmitry, Sean Grant, Jack Kroger, and Melissa Bauman, RAND Methodological Guidance for Conducting and Critically Appraising Delphi Panels. Santa Monica, CA: RAND Corporation, 2023. https://www.rand.org/pubs/tools/TLA3082-1.html.

EVOLUTION OVER TIME

EXPANDED SECTORS

PRACTICE MODIFICATIONS

COMMON VARIATIONS



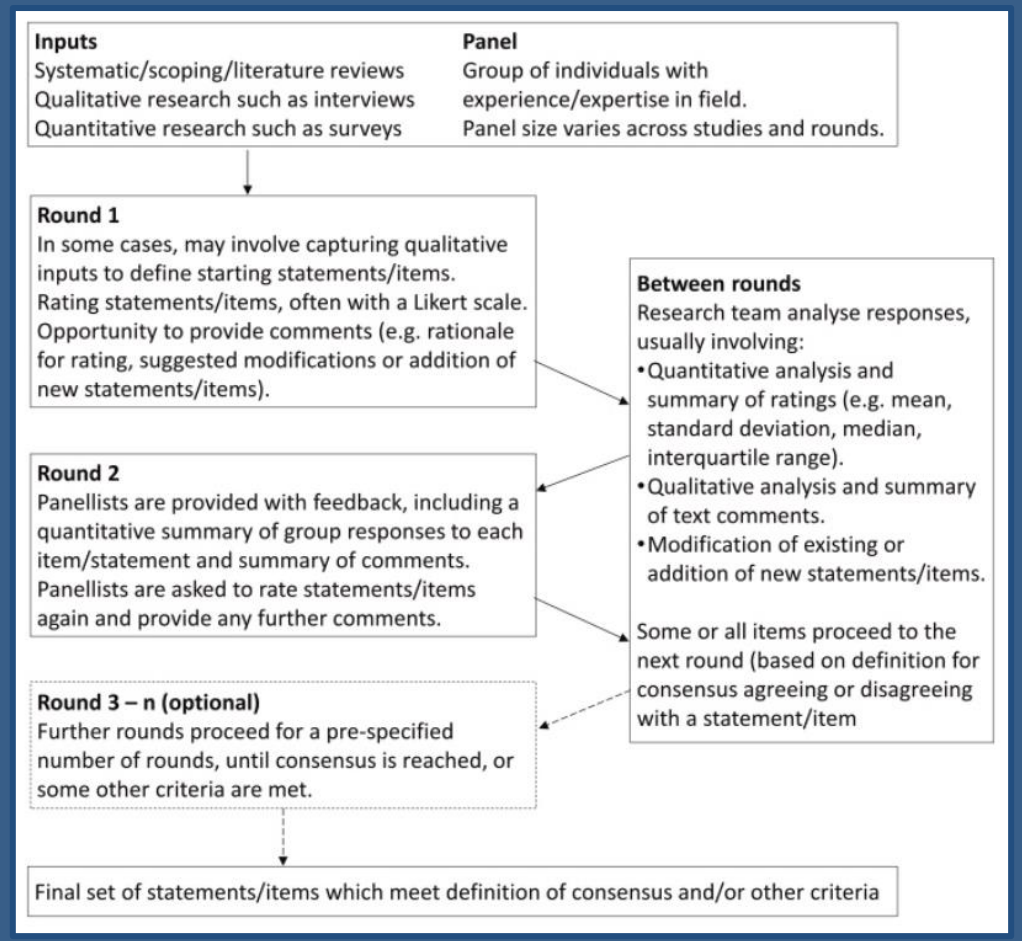
Source: https://doi.org/10.1016/j.mex.2021.101401 2215-0161/

- Policy Delphi
- Modified Delphi
- eDelphi & ExpertLens

Delphi Methodological approach should be carefully selected based on research objectives. May also be influenced by other contextual factors (e.g., time, budget).

WHAT DELPHI METHODOLOGY IS… VERSUS WHAT IT IS NOT

AN ITERATIVE PROCESS **vs.** OTHER QUALITATIVE METHODS



FOCUS GROUPS

SEMI-STRUCTURED INTERVIEWS

Source: Drumm, S., Bradley C., Moriarty, F. (2022). 'More of an art than a science'? The development, design and mechanics of the Delphi Technique, Research in Social and Administrative Pharmacy, 18 (1), 2230-2236.

DELPHI IN ACTION: UTILITY IN PATIENT EXPERIENCE DATA GENERATION

Concept Identification

After a literature review is conducted, Delphi panels can weigh in on key concepts and outcomes that are important to assess in clinical research.

COA Item Reduction

Delphi panels can be useful to help refine and reduce COA items during the psychometric evaluation phase.

Meaningful Change

Delphi panels can be a useful method to confirm and/or establish meaningful change thresholds (e.g., progression, improvement).

DELPHI IN ACTION: HIGHLIGHT – MEANINGFUL CHANGE

A modified Delphi panel to establish a threshold of meaningful progression on MDS-UPDRS Part III

Dylan Trundell,[1] Louise Barrett,[2] Rebecca Rogers,[2] Evan Davies,[3] Stefano Zanigni,[3] Nathalie Pross,[3] Gennaro Pagano,[4,5] Tania Nikolcheva,[3] Stefan Cano[2]

1. Roche Products Ltd, Welwyn Garden City, UK; 2. Modus Outcomes, Letchworth Garden City, UK; 3. F. Hoffmann-La Roche Ltd., Product Development Neuroscience, Basel, Switzerland; 4. Roche Pharma Research and Early Development (pRED), Neuroscience and Rare Diseases Discovery and Translational Area, Roche Innovation Center, F. Hoffmann-La Roche Ltd, Basel, Switzerland; 5. University of Exeter Medical School, London, UK.

What does this mean for the Parkinson's disease (PD) community?

- This study supports the definition of a change threshold for assessing meaningful progression of the motor signs that result from PD, as measured by the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III.
- This change threshold can be used in clinical trials to better understand the impact of potential treatments that aim to modify the progression of PD.
  - For example, PADOVA (NCT04777331); a Phase II, randomised, double-blind, placebo-controlled study evaluating the efficacy of prasinezumab in participants with early-stage PD on stable symptomatic PD medication) uses this threshold as the primary endpoint.

Objective

- To establish a threshold for meaningful progression on the MDS-UPDRS Part III in an early-stage PD population (Hoehn and Yahr [H&Y] Stages I–II) through clinical expert consensus via a modified Delphi panel.

Background

- The MDS-UPDRS Part III is a clinician-rated assessment of motor signs, commonly used in clinical trials, practice and studies.[1]
- Establishing a threshold for meaningful progression allows for the use of the MDS-UPDRS Part III in progressor-based (including time-to-event) endpoints.
- Previously, anchor-based analyses have been conducted to estimate a threshold, suggesting a threshold of 5 points.[2]
- To support these findings, clinical expert consensus was sought via a modified Delphi panel.

Methods

- A sponsor-/researcher-blind panel of expert clinicians (N=13) was recruited.
- The panellists had 8–40 years' experience in PD (mean=19 years), a H-index of 20–119 (mean=40), and represented seven countries across North America (USA [n=2] and Canada [n=2]) and Europe (France [n=2], Germany [n=3], Italy [n=2], Spain [n=1] and UK [n=1]).
- The panellists received an online survey in two rounds and provided responses anonymously. The overall study design is shown in **Figure 1**.
- Round 1 explored initial opinions on the threshold for meaningful progression, and differences between medication state (ON vs. OFF), disease stage (H&Y Stage I vs. II) and treatment status (naïve vs. stable symptomatic).
- Round 2 was conducted in two parts:
  - 1) section A: an aggregated overview of Round 1 followed by a question on agreement that the threshold for meaningful progression (OFF medication state) lies within 4–6 points; and
  - 2) section B: an overview of prior anchor-based analyses,[2,3] followed by an evaluation of agreement that the threshold for meaningful progression (OFF medication state) lies in the range of 4–6/is 5 points (two questions).
- A threshold of ≥70% was set for establishing consensus.

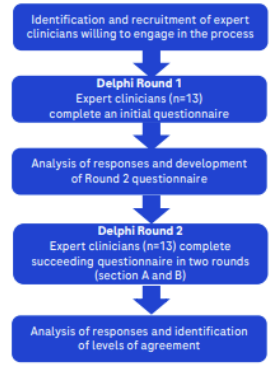


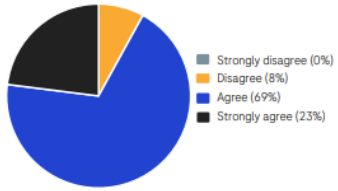
Figure 1. Modified Delphi panel study design

Results

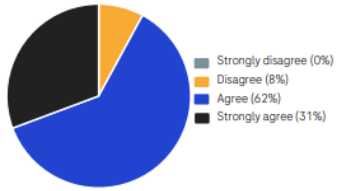
Round 1:
A range of 2–10 points (median=5) was suggested as a threshold for meaningful progression.
- n=11 (85%) reported that the threshold depends on medication state.
- n=8 (62%) reported no difference by H&Y Stage (I vs. II).
- n=9 (69%) reported no difference by treatment status.

Round 2:
The key findings are presented in **Figure 2.**
Round 1: n=12 (92%) agreed that the threshold lies within 4–6 points.
Round 2: n=12 (92%) agreed that the threshold lies within 4–6 points.
Round 2: n=12 (92%) agreed with the use of 5 points to define a threshold for clinically meaningful progression.

Section A: Considering OFF state, do you agree that the change in MDS-UPDRS Part III score (motor examination) that represents minimum clinically meaningful worsening lies within the range of 4–6 points?



Section B (Q1): Given the sponsor's intent to assess worsening of motor signs (OFF medication state) in a clinical trial, to what extent do you agree that the change in MDS-UPDRS Part III score (motor examination) that represents minimum clinically meaningful worsening lies within the range of 4–6 points?



Section B (Q2): Given the sponsor's intent to assess worsening of motor signs (OFF medication state) in a clinical trial, to what extent do you agree that the change in MDS-UPDRS Part III score (motor examination) that represents minimum clinically meaningful worsening is 5 points?

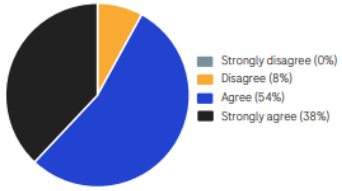


Figure 2. Key results from Round 2

Conclusions

The modified Delphi panel proved to be a useful method to support previous findings and establish a threshold of an increase of 5 points for clinically meaningful progression on the MDS-UPDRS Part III (OFF medication state) in an early-stage PD population.

Acknowledgements
This study was funded by F. Hoffmann-La Roche Ltd. The authors thank the members of the modified Delphi panel for their participation, and Kiran Verma, of Chrysalis Medical Communications, for providing editorial support for this poster, which was funded by F. Hoffmann-La Roche Ltd in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

Abbreviations
H&Y, Hoehn & Yahr; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease; Q, question.

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2. Horváth K, et al. *Parkinsonism Relat Disord.* 2015; 21:1421–1426;
3. Zanigni S, et al. *AD/PD International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders.* 2022; Abstract 407.

Please scan using your QR reader application to access this poster on your mobile device. NB: there may be associated costs for downloading data. These costs may be high if you are using your smartphone abroad. Please check your mobile data tariff or contact your service provider for more details. Alternatively this can be accessed at: https://bit.ly/3B2uTMS

Presented at MDS (2022) 26th International Congress of Parkinson's Disease and Movement Disorders; 15–18 September 2022

ADVANTAGES & LIMITATIONS

KEY ADVANTAGES

Structured Communication
Facilitates consensus for complex issues

Anonymity
Encourages honest, unbiased feedback

Flexibility
Allows participation among geographically disbursed experts

Efficiency
Cost and time-efficient, when compared to face-to-face meetings

Diversity
Can include diverse stakeholders (e.g., patients, clinicians; homogenous or mixed groups).

KEY LIMITATIONS

Limited Discussion
Lack of open discussion can hinder in-depth insights gathering

Timing Misalignment
Timing of robust Delphi process may not align well with internal research milestones

Consensus Pressure
Risk of consensus pressure could reduce opinion diversity

Expert Selection Quality
Reliance on high bars for expertise could preclude timely panelist selection, potentially delaying study timelines

Source: Drumm, S., Bradley C., Moriarty, F. (2022). 'More of an art than a science'? The development, design and mechanics of the Delphi Technique, Research in Social and Administrative Pharmacy, 18 (1), 2230-2236.

THANK YOU!

Ebony Dashiell-Aje, PhD
Executive Director & Head, Patient Centered Outcomes Science
BioMarin Pharmaceutical, Inc.

Delphi methodology: study examples

Holly Peay, PhD

Dec 13, 2024

RTI INTERNATIONAL

Example 1: Patient-Centeredness of Care Guidelines

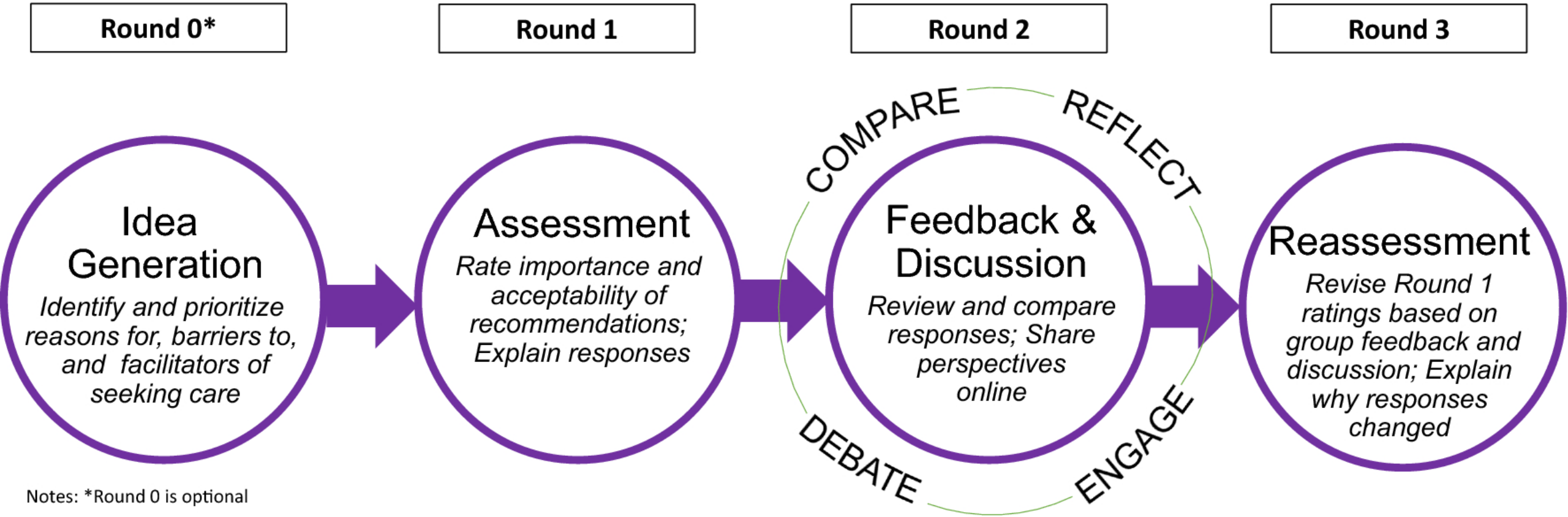
Context: Duchenne muscular dystrophy (DMD), an inherited neuromuscular disorder

Objective: Determine patient-centeredness of DMD endocrine and bone care guidelines

Method: Modified Delphi (RAND/PPMD Patient-Centeredness Method)

Participants in Delphi panels: Patient and caregiver representatives

Reference: Khodyakov et al., 2019 (https://doi.org/10.1177/0272989X1988)



Reference: Khodyakov et al., 2019 (https://doi.org/10.1007/s40271-019-00389-4)

Recommendation 1: Assessment of growth

Height and length measurements for patients with Duchenne should be assessed every 6 months until puberty is complete and final height is reached.

Clinical reason for recommendation: To identify any growth delays early on by comparing individual's height to the height of children of similar age.

Process: Track height/length on a standard growth chart twice a year until puberty.

Additional information: Height and length measurements are typically taken during a routine health visit, and should be tracked every 6 months until puberty/final height is reached.

How important is the clinical reason for recommendation 1 for a typical individual/family with Duchenne?

	1	2	3	4	5	6	7	8	9	
Not very important	○	○	○	○	○	○	○	○	○	**Very important**

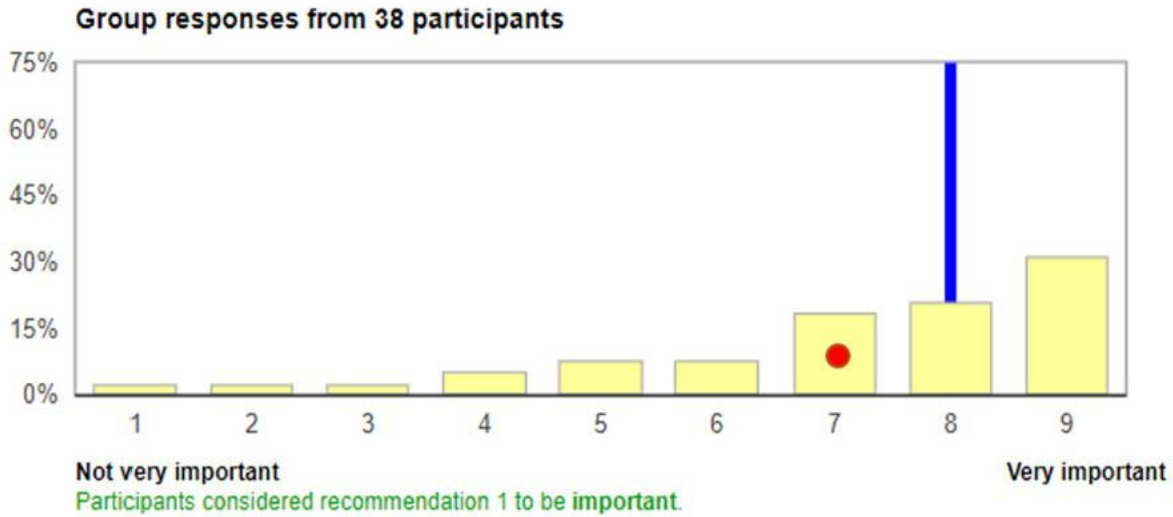
Please briefly explain your response. What factor(s) affected your response the most?

How acceptable is the process of following recommendation 1 to a typical individual/family with Duchenne?

	1	2	3	4	5	6	7	8	9	
Not very acceptable	○	○	○	○	○	○	○	○	○	**Very acceptable**

Please briefly explain your response. What factor(s) affected your response the most?

How important is the clinical reason for recommendation 1 for a typical individual/family with Duchenne?



Reasons For	Comment Summary
Low Ratings (1-3)	• Height is not that important (**Both**) • Height is an impediment to ambulation, if non ambulatory not important unless abnormally small (**Individuals w/DMD**)
Uncertain Ratings (4-6)	• Important but not as important as other issues (**Both**) • Somewhat important, and an easy measurement to take if ambulatory (**Individuals w/DMD**) • Measuring height is extremely difficult once non ambulatory and not very accurate (**Individuals w/DMD**)
High Ratings (7-9)	• Important to ensure that the measurements are correct for the corresponding age (**Individuals w/DMD**) • Important to make sure that the measurements are somewhat lining up with what others in the age group are (**Indivduals w/DMD**) • Important for early detection (**Caregivers**)

View Participants' Round One Comments ▸

Round Two Discussion

New Discussion Topic

Participants have stated that there are more important issues in DMD t ▸

Depending on a child responds to the Growth Hormone treatment, they ma ▸

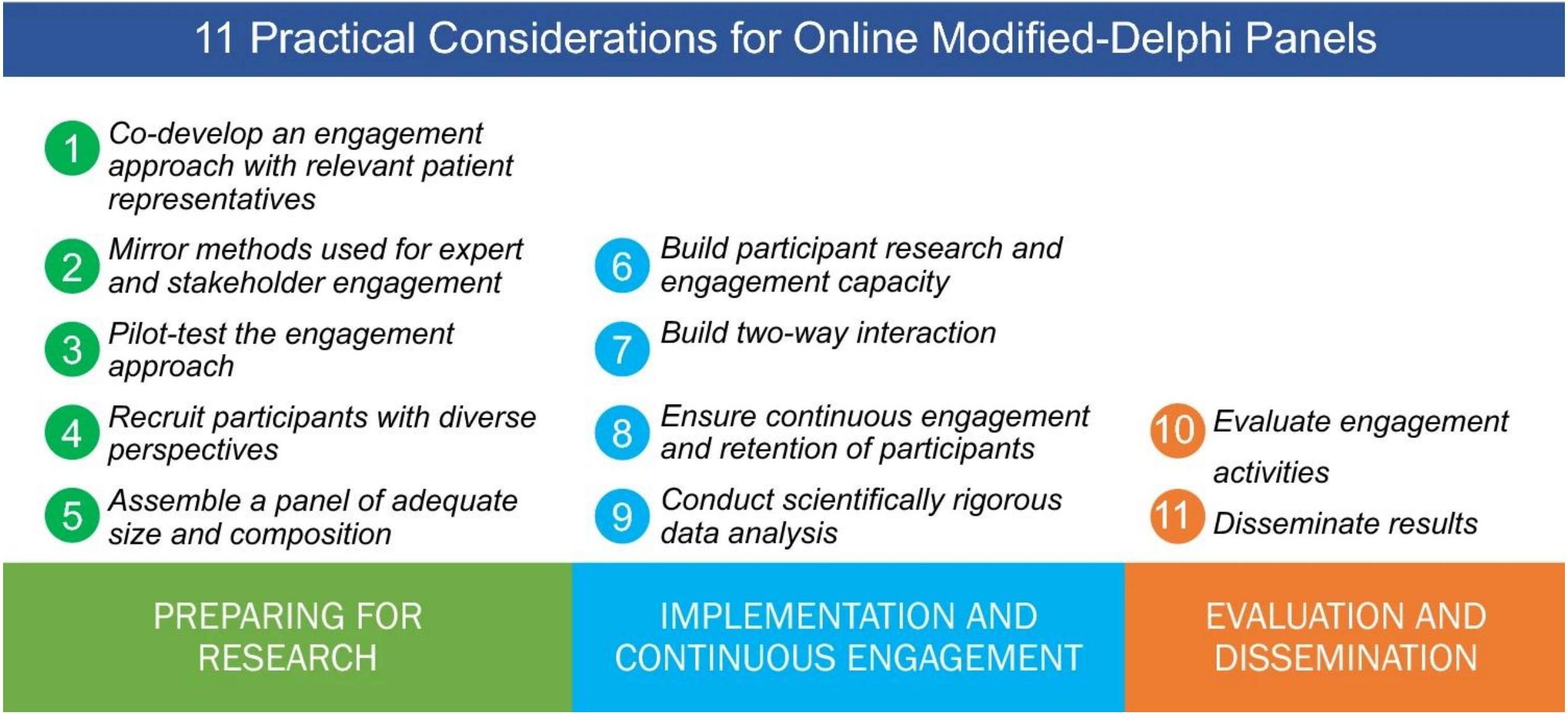
There are many issues to consider, caring for a child who has DMD. Di ▸

Reference: Khodyakov et al., 2019 (https://doi.org/10.1177/0272989X1988)

Characteristic	Panel A (*n* = 27)				Panel B (*n* = 27)				Patient-Centered[b]
	Importance		Acceptability		Importance		Acceptability		
	Median	Decision	Median	Decision	Median	Decision	Median	Decision	
Vertical growth									
Assessment of growth	8	+	8	+	7	+	9	+	Yes
Identification of impaired growth (7 years of age and younger)	7	+	7	+	7	+	8	+	Yes
Identification of impaired growth (between 8 and 12 years of age)	8	+	8	+	7	+	8	+	Yes
Identification of impaired growth (between 13 and 18 years of age)	8	+	8	+	6	u	7	+	No
Identification of reasons for impaired growth and development of a treatment plan	8	+	8	+	7	+	8	+	Yes
Treatment of impaired growth with growth hormone therapy (7 years of age and younger)	5	u	5	u	5	u	5	u	No
Treatment of impaired growth with growth hormone therapy (between 8 and 12 years of age)	6	u	5	u	6	u	5	u	No
Treatment of impaired growth with growth hormone therapy (between 13 and 18 years of age)	6	u	5	u	5.5	u	5	u	No

Reference: Khodyakov et al., 2019 (https://doi.org/10.1177/0272989X1988)

11 Practical Considerations for Online Modified-Delphi Panels



Reference: Khodyakov et al., 2019 (https://doi.org/10.1007/s40271-019-00389-4)

Example 2: Consensus on core outcome set

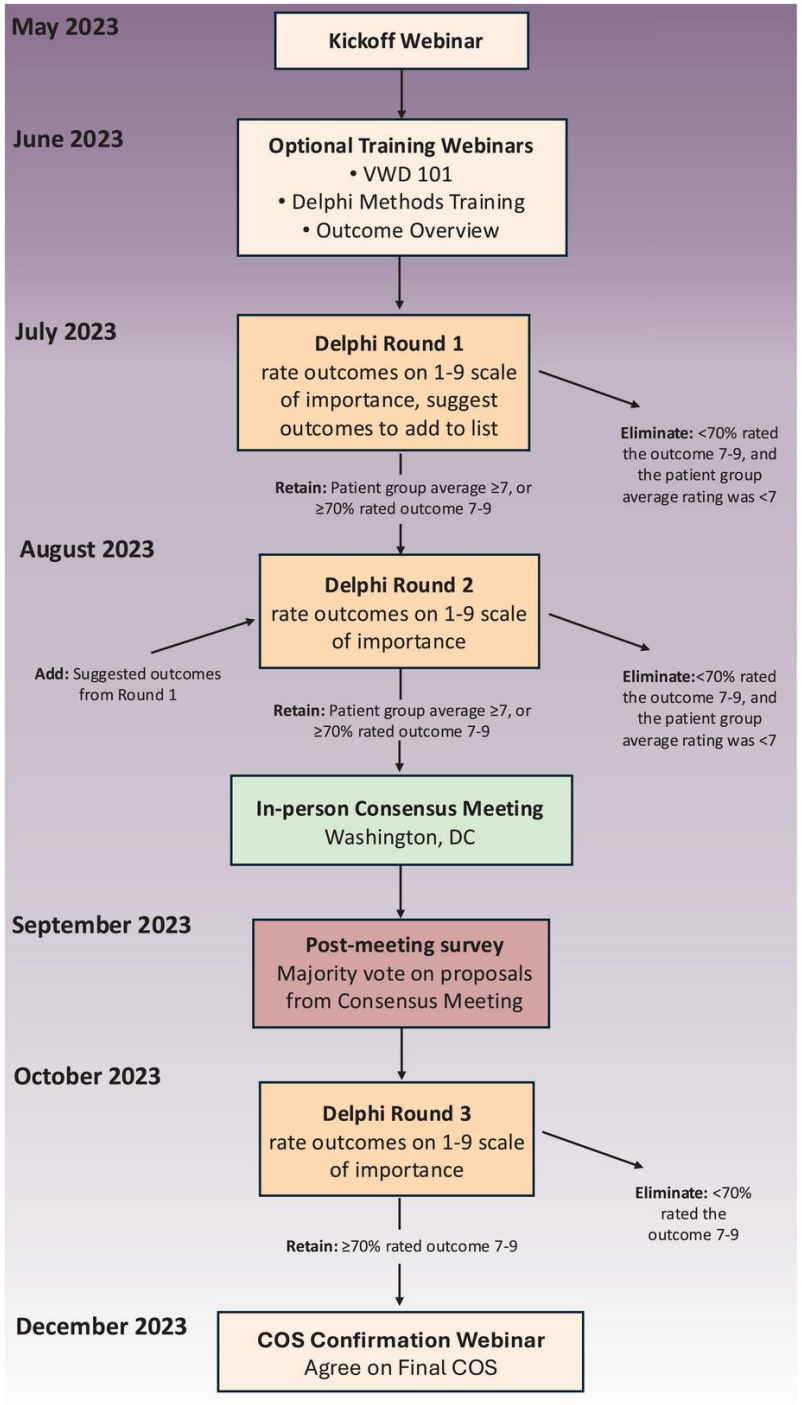
Context: Von Willebrand disease (VWD), an inherited bleeding disorder

Objective: Develop a core outcome set (minimum set of standardized outcomes that should be measured and reported for the health area)

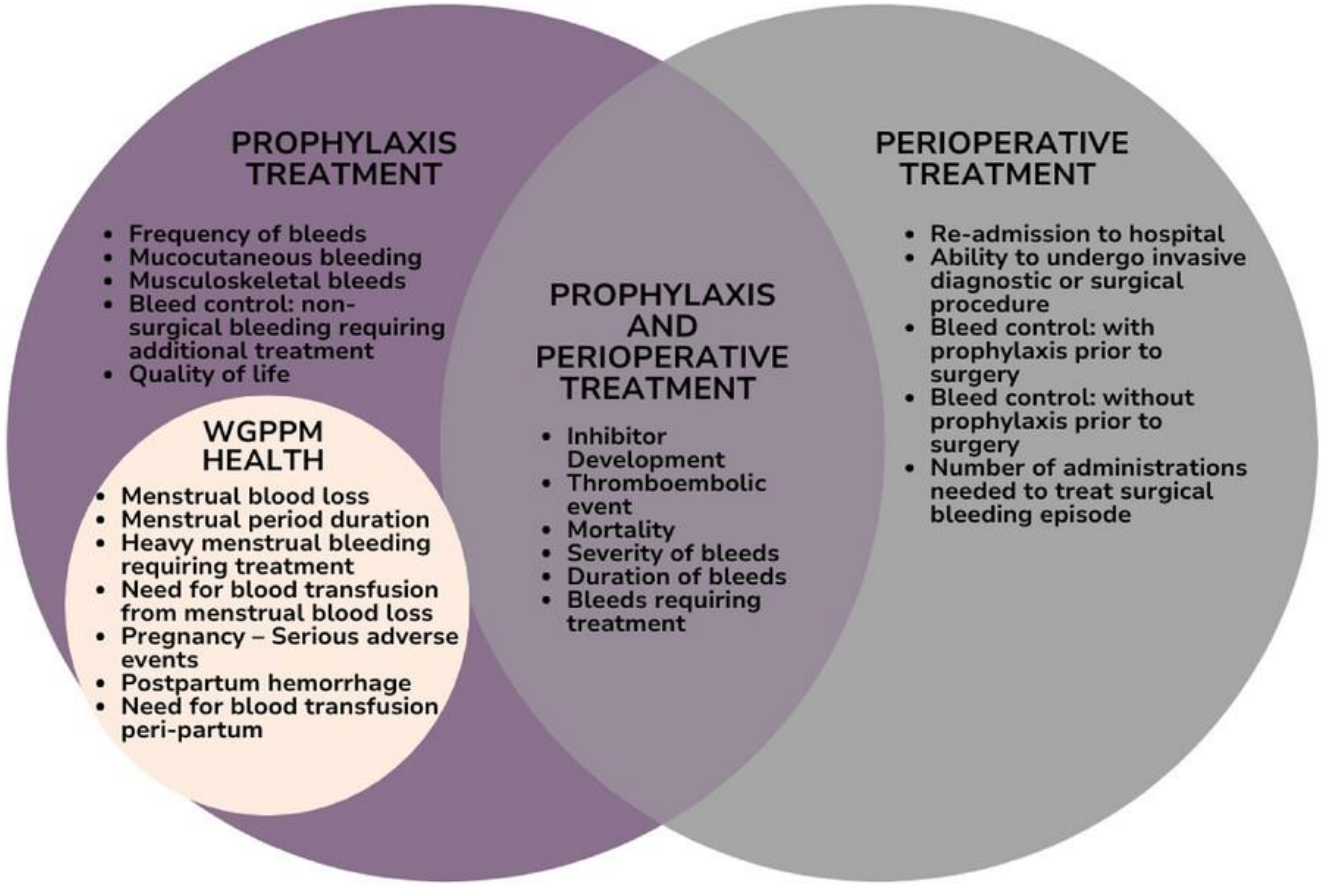
Method: Modified Delphi structured consensus process

Participants in Delphi panels: Patient representatives, clinicians, pharma company representatives, regulatory representatives

Reference: Clearfield et al., 2024 (https://doi.org/10.1111/hae.15122)



Reference: Clearfield et al., 2024
https://doi.org/10.1111/hae.15122



Thank you!

Holly Peay, PhD
RTI International
hpeay@rti.org


Panel Discussion
followed by
Q+A

Qualitative/Embedded Interviews

RTI (h)(s)
Health Solutions

13 December 2024

Patient-Focused Drug Development Virtual Workshop – Methodological and Other Challenges Related to Patient Experience Data

Design Considerations for In-Trial Qualitative Interviews

Dana DiBenedetti and Lynda Doward

The power of **knowledge.**
The value of **understanding.**

What are in-trial qualitative interviews?

- Interviews conducted during clinical trials is an evolving field of research
- The importance and value of conducting in-trial interviews has been emphasized by the FDA
- In-trial interviews are increasingly used to capture the patient voice to more fully understand the patient experience of the study treatment and trial processes

The collection of (mostly) qualitative data from clinical trial participants (or caregivers)

Patient (or caregiver) experiences and perspectives regarding treatment benefit may not be fully captured with traditional COAs

COA = clinical outcomes assessment.

Source: DiBenedetti et al. (2018).

Key Terminology of In-trial Interviews

Embedded vs. Stand-alone

Qualitative interviews embedded within clinical trial protocol

Advantages

- Generally, more efficient (time, costs)
- Maximizes participation (more likely to get buy in from both sites and patients)
  - Increases site and patient willingness and compliance, especially if included as another trial assessment
- Additional protocol amendments and IRB/ethics reviews may not be needed
- Can be included as a component of a clinical trial for select countries (does not have to be for the entire study)
- Does not significantly add to site burden

Challenges

- TIMING of clinical development program and preparing for and implementing the interview activities
- May require amendments to protocol and IRB/ethics reviews

vs

Interviews as independent stand-alone study (not in trial protocol)

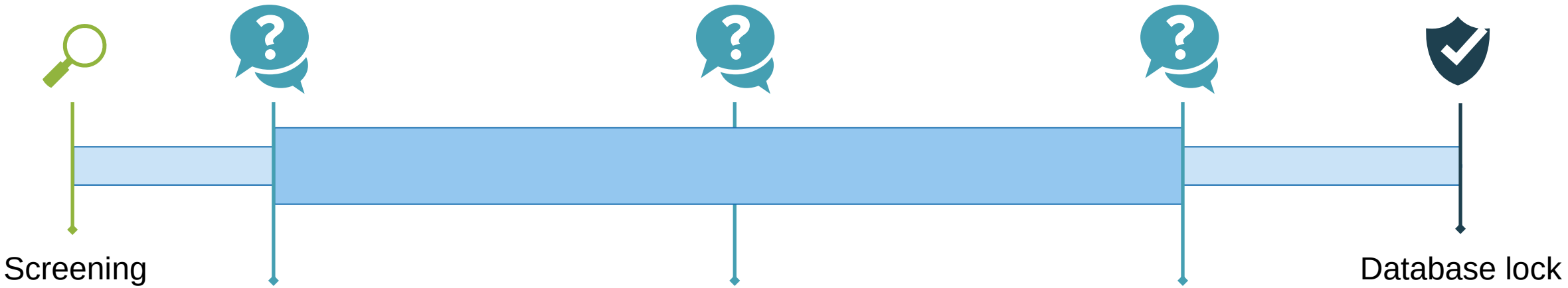
Advantages

- Do not have to amend current trial protocols or submit to IRB/ethics review
- Site contracting and IRB/ethics submissions managed by external partner
- Can implement interview study even after the trial is over

Challenges

- It is a whole new, independent study requiring
  - New contracts with sites and new IRB/ethics submissions
- Recruitment is often more challenging when QIs are outside of the clinical trial (or added late in the game)
  - Rely on BOTH sites and patients to volunteer
- TIMING required for new site contracts and IRB/ethics submissions
  - In some cases, may not be completed until after patients have already exited the trial

Key terminology of in-trial qualitative interviews



EOT = end of treatment; ET = early termination.

What kind of PED are collected in in-trial interviews?

Sample Interview Topics

Pre-study/treatment Experiences

- Disease-related symptoms prior to study and symptom bothersomeness ratings
- Impact of disease on patients' lives before starting trial
- Expectations of treatment

Post-study/treatment Experiences

Changes noticed, impact and importance of changes

- Changes/outcomes noticed, onset of changes
- Impact of treatment on most important/bothersome symptoms
- Impact of treatment on daily life/ functioning
- How well treatment addresses most important/bothersome symptoms

Treatment satisfaction

- Satisfaction ratings, reasons for satisfaction

Post-study/treatment Experiences

Perspectives of clinical trial

- Convenience of treatment
- Managing treatment schedule
- Perceptions of trial design (e.g., visit schedule, trial procedures)
- Challenges with clinical trial participation

PED = patient experience data.

Sources: DiBenedetti (2017); DiBenedetti et al. (2018).

How do we decide whether to include in-trial qualitative interviews?

What is your research question?

What questions are you trying to answer with the interviews?

Define the rationale

How do you plan to use the interview data?

- To support regulatory submissions?
- Reimbursement?
- Market access?
- Publication strategy?
- ***Define the objectives***

The research question and objectives drive the optimal design

How do we decide whether to include in-trial qualitative interviews?

RTI (h)(s) Health Solutions

Potential 'Good' Reasons

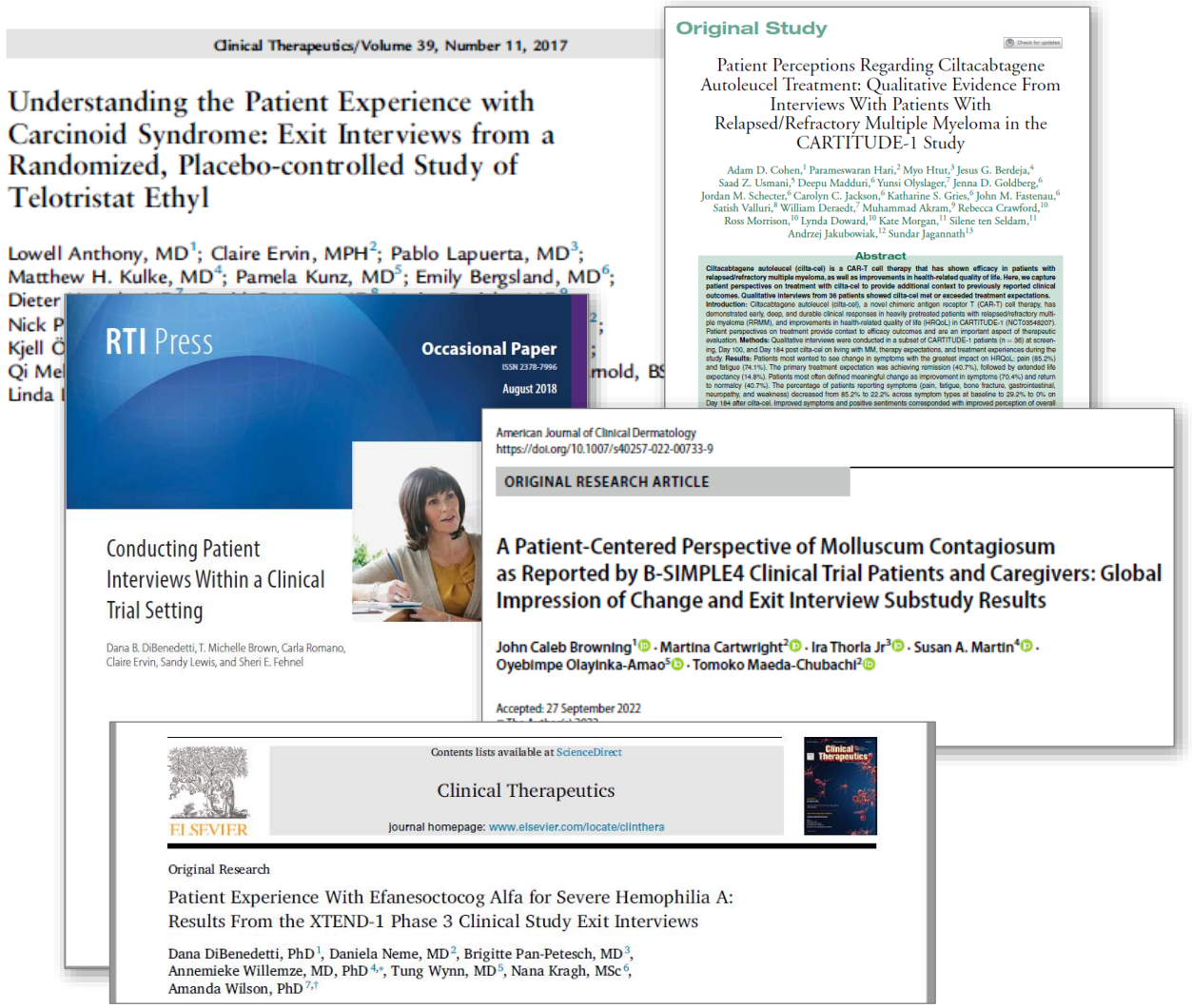
- To collect (mostly) qualitative data from trial participants to support COA-based (and clinical) endpoints
- To provide a better understanding of the disease and of patient experience
- To understand patients' evaluation of treatment received
- To describe meaningful treatment-related changes (positive and negative)
- To identify unanticipated treatment benefits
- To explore the impacts of the investigational product
- To identify unmet needs
- To generate evidence to support the content validity of a COA
- To capture patient experience of participating in a clinical trial

Less 'Ideal' Reasons

- Regulators *expect* to see in-trial interview data
- You've been asked to include them (e.g., by internal colleagues, via regulatory feedback) but you are not sure why
- You had them in your last trial
- You think it will be helpful or interesting
- Everyone else is doing it

All of these come under the banner of 'it seems like a good idea' but there is not always a clear understanding of precisely what research questions the team is trying to address

Where can in-trial interviews add value?



Regulatory Stakeholders

- Justify patient-perceived relevance of concepts selected for measurement
- Justify/support trial COAs (e.g., content validity, meaningfulness of change)
- Provide rich qualitative evidence to support trial endpoints
- Provide additional data to be considered in regulatory decisions

Reimbursement/HTA

- Support clinical benefit of product from patient perspective
- Provide PED beyond COA measurement to inform on outcomes not typically collected in clinical trials
  - For example, satisfaction, preferences for mode of administration
- Support unmet need, burden of illness
- Provide rich qualitative evidence to support patient-perceived benefit of intervention

Other (healthcare professionals, patient advocates)

- Provide rich qualitative evidence beyond what is typically collected in a clinical trial
  - Provide PED beyond COA measurement to support prescribing decisions
  - Helps payers/patient advocates understand how patients feel about the intervention
- Provide data to support advocacy/lobbying activities

Value of in-trial interviews: example

Exit interviews with clinical trial participants with carcinoid syndrome

- RTI-HS designed and implemented a qualitative study to explore perceptions and experiences of patients following their participation in a clinical trial
  - Specifically, telephone exit interviews were conducted with a subset of patients enrolled in a multinational phase 3 clinical trial to assess participant experiences with their disease as well as perceived benefits of the study treatment
  - Interview discussions also focused on the **patient-reported meaningfulness** of specific symptom improvements (including those assessed by the primary endpoint measure) and their associated impact on patients

- Study results
  - Cited by the FDA as supportive for drug approval[1]
  - Published in *Clinical Therapeutics*[2]
  - Presented at 2 professional conferences[3,4]

Sources: [1] CDER (2017); [2] Anthony et al. (2017); [3] Anthony et al. (2016); [4] Pavel et all. (2016).

Exit interviews with clinical trial participants with carcinoid syndrome

- CDER review of evidence from exit interviews conducted by RTI-HS[1]

> The review concludes that the evidence submitted by the applicant is adequate to demonstrate that the Number of BM Question in the DiaryPRO is adequate to measure the frequency of BM in the proposed context of use. The patient exit interview study and PRO psychometric analysis suggested that reduction of two BMs or 30% from baseline per day was considered meaningful by the patients.

- Interview data reviewed by EMA and by agencies in France, Wales, and Canada to support reimbursement[2]
- AWMSG noted the interviews provided additional value for their economic valuation[2]
- CADTH noted that quotations from patient interviews supported their decision on the drug[2]

AWMSG = All Wales Medicines Strategy Group; CADTH = Canadian Agency for Drugs and Technologies in Health.

Sources: [1] CDER (2017); [2] Michel et al. (2023).

Issues to consider in implementing in-trial qualitative interviews

Interview population	• Geographic location of patients • Sample size (all or sample of patients)	• Population-specific challenges • Respondent burden
Stand-alone vs. part of trial protocol	• Ability to amend clinical trial protocol influences design • Ease of recruitment of sites and patients	• Impact on timelines
Multi- vs. single-country interviews	• Multiple geographical locations add complexity, time, and cost • Number of countries is key factor in costs and operations	
Selection of study sites	• Successful study requires support/buy-in for study site staff • Number of sites is big resource driver	
Timing of interviews	• Timing during the clinical trial design process to plan for in-trial interviews • Timing of interviews (e.g., exit only, pre- and post-, multiple timepoints, “reach back” – after the trial has ended)	
Site-based vs. external interviewers	• Experienced, trained qualitative interviewers • Site personnel conduct highly structured interviews	
Budget considerations	• Interviews as part of clinical trial or stand-alone study • Number and location (country) of sites)	

Source: DiBenedetti et al. (2023).

Issues to consider in implementing in-trial qualitative interviews

Other Logistical Considerations

- Buy-in from stakeholders (i.e., senior management, trial teams, sites, co-sponsor)
- Timelines of clinical development program
- Languages/translations needed
- Budget
- Mandatory vs. optional qualitative interviews
- Adverse event reporting
- Site training for interview activities

Source: DiBenedetti et al. (2023).

Summary

Design Planning

Research Questions

Interview timing

Methodological considerations

Logistical considerations

Sources: DiBenedetti (2023); Kitchen et al. (2023).

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Disclaimer

- Dana DiBenedetti and Lynda Doward are salaried employees of RTI-HS.
- The views and opinions expressed in the following slides are those of the individual presenters and should not be attributed to RTI-HS or to the FDA.
-

PFDD Virtual Workshop – Qualitative & Embedded Interviews

Lundbeck Case Example – Development of a pediatric eDiary assessing treatment benefits in migraine

Anna-Karin Berger, Monika Rosen, Annika Lindsten, Melissa Herman, Bjørn Sperling

December 13, 2024

Patient Experience Data – Presentation Overview

The Journey

Development & validation of a pediatric headache eDiary, serving as primary endpoint in a pediatric migraine program by using Patient Experience Data (PED)

Step 1: Standalone Qualitative Interview Study	Step 2: FDA Type C Consultation - Feedback	Step 3: Embedded/Exit Interview Study
PED - inform the content and design of the pediatric eDiary	Strengthen strategy - bridging evidence gaps in early data using PED – embedded/exit interviews – obtaining further evidence	PED - support eDiary clarity, meaningfulness, ease of use, feasibility, patient- burden

Step 1

Development of the Pediatric eDiary – Qualitative Standalone Study*

- Concept elicitation and cognitive interviews were conducted in children and adolescents with migraine, as well as the primary caregivers (young children 6-11 years)

Objectives:

1. eDiary content **relevant and meaningful** based on **experience**
2. explore participants **understanding** of the diary
3. feasibility of **self-reporting** without parent/caregiver assistance

Part 1 - Concept elicitation interviews

1: Migraine experience 2: Symptoms 3: Impact on daily activities

Part 2 - Cognitive interviews

1: eDiary introduction 2: Understanding 3: Explore cognitive maturity

- Participants were stratified into **pre-specified age-bands** to explore cognitive developmental stage and language level

Table: Participants Recruited by Age Band and Subgroup

	Children (6 – 11 years)*			Adolescents (12-17 years)		
	6-7 years	8-9 years	10-11 years	12-13 years	14-15 years	16-17 years
Targeted N for recruitment within age band	3	4	3	3	4	3
Recruited within age band	3	2	3	2	4	3
Totals	**Total Children Interviewed: 8**			**Total Adolescents Interviewed: 9**		

* Primary caregivers for children 6-11 years were also interviewed

Population:

- Participants enrolled from **4 clinical sites** in the US (May 2020 and July 2021), with **confirmed diagnosis** of migraine
- Screened on socio-demographic characteristics
- In total **8 children/parents and 9 adolescents** were interviewed – **Target sample n = 30;** 10 children + caregivers and 10 adolescents

*Standalone study conducted by Evidera

Step 1

Standalone Interview – Outcomes & Conclusions

Concept elicitation Interviews

- Headache pain severe symptom – all age-bands
- Core migraine symptoms confirmed – all age-bands:
  - Pounding/throbbing pain
  - Nausea/vomiting
  - Sensitivity to light
  - Sensitivity to sound
- Other symptoms – sub-set of children & adolescents:
  - Visual aura
  - Tiredness
  - Light-headedness
  - Difficulty concentrating
  - Moodiness

Conclusion: Symptoms in ICHD-3 Migraine Diagnostic Criteria covered and **confirmed as meaningful** → **content validity** of pediatric headache diary verified.

Cognitive Interviews

Child interviews (6-11 years):

- Youngest children had challenges with some items (due to developmental maturity e.g., medication intake, dose etc).
- Revision – diary split, children self-report core symptoms and impact; parent report duration, medication intake and dose

Adolescent Interviews (12-17 years):

- Clearly understood all items except “aura”
- Revision – add description of aura symptom to the item (visual aura)

Conclusions: Minor revisions and to enhance **reliable self-reporting**, complimentary eDiary video and training materials were needed.

Step 2

Challenges & Strategy Forward

Pressed timelines due to regulatory agreement to start pediatric program forced the **qualitative study to close prior to all age bands being filled**

Lundbeck submitted request for **FDA Type-C meeting** - seek alignment/feedback on eDiary content validity etc.

FDA recommendation – further eDiary validation in phase III through **embedded exit interviews** and to inform the feasibility and burden of daily completion (impacting data quality primary and secondary endpoints) – **PED bridging evidence gaps** (by adding user experience)

Phase III implementation of **exit interviews** conducted with **40 consenting children and adolescents**.

Step 3

Embedded Exit Interviews & Trial Integration

Interview objectives:

- To gather additional evidence of **feasibility and content validity** of the pediatric diary
  - Understandability of diary items and instructions and child's ability to answer questions directed to them
  - Overall feasibility of the e-Diary design (for children 6-11 years old, completion of questions together with parent/guardian) and adolescents to manage without support
- Explore patient **perception of burden** regarding completion of the daily headache diary

Protocol Integration	Schedule of Assessment	Cohort	Interview Logistics
Exploratory endpoint within the trial protocol, optional assessment	Within 14 days of the participant's completion visit	40 Interviews in 8 countries 20 Adolescents (12-17); 20 Children/parents (6-11)	30 min. telephone interview by professional qualitative interviewer in local language

Cohort

Population	Age	Number of subjects	Interview Administration
Children	6-8 years	10	Parent/Child Dyads (child with parent first part for assistance and security; parent only second part)
	9-11 years	10	
Adolescents	12-15 years	10	Adolescent participants interviewed independent of parent/guardian
	16-17 years	10	
Total subjects:		**40**	

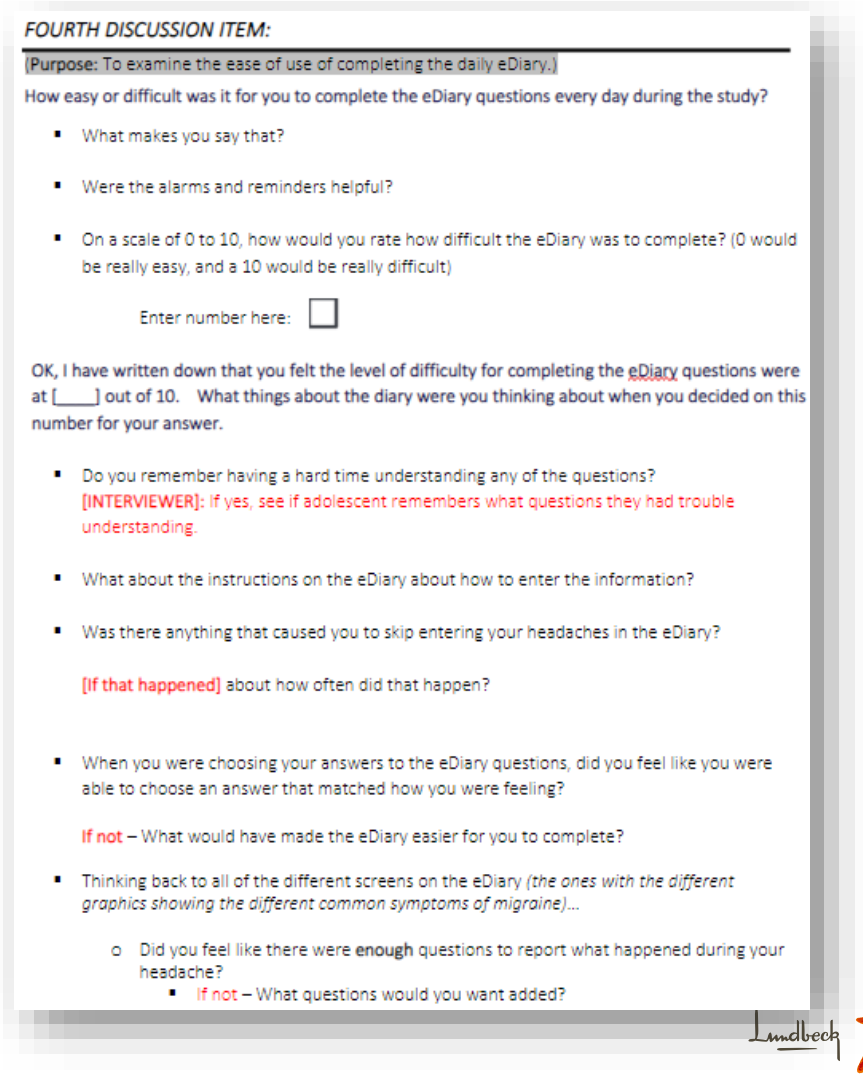
Considerations for country selection to enable cohort:

- Interviews optional in all countries selected
- Optional consent rate in previous adult migraine trials
- Cohort/country representation in global trial
- Planned order of country activation
- Per country evaluation, e.g., number of sites, number of enrolled participants, secure 25% children

Step 3

Interview Guide Example Topics & Questions

- **Overall clinical trial experience**, incl. most difficult and easiest aspects of trial participation
- **Logistics of completing the daily eDiary** (i.e., time of day, how it fit into daily routine, time to complete with and without headache)
- **Perspective and feelings about completing eDiary** (i.e., if and how it was a burden to complete, reasons for missed entry incl. headaches, overall likes and dislikes about the eDiary)
- **Ease and challenges of completing the daily eDiary** (i.e. question and instruction comprehension, relevance and clarity of questions and answer options
- Any suggestions to the eDiary (**improvements**)?



FOURTH DISCUSSION ITEM:

(Purpose: To examine the ease of use of completing the daily eDiary.)

How easy or difficult was it for you to complete the eDiary questions every day during the study?

- What makes you say that?
- Were the alarms and reminders helpful?
- On a scale of 0 to 10, how would you rate how difficult the eDiary was to complete? (0 would be really easy, and a 10 would be really difficult)

  Enter number here: ☐

OK, I have written down that you felt the level of difficulty for completing the eDiary questions were at [____] out of 10. What things about the diary were you thinking about when you decided on this number for your answer.

- Do you remember having a hard time understanding any of the questions?
  [INTERVIEWER]: If yes, see if adolescent remembers what questions they had trouble understanding.
- What about the instructions on the eDiary about how to enter the information?
- Was there anything that caused you to skip entering your headaches in the eDiary?

  [If that happened] about how often did that happen?

- When you were choosing your answers to the eDiary questions, did you feel like you were able to choose an answer that matched how you were feeling?

  If not – What would have made the eDiary easier for you to complete?
- Thinking back to all of the different screens on the eDiary *(the ones with the different graphics showing the different common symptoms of migraine)*…
  - Did you feel like there were **enough** questions to report what happened during your headache?
    - If not – What questions would you want added?

Patient Experience Data - Summary & Recommendations

Considerations in planning phase:

Standalone Interviews:

- Representative sample – socio-demographic characteristics (age, gender, education, ethnicity…)
- Participants – matching clinical trial population (inclusion/exclusion-criteria)
- Confirmation of clinical diagnosis - recruitment pathway - clinical sites vs other sources (e.g., PAGs, social media)

Embedded Interviews:

- Protocol integration – endpoint, timing, cohort
- Population of trial participants
- Define enrollment strategy
- Optional vs mandatory interviews
- Careful planning of country selection (geographical spread, country/site activation)
- Embedded interviews follow GCP

Well-designed standalone interviews can inform:

- Meaningfulness and relevance of trial assessments and endpoints (confirm validity of clinical endpoints)
- Reliability & feasibility around assessments and endpoints – prior to implementation to optimize clinical trial data quality

Well-designed embedded interviews can provide insights:

- Trial experience, e.g., patient-burden, feasibility of procedures/assessments, compliance, understanding missing data and risk of drop-outs
- Patient experience of the trial population, e.g., symptom experience, treatment benefit, meaningful change etc.

Seek alignment with FDA - primary or secondary endpoints to support label claims, to be used for treatment benefit/risk evaluation and support regulatory decision making

Acknowledgement

Lundbeck is grateful
to all the children, adolescents and caregivers
who participated in the headache eDiary
development and validation, and to the Evidera
team conducting the standalone study and the
exit interviews in the 19357A trial

Case Study

*An embedded mixed-methods exit study to contextualize and assess meaningfulness of treatment for Hypoactive Sexual Desire Disorder (HSDD)**

Hilary Wilson, PhD
Director, US Medicine
Boehringer Ingelheim

Presenter served as co-primary investigator of this mixed-methods study and was employed by Evidera at the time of study conduct, analysis, and publication. Study sponsor was Palatin.

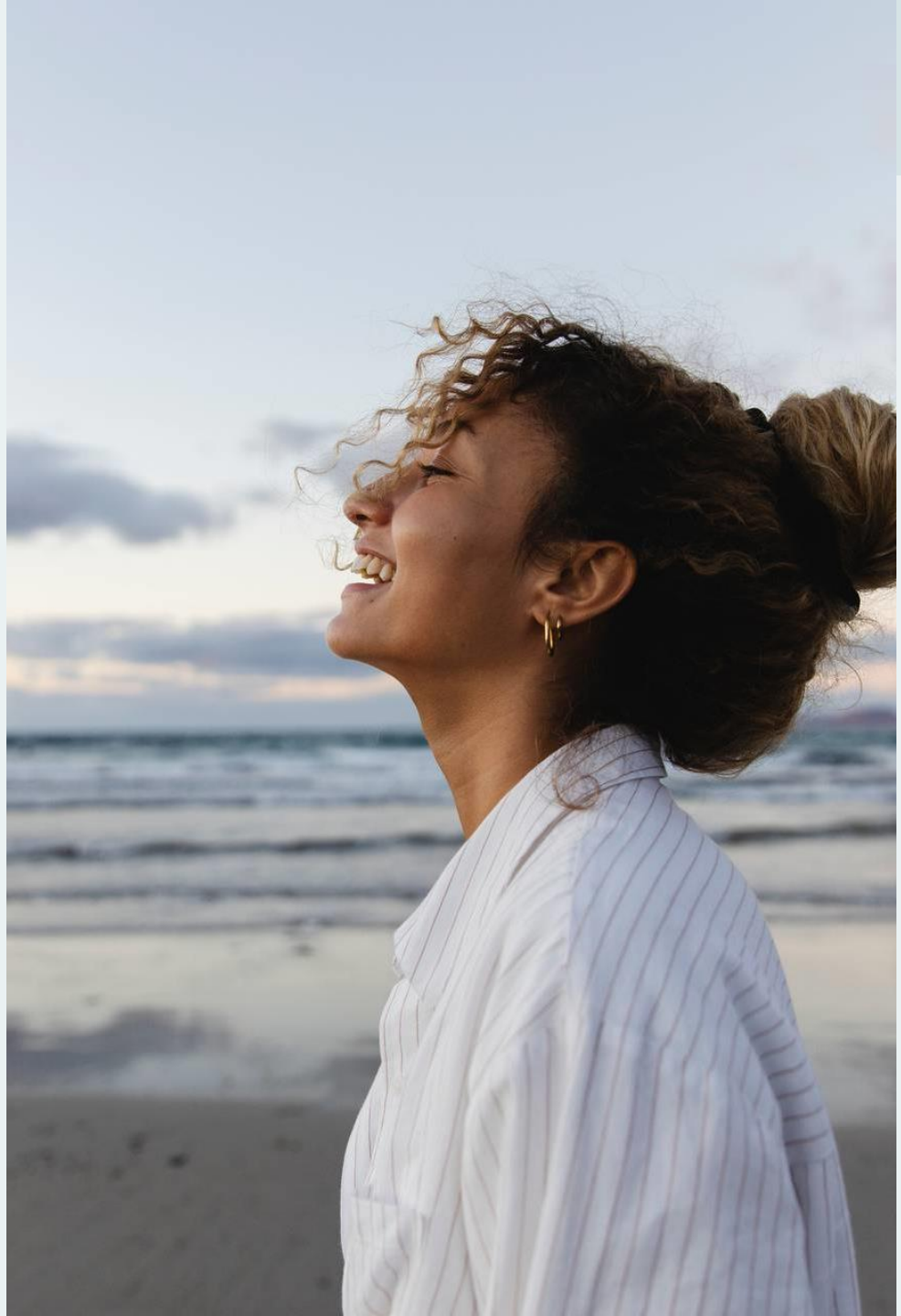
Background

The safety and efficacy of **bremelanotide** for the treatment of **hypoactive sexual desire disorder (HSDD)** was being evaluated in two identically designed, randomized, placebo-controlled, phase 3 clinical trials (RECONNECT).

Co-primary endpoints

- **Sexual Desire.** Change from baseline to end-of-study in the Female Sexual Function Index (FSFI) desire domain
- **Personal distress related to sexual desire.** Change from baseline to end-of-study in Item 13 *(bothered by low desire)* of the Female Sexual Distress Scale-Desire/Arousal/Orgasm (FSDS-DAO)

Additional evidence was needed to substantiate the **interpretation thresholds** for the **co-primary endpoints**.

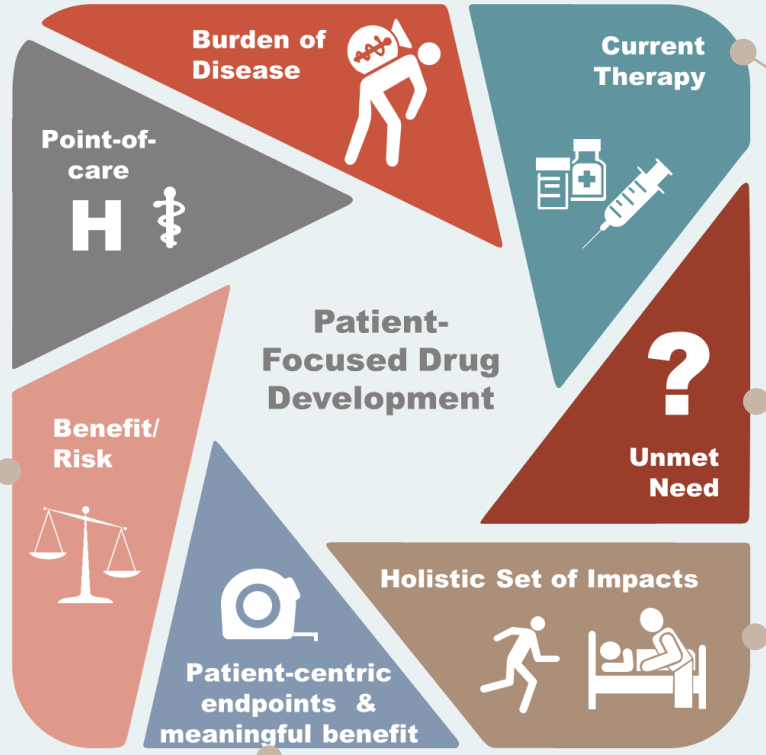


Approach

Embedded Exit Study to Contextualize Patient Experience and Treatment Benefit in Patients with HSDD in RECONNECT Trials

Characterize **symptom onset,** and experience with **key symptoms.**

Understand **experience** with the **auto-injector device**.



Understand **experience with existing treatments** and motivations and goals **for new treatments.**

Confirm the **most important impacts of** HSDD.

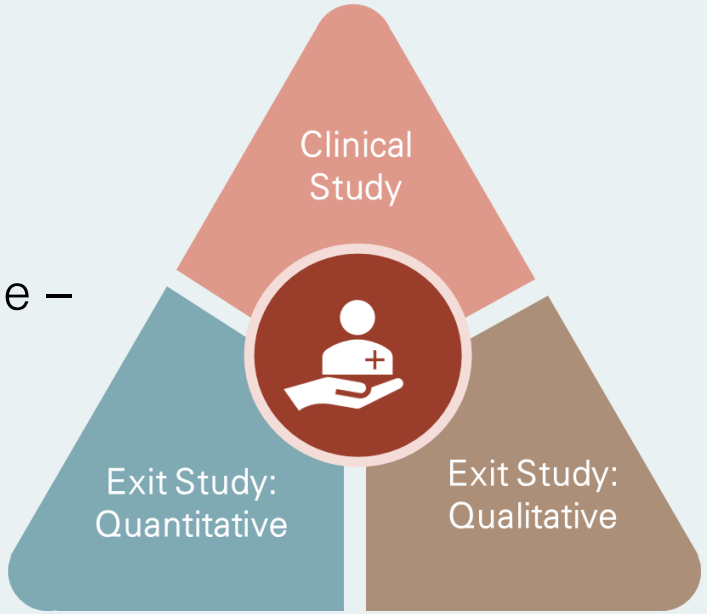
Contextualize what amount of **change in co-primary endpoints** is **meaningful** to patients.

Exit Study Method

Combined qualitative and quantitative, embedded in trial

Clinical Data

Co-primary endpoints



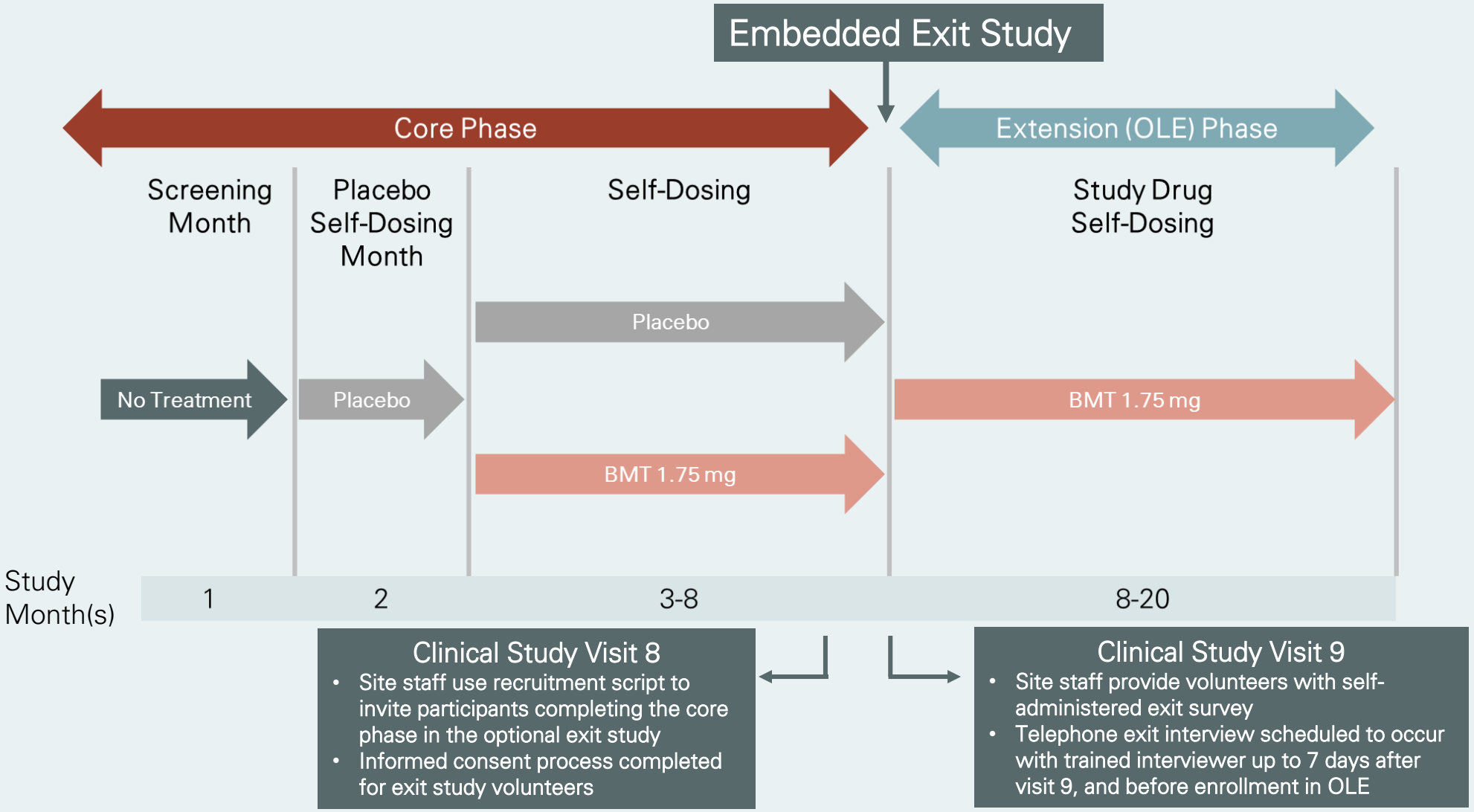
Survey (17-items)

- Anchor for meaningful change – overall and by 8 domains
- Experiences with study treatment and device
- Treatment satisfaction
- Most important treatment impacts
- **Sample size**: Up to 250

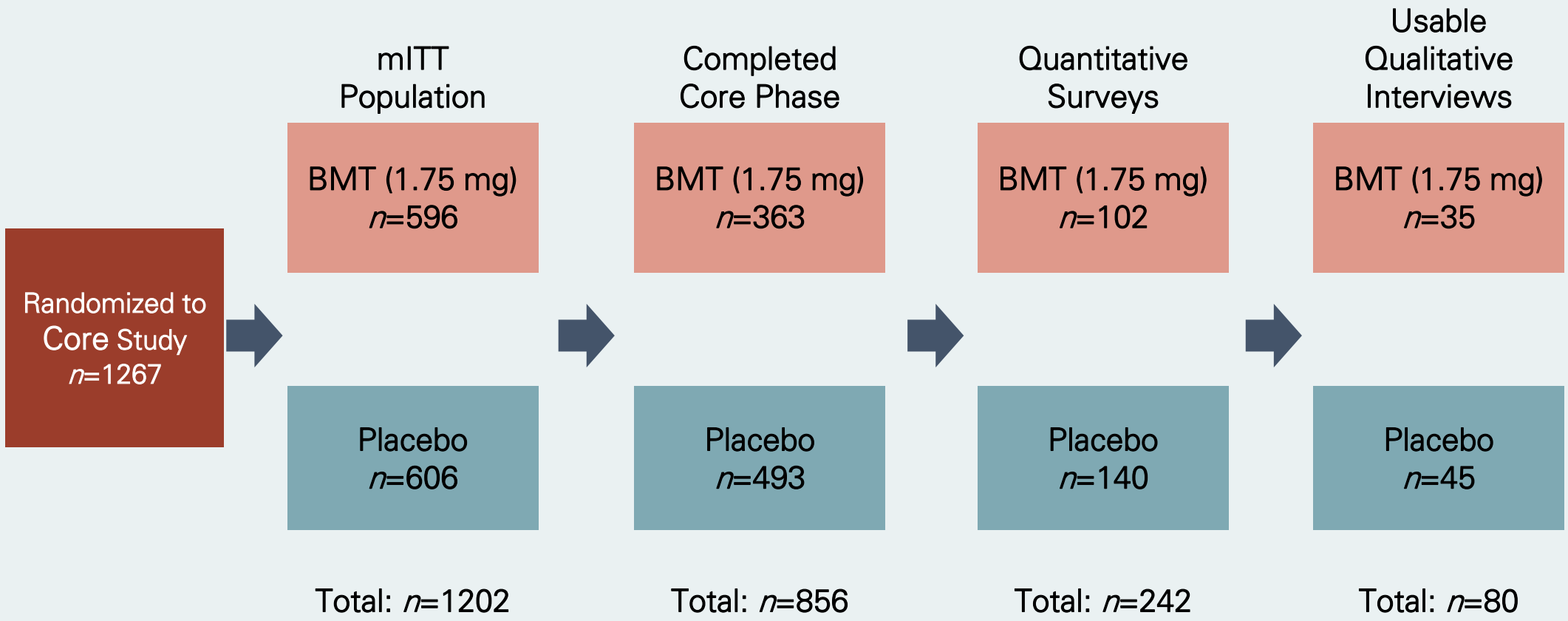
Interview (60 mins)

- Characterize onset of symptoms
- Experience with existing treatments
- Treatment preferences
- Most important impacts
- Meaningful treatment benefit
- **Sample size**: Up to 80

Phase 3 RECONNECT & Exit Study Design



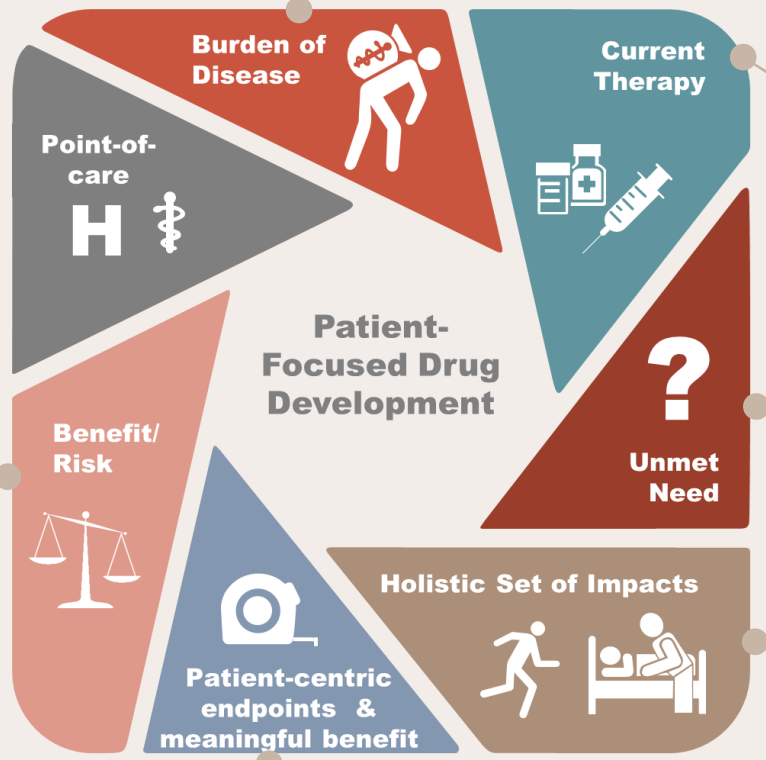
RECONNECT and Exit Study Enrollment



All participants, clinic staff and interviewers were blinded to study treatment.

Embedded Patient Experience Exit Study Insights[1]

- **Symptom onset** described as **gradual** by some and **sudden** by others
- Decreased **sexual interest & desire**, decreased **lubrication**, **less close to partner**, etc.



- **Device** well **accepted**
- **Mixed preference** for either a pill taken daily or or an injection as needed

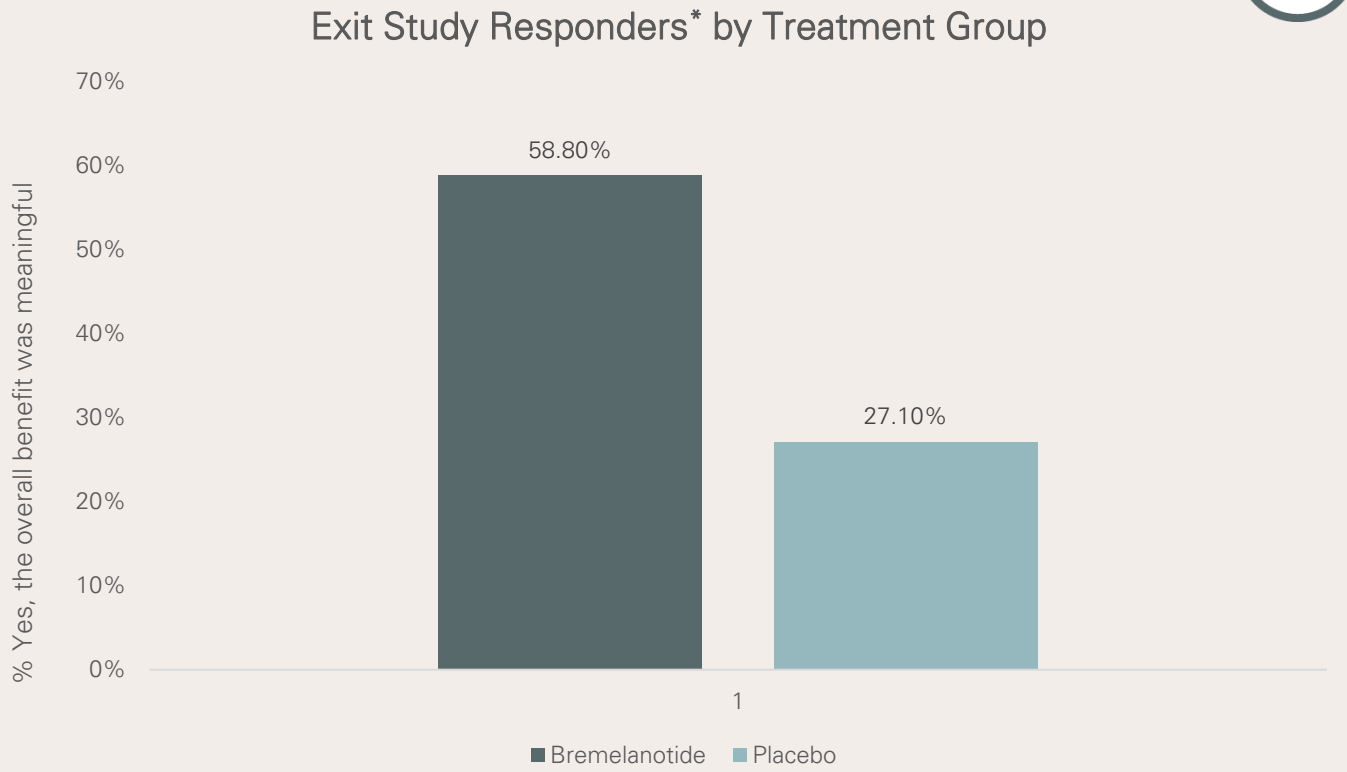
- Coping techniques and/or treatments women had tried to date **did not provide sustained benefit**.
- Most common motivation for treatment was to **increase desire**, improve **closeness with partner**, etc.

- Multi-dimensional **physical** (e.g. decreased lubrication), **emotional** (e.g. decreased confidence), and quality of life **impacts.**

- Women in **bremelanotide** group were more likely to report **meaningful benefit** and **tx satisfaction**.

[1]J Womens Health. 2021 Apr;30(4):587-595. PMID: 33538638

Embedded Exit Study Results
Clinical meaningfulness



*Exit Study Responders replied "Yes, overall, I benefitted from the study medication, and the benefit was meaningful to me" on Item 1 in Exit Survey.

Consistent themes in women in the **placebo arm: treatment expectations were not met**, and they either felt **no benefit**, or experienced benefit in **mental or emotional** changes.

Common themes in women in **bremelanotide arm**: **treatment expectations were met/exceeded**, and meaningful benefit detailed **mental**, **emotional,** and **physical** changes.

Bremelanotide

Women in bremelanotide treatment arm described **physical** effects, increased desire, **and emotional** effects.

*"So, after I would inject myself, I would—um, it would kind of give me a **little heat**—heat flash, um, so a little **warmness**, **a tingling**. I noticed it would just kind of run through my body."*

*"I would say definitely overall [it met expectations], just because, you know, it did give me **that increase** and **that boost**, uh, to—**to want to do that** and, um, increased, you know, the sexual activity like I said from zero to two to three times a month. So, to go from not having, you know, any sex drive or even being remotely interested at all to doing that and being close with my husband, I would say **it definitely**, you know, um, **worked for me**."*

Placebo

Women in placebo arm described **either no effects** – or effects **limited to emotional benefit.**

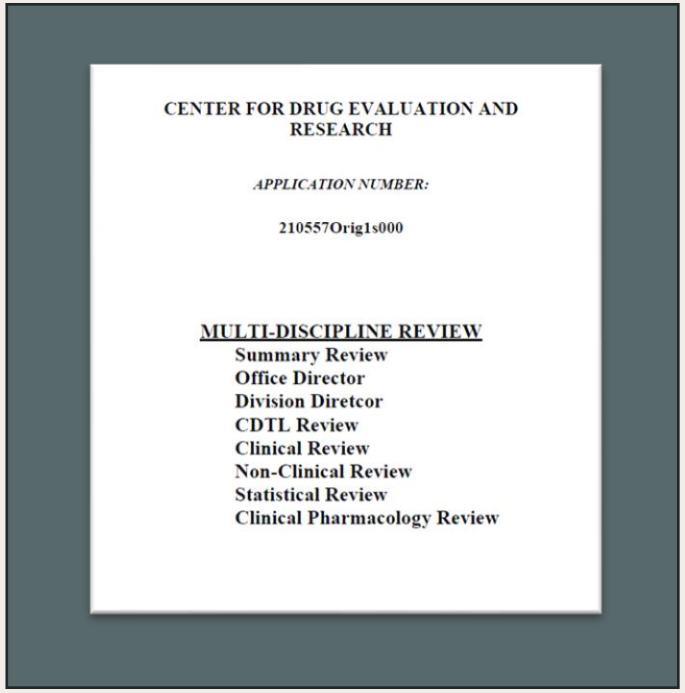
*"I was sort of looking forward to something that helped me and it sort of fell short. I didn't get anything out of the study. There **was no change in my desire,** and I was kind of bummed about that."*

*"Uh, the **emotional changes** I noticed would be more of my commitment to having intimate—an intimate relation—or intimate evening with my husband. **But physically I didn't feel anything** different."*

*"I feel like it—**it was very psychological** and **not so much physical**. I was kind of hoping it would be a physical reaction, that I would just, you know, have this like overwhelming desire and I never really felt that."*

Embedded Exit Study Impact on NDA

The Exit Study Report was leveraged together with psychometric analysis of the clinical trial data as supportive evidence of **meaningful clinical benefit** in the New Drug Application for bremelanotide, as referenced in the COA consult within the multi-disciplinary review package.



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210557Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Division Diretcor
CDTL Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

Review of exit study & clinical data by the FDA COA scientist contributed to the selection of responder definition for FSFI Desire Domain.

Methodological Considerations for Embedded Interviews to inform Interpretation Thresholds

- Qualitative insights in this study were used to **provide complementary support** of **responder thresholds** proposed in the psychometric analysis by comparing descriptive themes in responders vs. non-responders and bremelanotide vs. placebo.
- Alternative analytic approaches include applying a **mixed-methods matrix analysis**[2], or **qualitative anchoring approach**[3]. The application of these methods is emerging and there are no industry guidelines or standards.
- An **advisory committee** with patient representatives, disease experts, and measurement scientists is a helpful approach to review and achieve consensus on interpretation thresholds.

[2]Miles M, Huberman A. *Qualitative data analysis: an expanded sourcebook*. Sage, 1994.
[3]Staunton H et al. J Patient Rep Outcomes. 2019 Mar 4;3(1):16. PMC6399361

Thank You

Women that participated in the RECONNECT and Exit Study

The Palatin Team, including external consultant Patricia Koochaki

Evidera Team, including Dennis Revicki, Robin Pokzryinski, Laura Swett, Julia Ingram, and Kellie Washington

Questions?

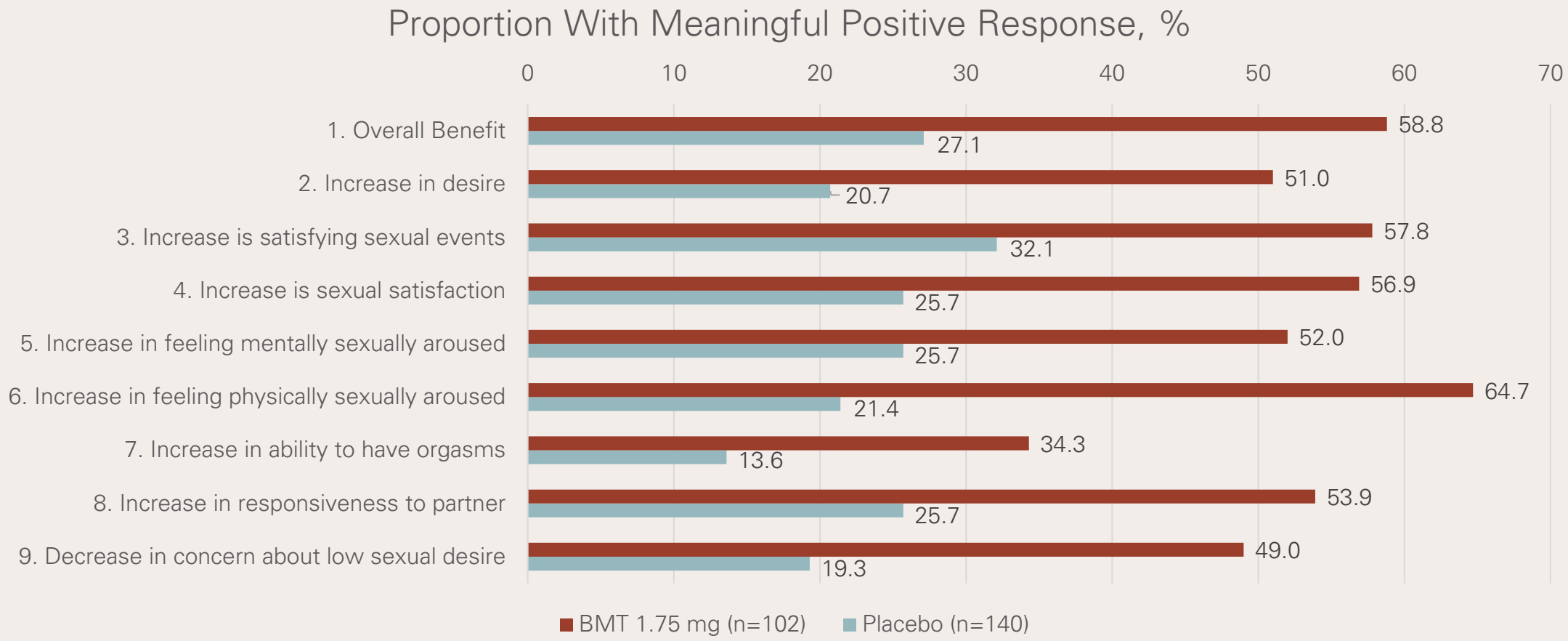
Hilary Wilson, PhD

hilary@devenwilson.com

Robin Pokrzywinkski, PhD, MHA

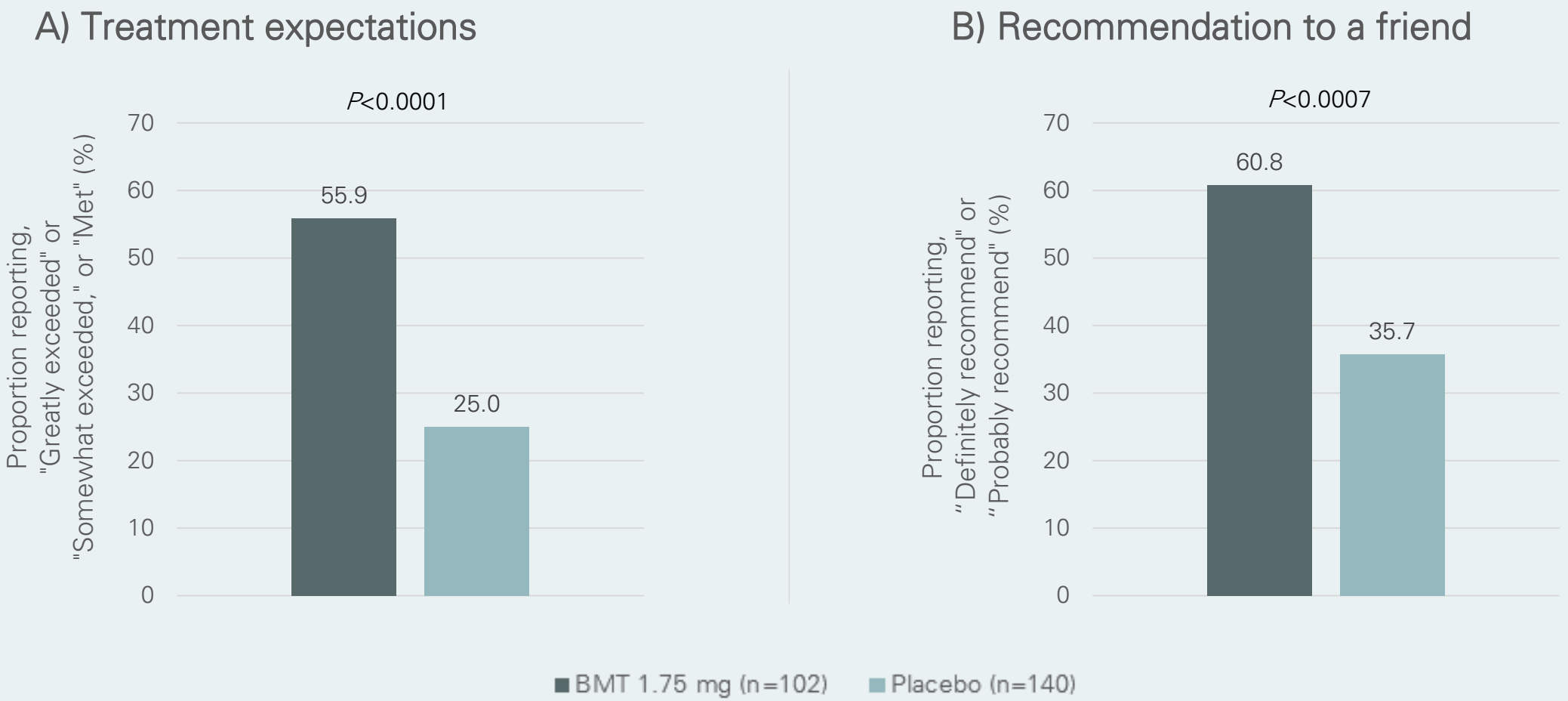
Robin.Pokrzywinski@evidera.com

Embedded Exit Study Results
Clinical meaningfulness



Survey Questions 1-9

Embedded Exit Study Results
Treatment expectations




Panel Discussion
followed by
Q+A

Break

Please return at 3:30 p.m. EST

Two Hot Topics: When to Consider Age-Normed Scores and Repurposing COAs for New Uses

Challenges related to using scales that were developed for use in clinical care then repurposed for use in clinical trials

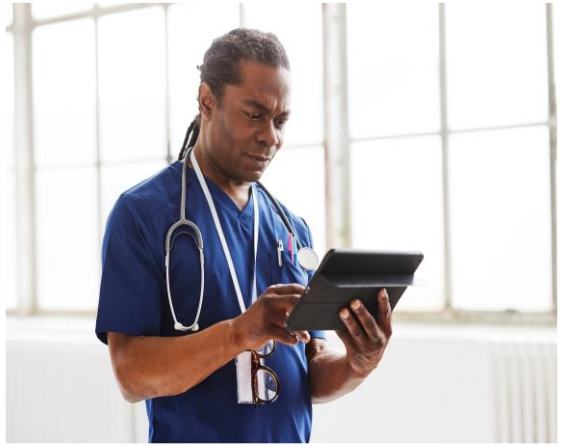
Cheryl D. Coon, PhD

Critical Path Institute

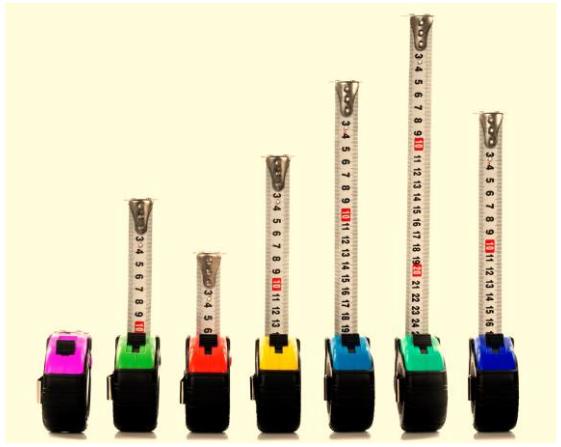
Critical Path Institute is supported by the Food and Drug Administration (FDA) of the Department of Health and Human Services (HHS) and is 56% funded by the FDA/HHS, totaling $23,740,424, and 44% funded by non-government source(s), totaling $18,881,611. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement by, FDA/HHS or the U.S. Government.

Why would we use scales developed for use in clinical care in clinical trials?

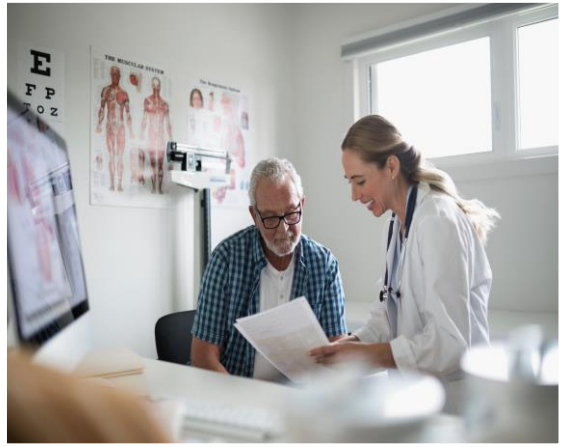
Available and ready to use



Clinicians are familiar with them



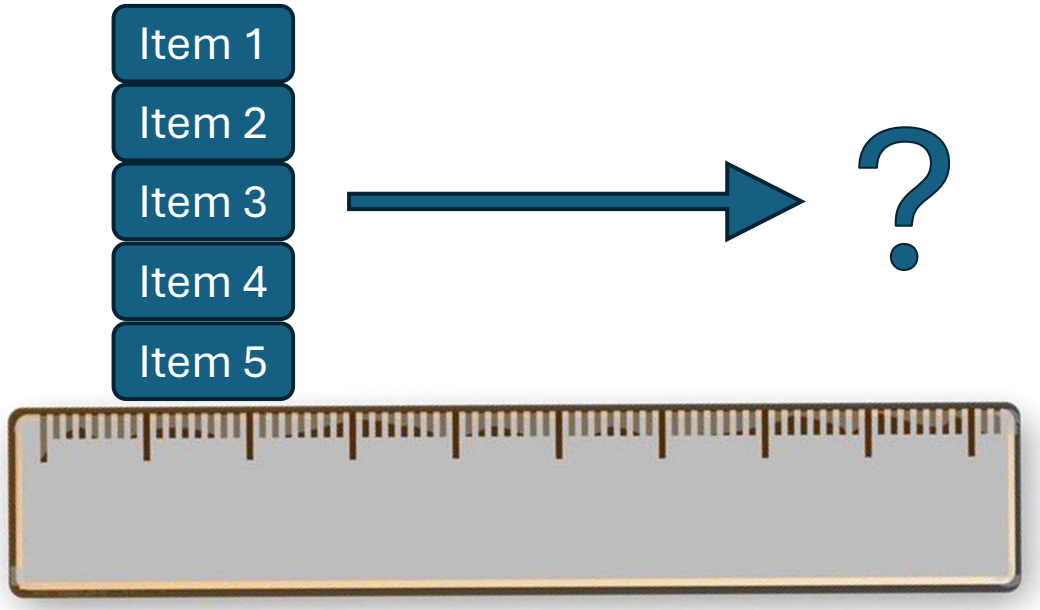
Can compare trial data to existing data



Clinicians can communicate trends using familiar metrics

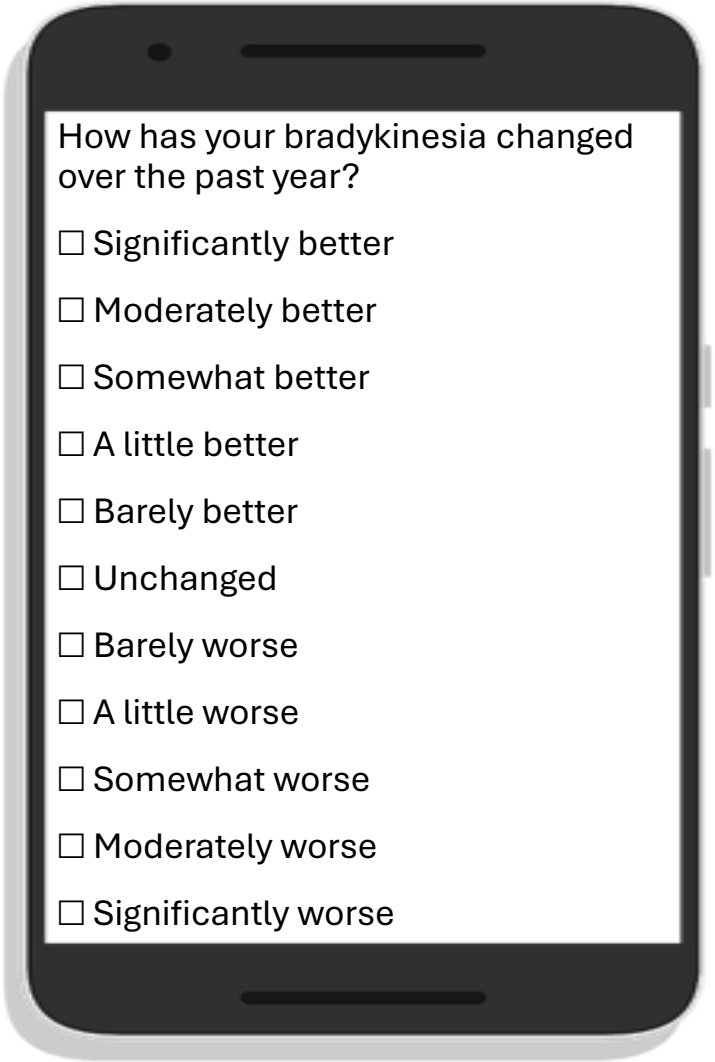
What are the potential risks with using scales developed for use in clinical care?

- If a scale was developed to screen or diagnose a condition, it might not be great for measuring changes over the course of treatment because its items may be targeted for a narrow range on the continuum of the condition.



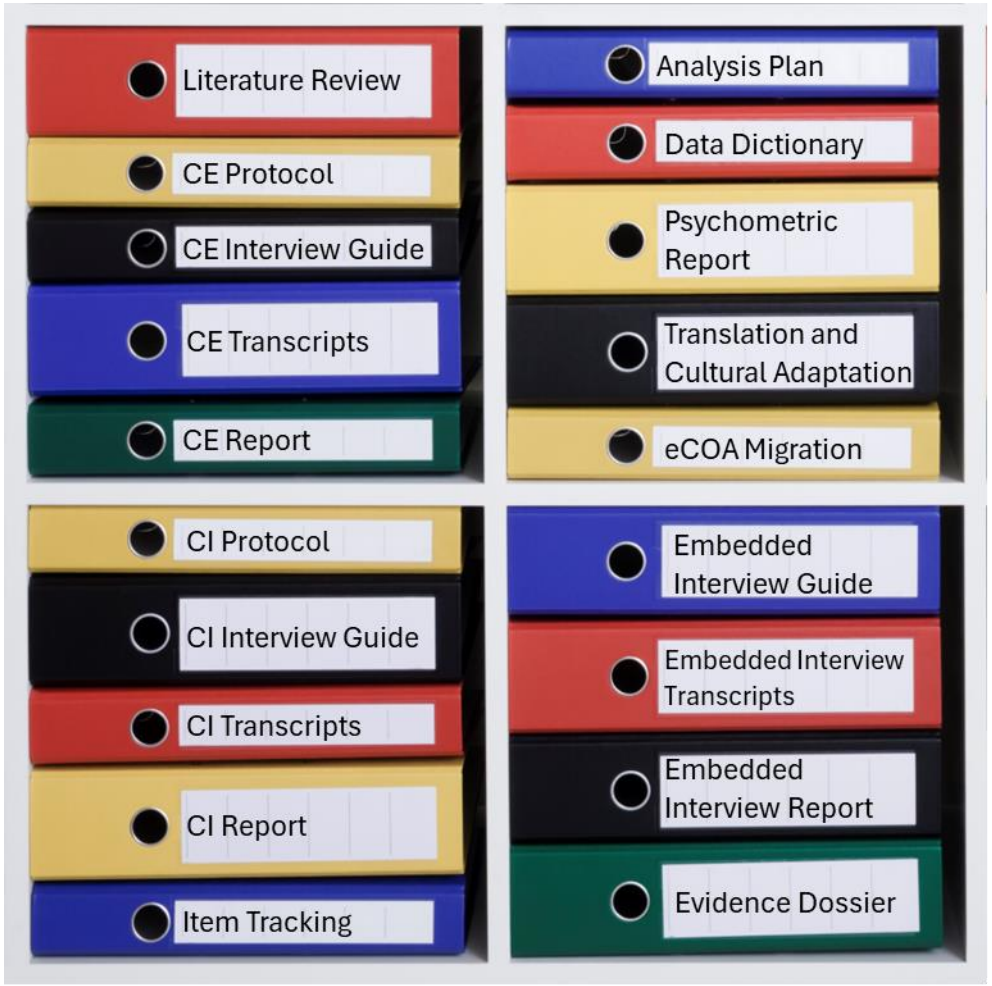
What are the potential risks with using scales developed for use in clinical care?

- If a scale was developed without regulatory expectations in mind, it might not have the type of recall period, response options, or patient involvement in its development that would be needed for clinical trial use.



What are the potential risks with using scales developed for use in clinical care?

- If a scale was developed without regulatory expectations in mind, it might not have its development evidence well-documented for regulatory submissions.



What are the potential risks with using scales developed for use in clinical care?

- A scale that allows for individualized measurement of a person over time in a clinical setting may make it too difficult to compare groups in a trial setting.

Summary

There are many good reasons for using scales developed for use in clinical care in clinical trials.

The use of a scale developed for use in clinical care in clinical trials is a decision that needs to be made with awareness.

Researchers must do their due diligence on the fit of the scale for the purpose of clinical trial endpoint construction.


Panel Discussion

U.S. FOOD & DRUG ADMINISTRATION

Using Age-Normed Scores to Evaluate Efficacy in Clinical Trials

Patient-Focused Drug Development: Workshop to Discuss Methodologic and Other Challenges Related to Patient Experience Data

December 13, 2024

Session 5: ***Two Hot Topics: When to Consider Age-Normed Scores and Repurposing COAs for New Uses***

What Are Age-Normed Scores?

Age-normed scores are scores that are ***adjusted*** for the patient's ***chronological age*** at the time of assessment.

EXAMPLE: Suppose we administer a performance-based measure of *oral expressive language development* to an individual patient.

The ***raw*** (non-normed) score indicates the individual's level of oral expressive language development.

Age-norming

The ***age-normed*** score indicates the individual's level of oral expressive language development **relative** to the individual's **same-age peers** in the **reference population** (e.g., general US population).

Utility of *Age-Normed* Scores

Clinically useful:

- In **clinical practice**, where understanding individual development or functioning relative to same-age peers can inform clinical decision-making (e.g., whether further clinical investigation or therapeutic intervention is needed).

- Defining **study eligibility criteria** (e.g., baseline symptom severity)

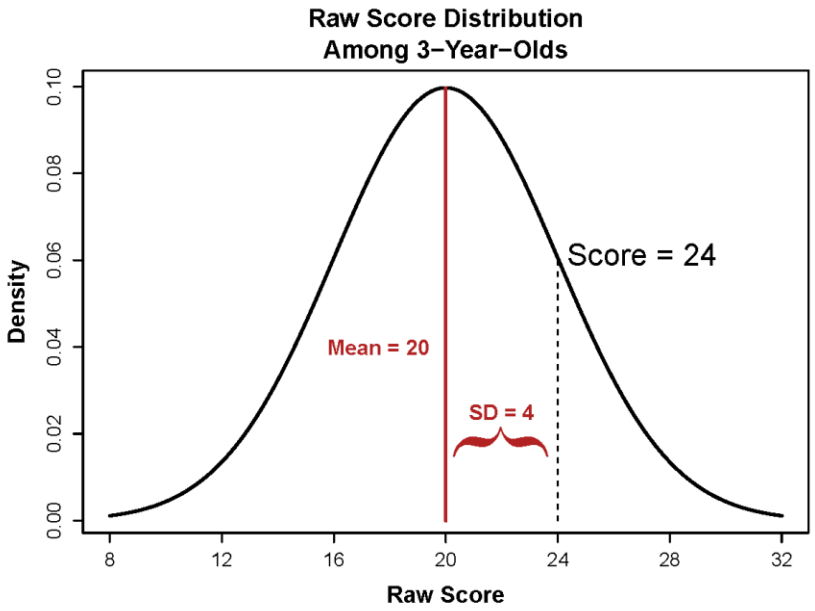
Limited utility:

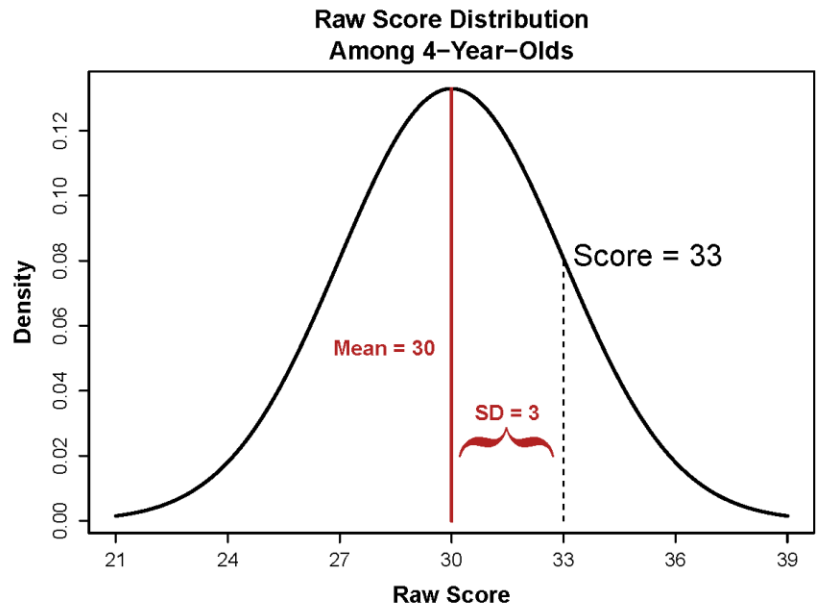
- Evaluating efficacy in clinical trials when scores are directly compared in analyses (analyzed continuously) and
  - Patients age out of one normative age group and into another over the course of a trial
  - Patients belong to different normative age groups *and any of the following:*
    - Treatment arms are **imperfectly balanced** with respect to normative age groups
    - **Insufficiently large** sample sizes overall and within each normative age group
    - Trial sample does **not** include a representative set of normative age groups

Behaviors, skills, and abilities associated with typical development *change* with chronological age.

Age-normed scores from different normative age groups that are numerically equivalent imply different levels of development.

EXAMPLE (continued):

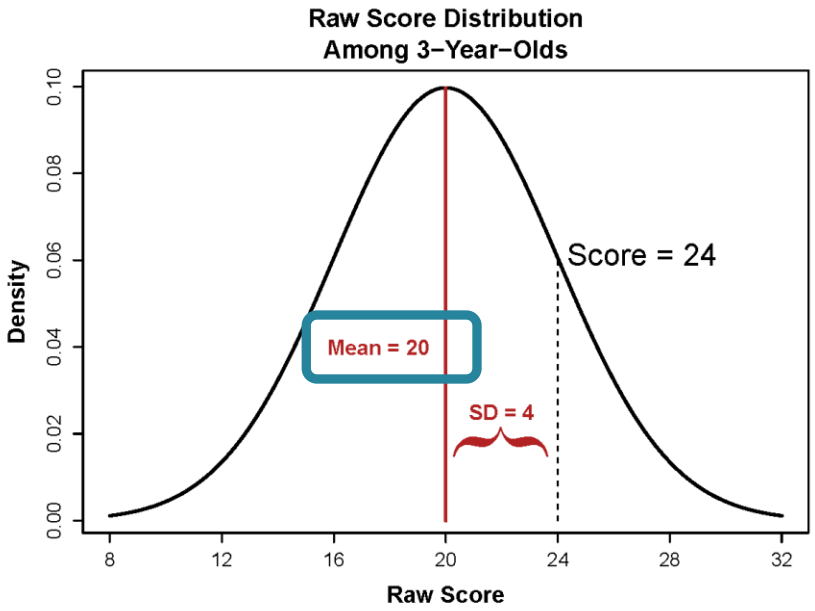


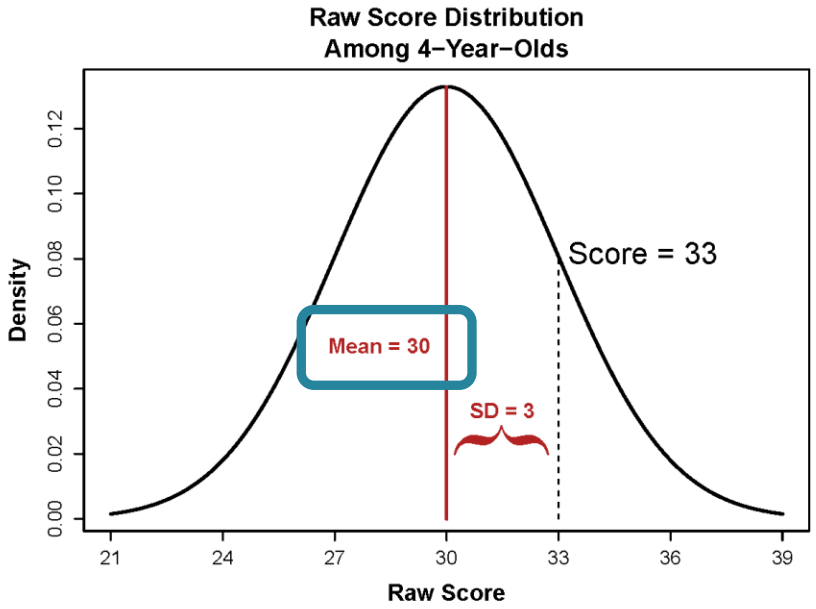


Suppose:

- We administer the performance-based measure of *oral expressive language development* to a **3-year-old** and a **4-year-old** and compute their raw scores.
- A *higher* raw score reflects a *higher* level of oral expressive language development.
- The reference population is typically developing individuals in the US population.

EXAMPLE (continued):

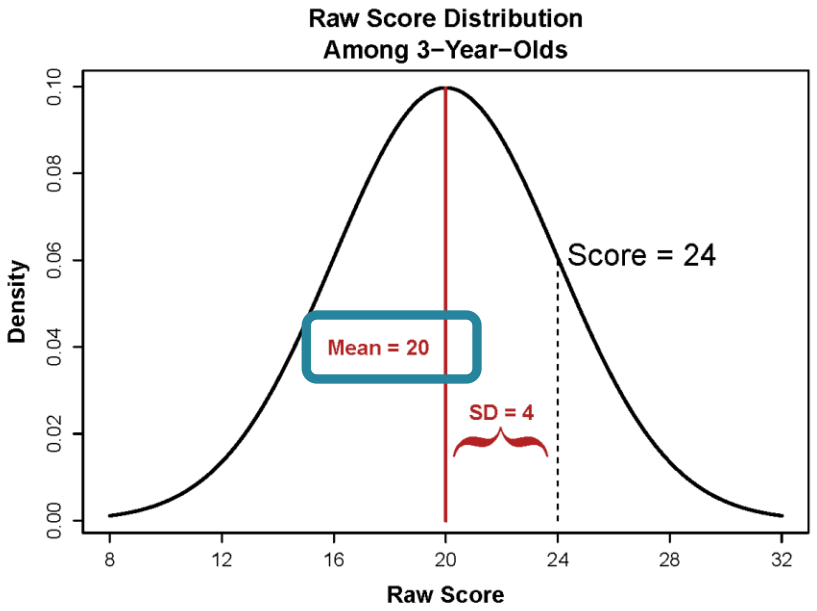


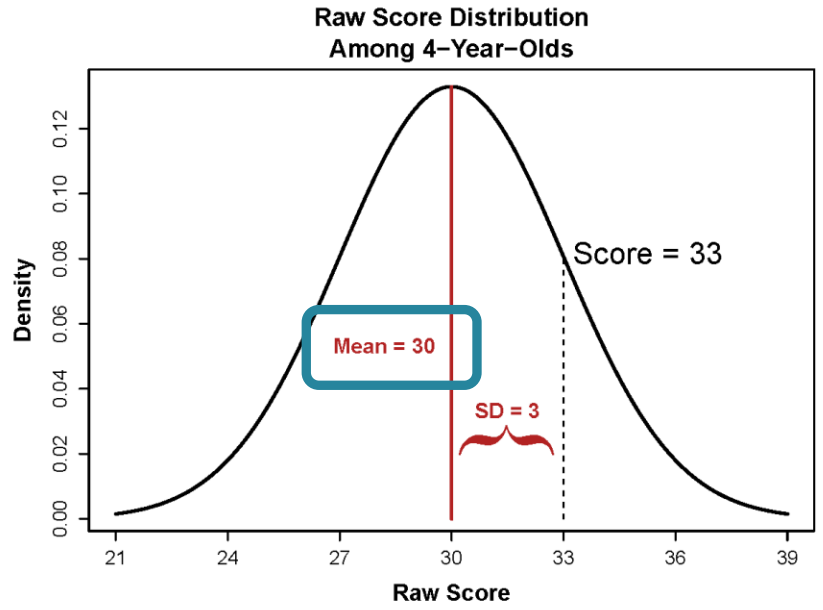


For children in the US population who are *typically developing* in terms of *oral expressive language* skills:

On average, 4-year-olds are further developed than 3-year-olds.

EXAMPLE (continued):



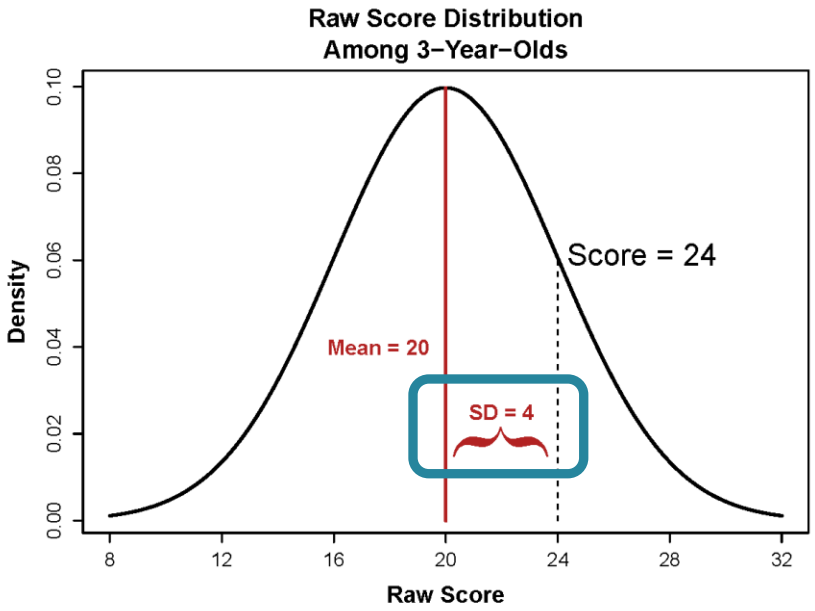


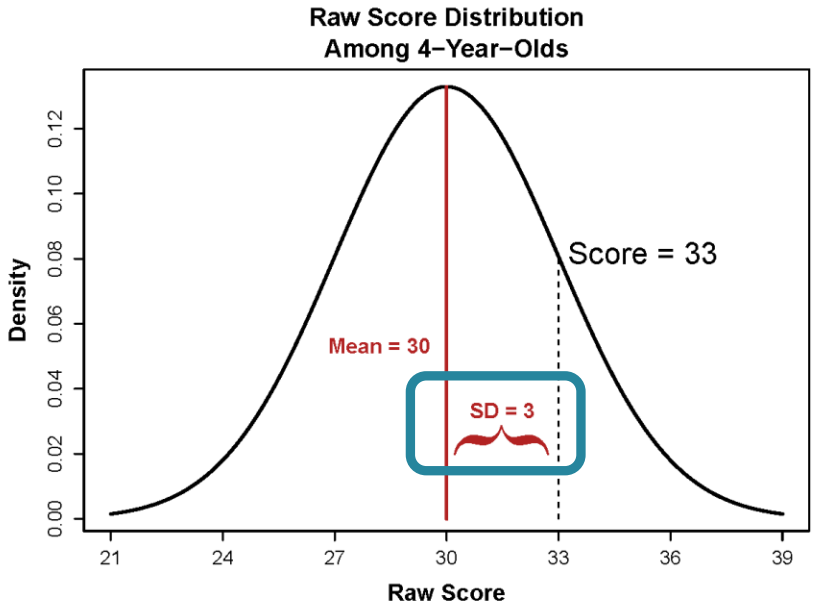
For children in the US population who are *typically developing* in terms of *oral expressive language* skills:

<u>On average</u>, 4-year-olds are further developed than 3-year-olds.

Oral expressive language behaviors, skills, and abilities associated with typical development *change* with chronological age.

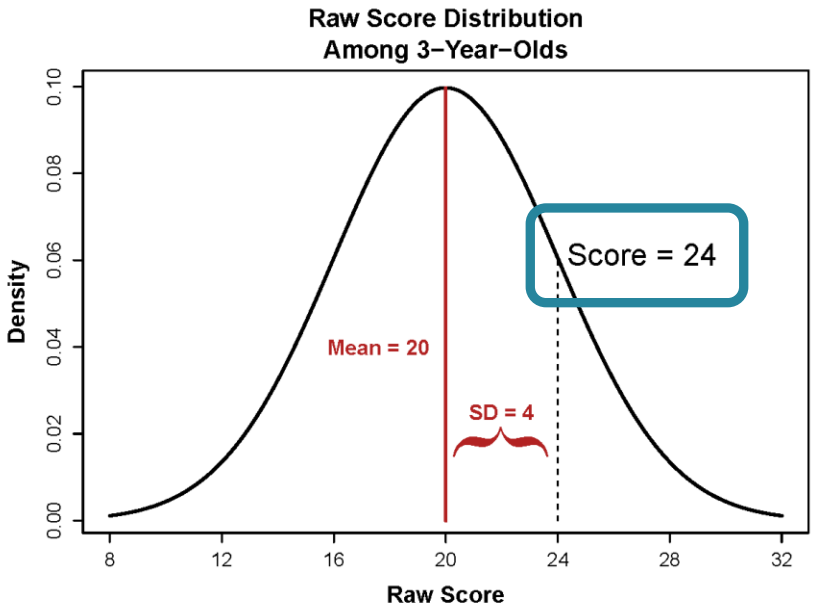
EXAMPLE (continued):

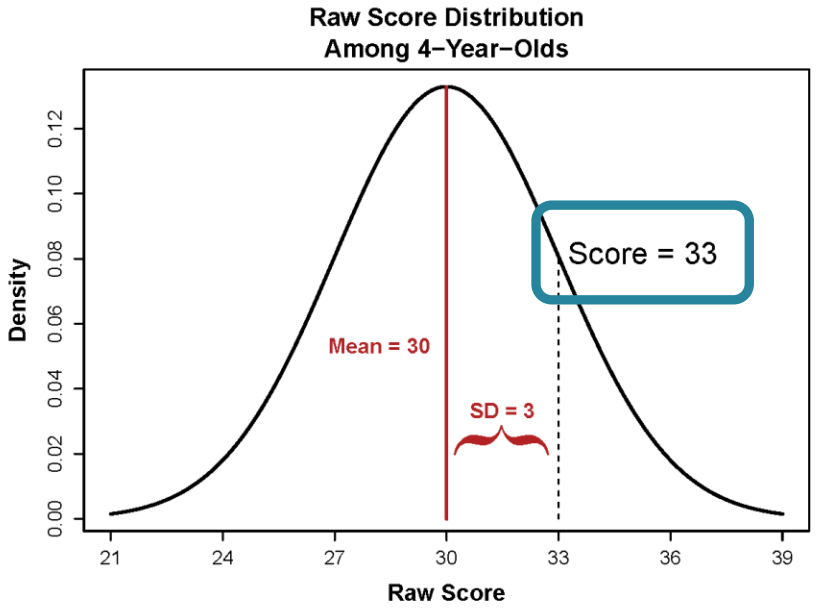




Variability in *level of oral expressive language development* decreases as children age from 3 to 4 years.

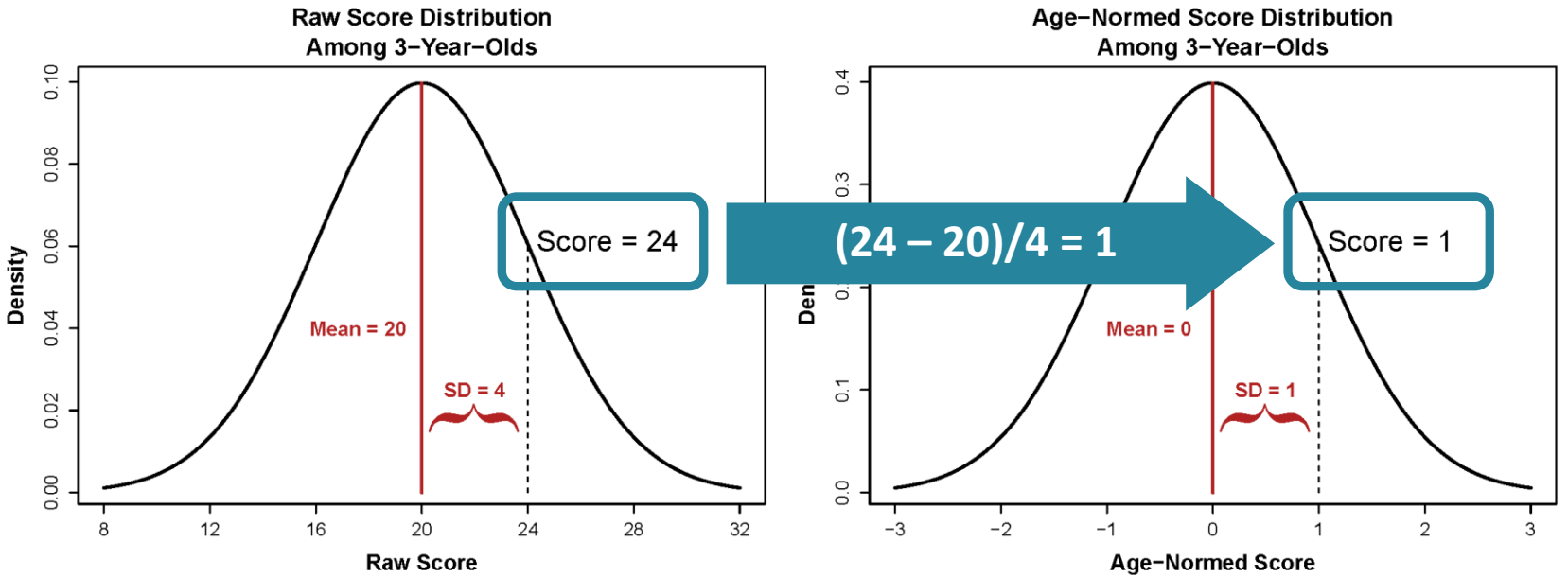
EXAMPLE (continued):

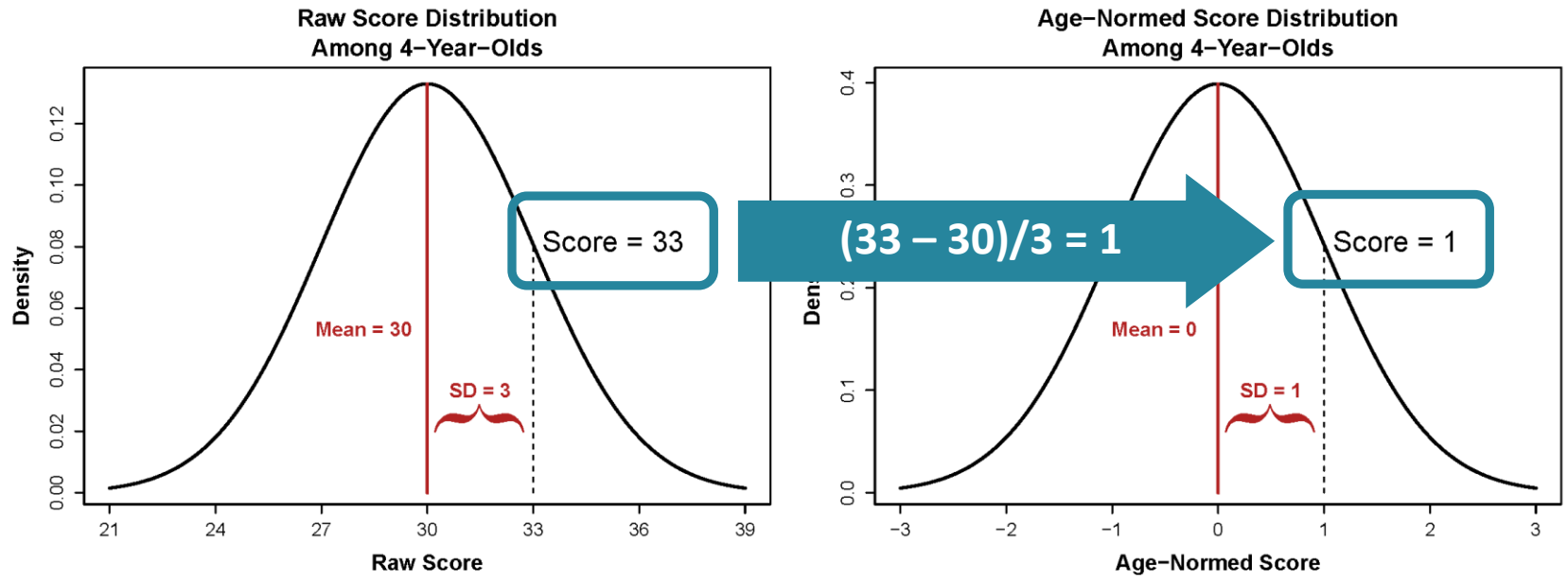




The **4-year-old** has a higher level of *oral expressive language development* than the **3-year-old**.

EXAMPLE (continued):



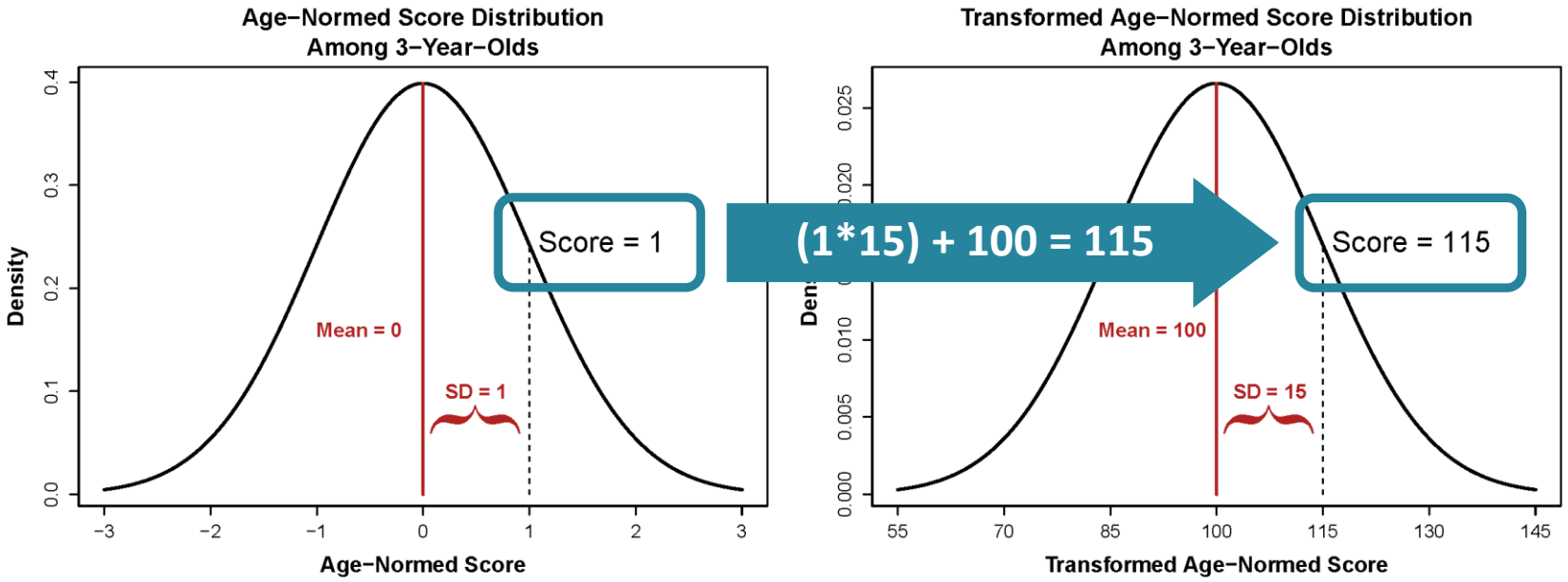


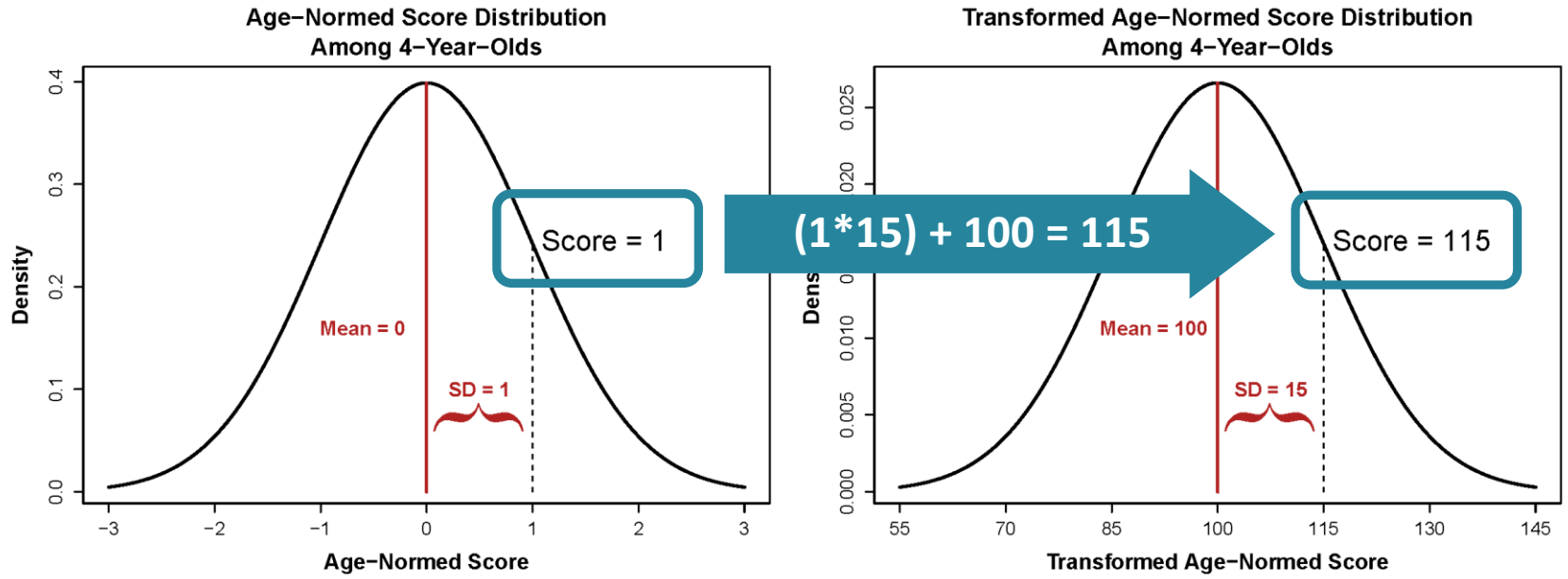
Both children are 1 SD above average relative to their same-age peers.

EXAMPLE (continued):

As such, they have the <u>same</u> age-normed score …

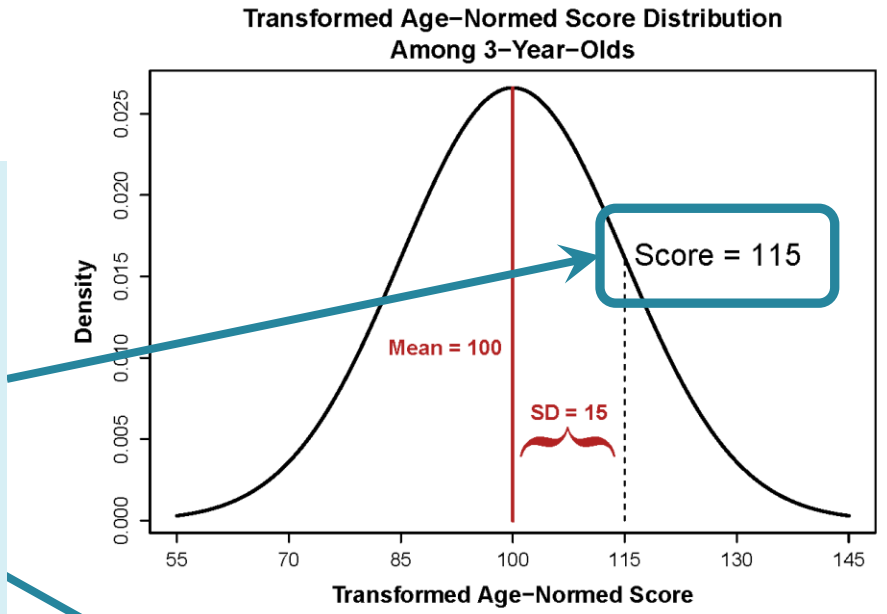
and the <u>same</u> *transformed* age-normed score.

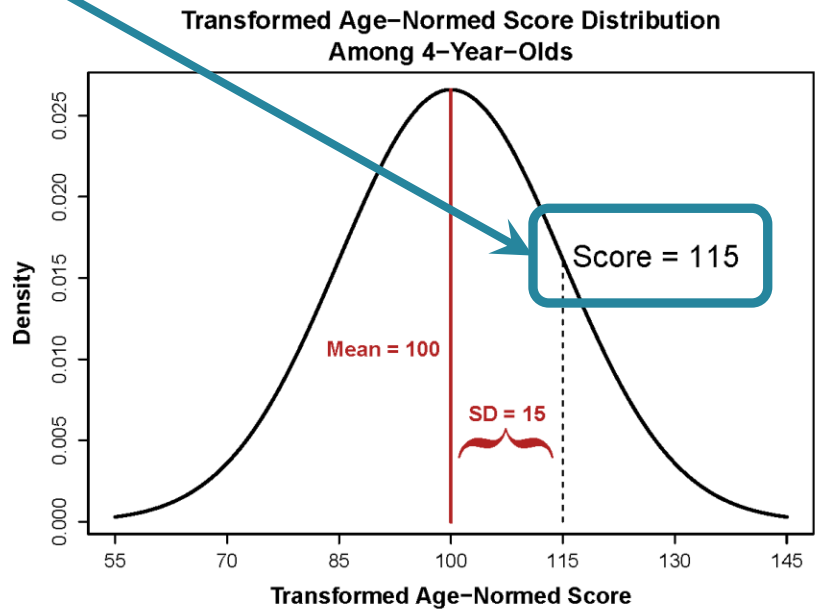




EXAMPLE (continued):

In an analysis of the *age-normed scores*, the 3-year-old and 4-year-old would be treated as though their *levels of oral expressive language development* are the same …

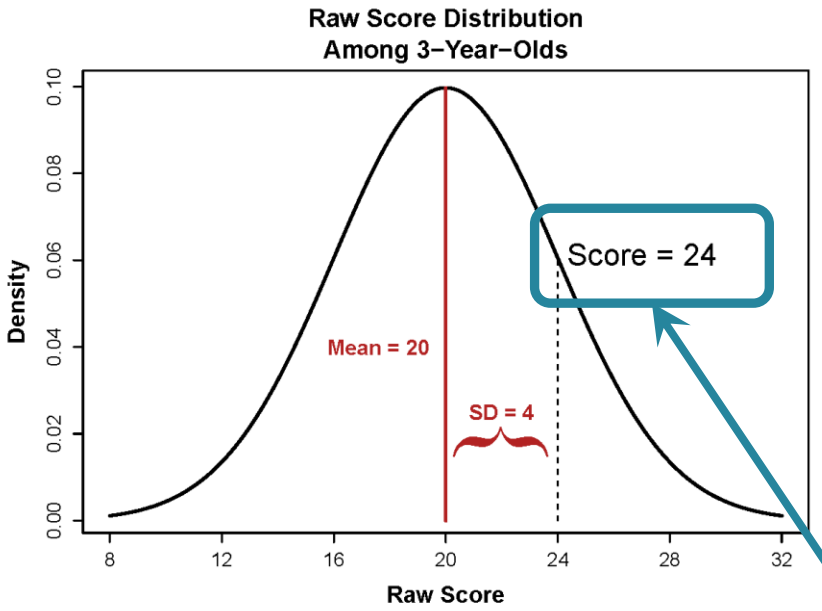


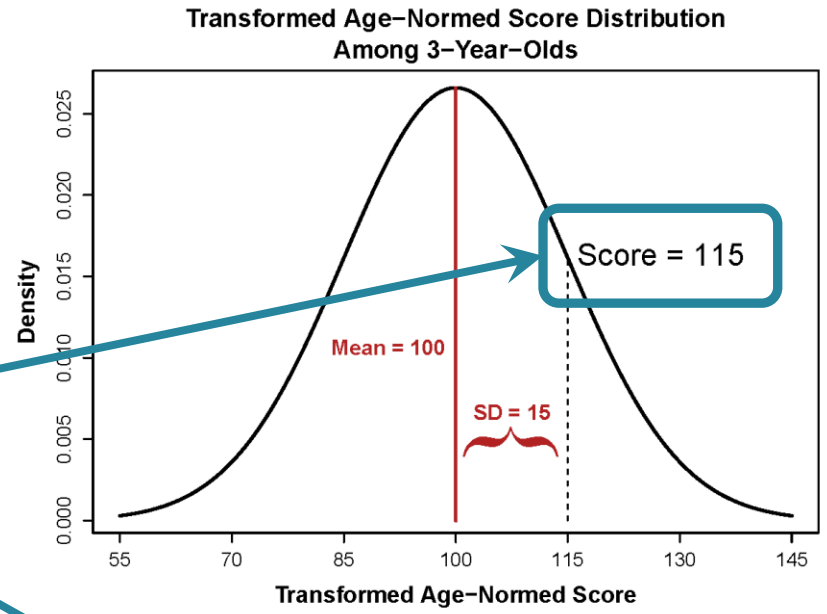


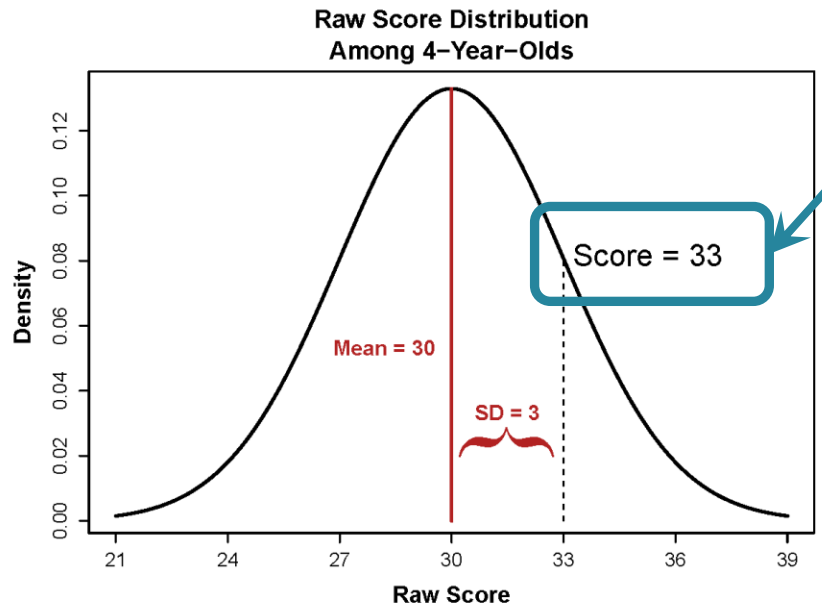
EXAMPLE (continued):

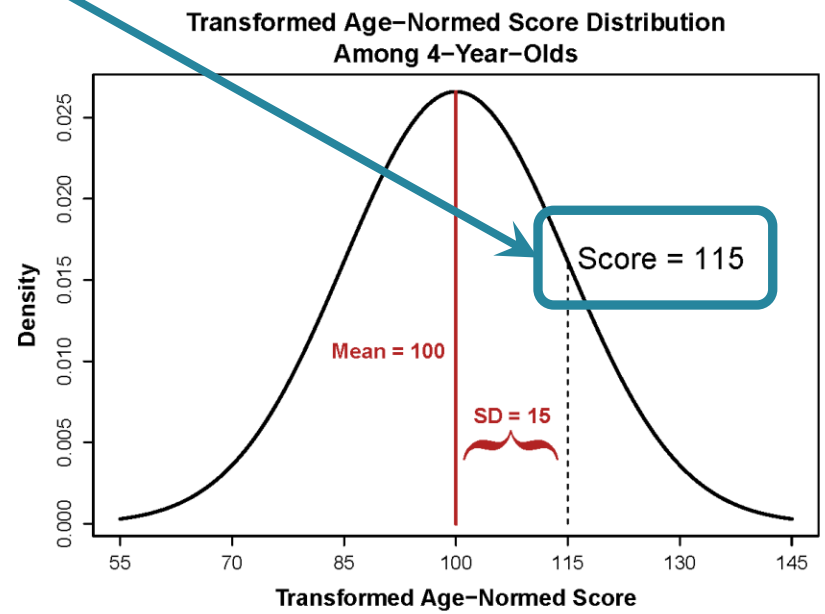
In an analysis of the *age-normed scores*, the 3-year-old and 4-year-old would be treated as though their *levels of oral expressive language development* are the same …

When they aren't

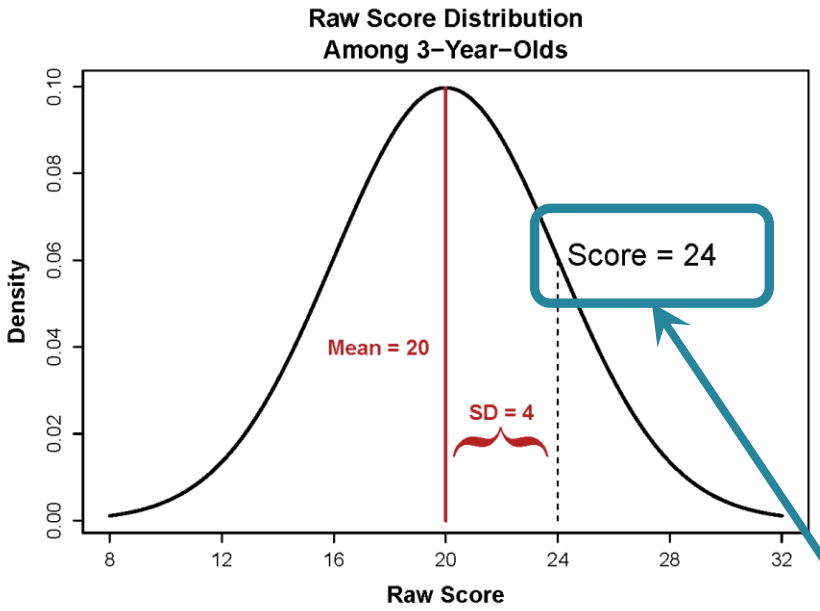




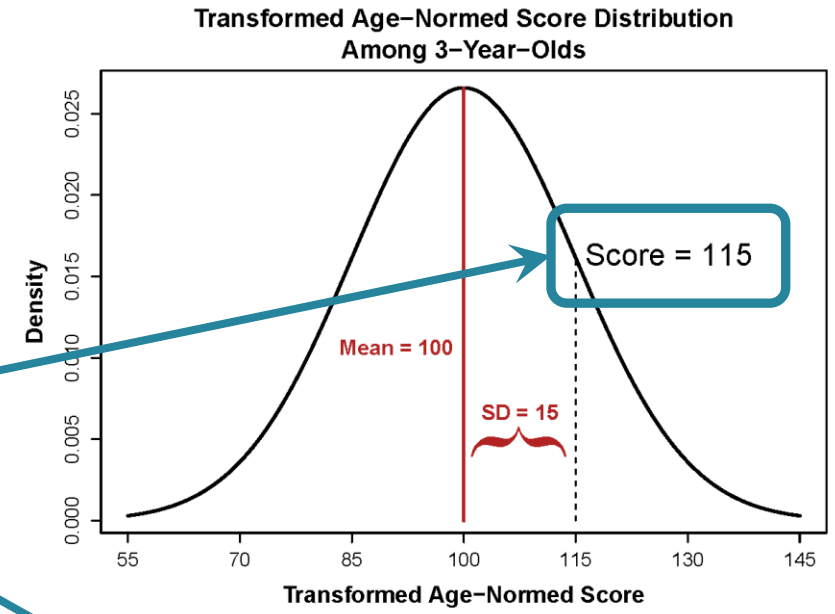




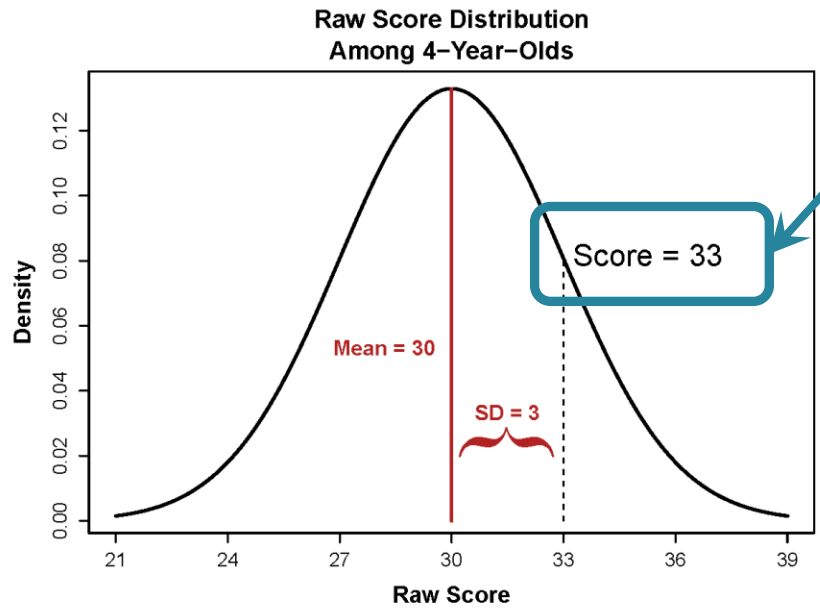
EXAMPLE (continued):



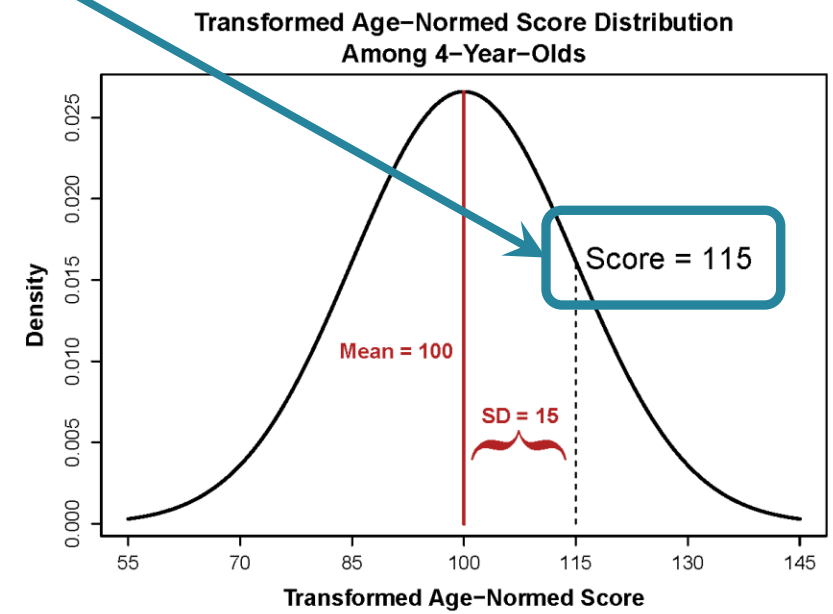
In an analysis of the *age-normed scores*, the 3-year-old and 4-year-old would be treated as though their *levels of oral expressive language development* are the same …



When they aren't



Age-normed scores from different normative age groups that are numerically equivalent imply different levels of development.



Two Additional Considerations

1) Age-specific variability in raw scores ***changes apparent treatment effect*** quantified by age-normed scores
   - **Example:** Same treatment effect (same raw score change) in 3-year-old and 4-year-old
     - Raw score variability is higher among 3-year-olds than 4-year-olds
     - ➢ Using age-normed scores, treatment effect is smaller for 3-year-old than 4-year-old

2) Because of differences among normative age groups in raw score distribution (e.g., mean, SD), aging out of one normative age group and into another can ***change apparent treatment effect*** quantified by age-normed scores
   - **Example:** 3-year-old experiences raw score increase indicating treatment benefit
     - 3-year-old turns 4 during the trial
       - Baseline score normed with respect to 3-year-olds
       - End-of-study score normed with respect to 4-year-olds
     - 4-year-old age group has higher raw score mean and less raw score variability than 3-year-old group
     - ➢ Using age-normed scores, 3-year-old appears to have declined rather than improved

Using Age-Normed Scores to Evaluate Efficacy in Clinical Trials

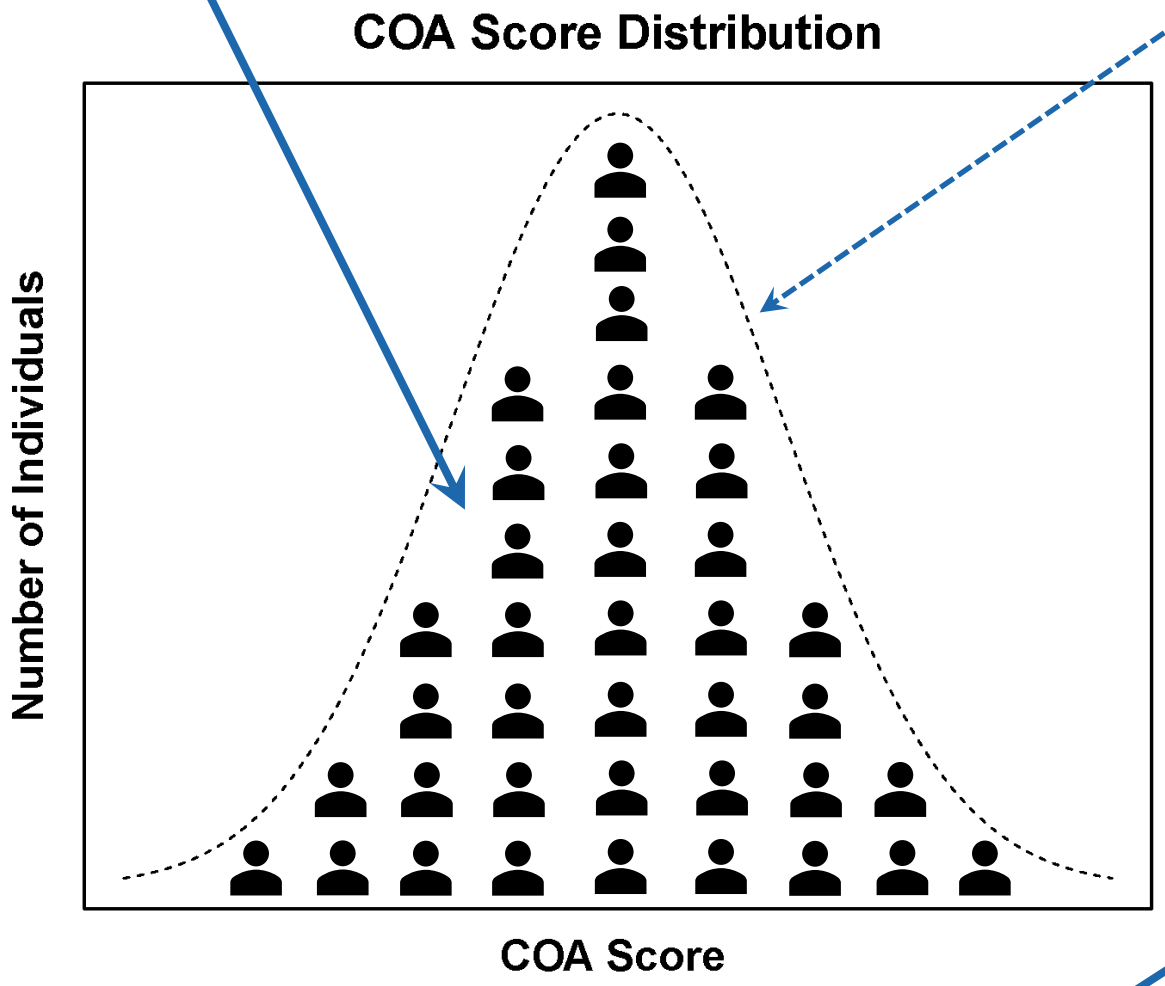
Because age-normed scores from different normative age groups cannot be directly compared, age-normed scores have limited utility for quantifying treatment effects in clinical trials when scores are analyzed continuously and:

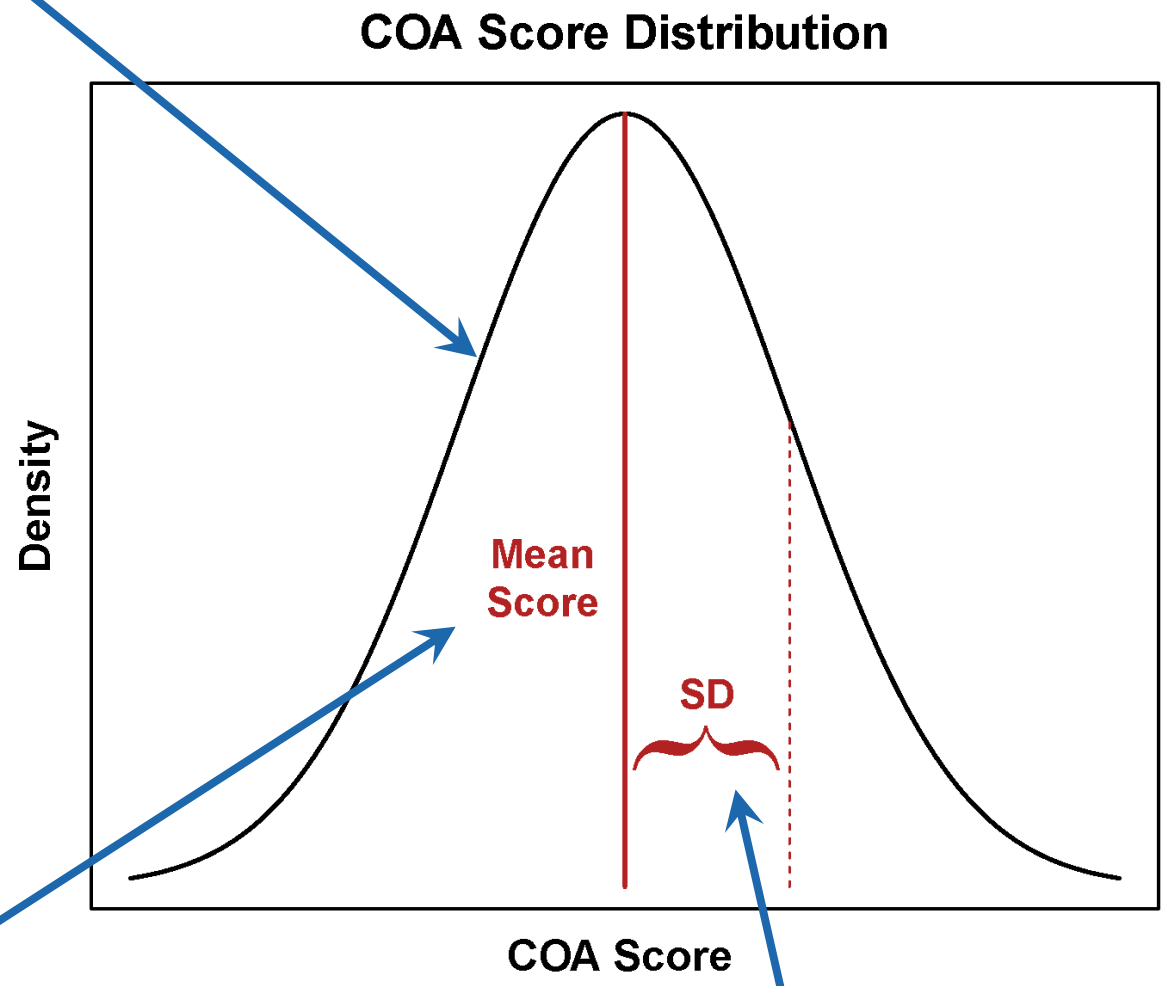
- **Patients age out of one normative age group and into another over the course of a trial**; and/or
- **Patients belong to different normative age groups** (because scores are aggregated across patients within treatment arm in efficacy analyses) ***and any of the following are true at any point during a trial*** *(otherwise, an apparent treatment effect could be misleading and merely an artifact of baseline age distribution, symptom heterogeneity, and/or sampling variability):*
  - Treatment arms are **imperfectly balanced** with respect to normative age group
  - Patients **age out** of their baseline normative age group
  - **Insufficiently large** sample sizes overall and within each normative age group
  - Trial sample does **not** include a representative set of normative age groups to support inferences about treatment effects relative to patients' "same-age peers"

BACK-UP SLIDES

These are **data**.

The **shape** of these data might be described by a **normal distribution**.



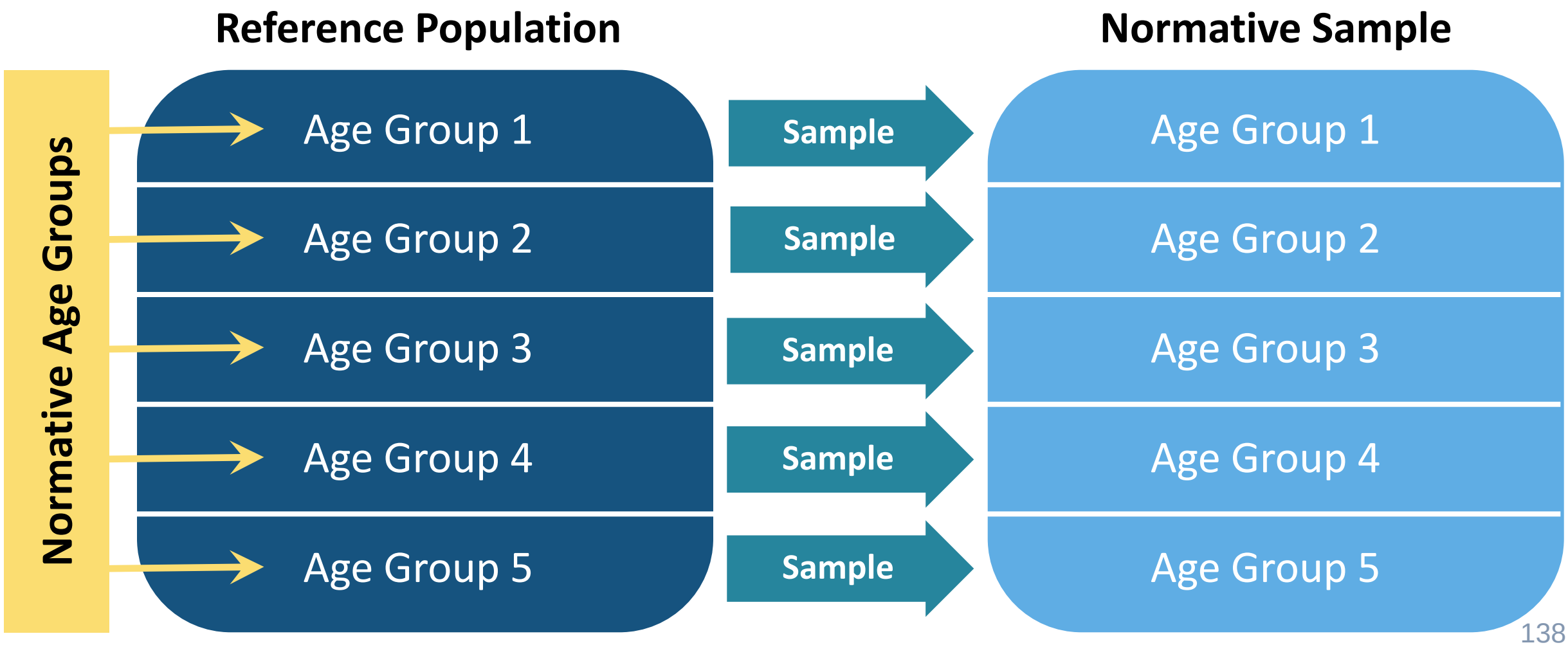


The **mean** is the **average** or **expected value**. It is the **center** of the normal distribution.

The **standard deviation (SD)** quantifies the amount of **variability** (higher SD → more variability).

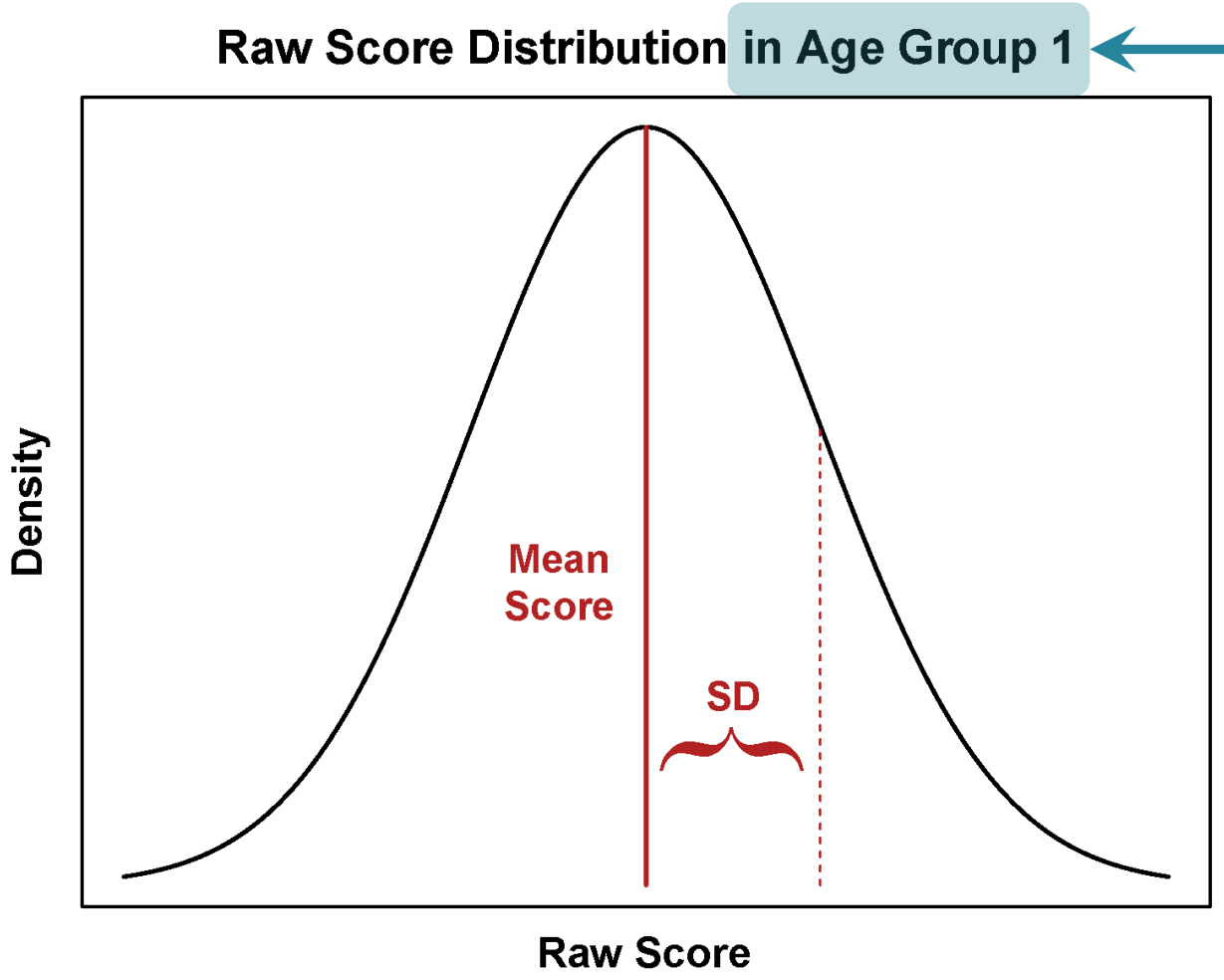
How Are COA Scores *Age-Normed*?

For a given measure/COA:



What Are Age-Normed Scores?

For a given measure/COA:



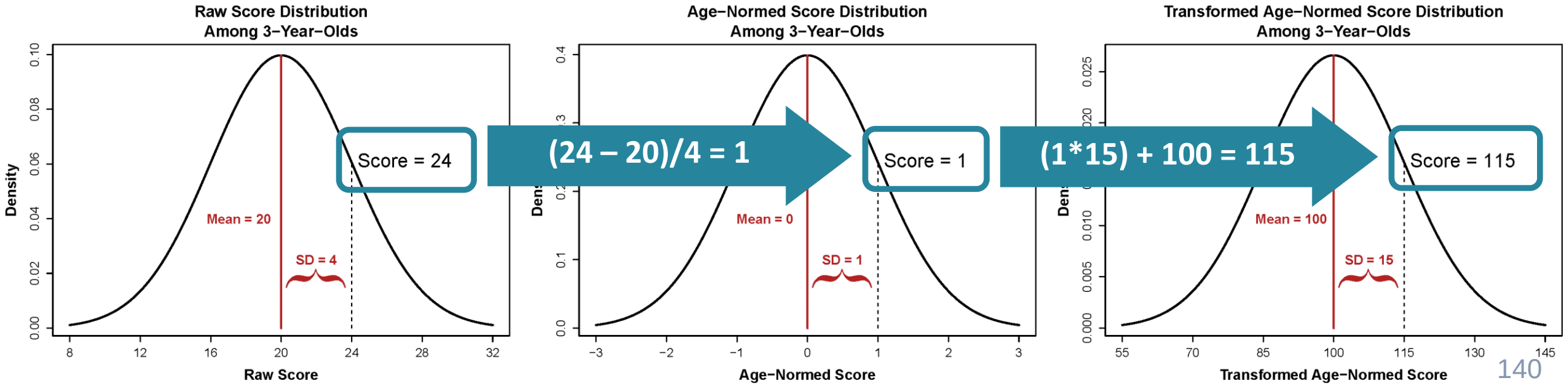
Normative Sample

- Age Group 1
- Age Group 2
- Age Group 3
- Age Group 4
- Age Group 5

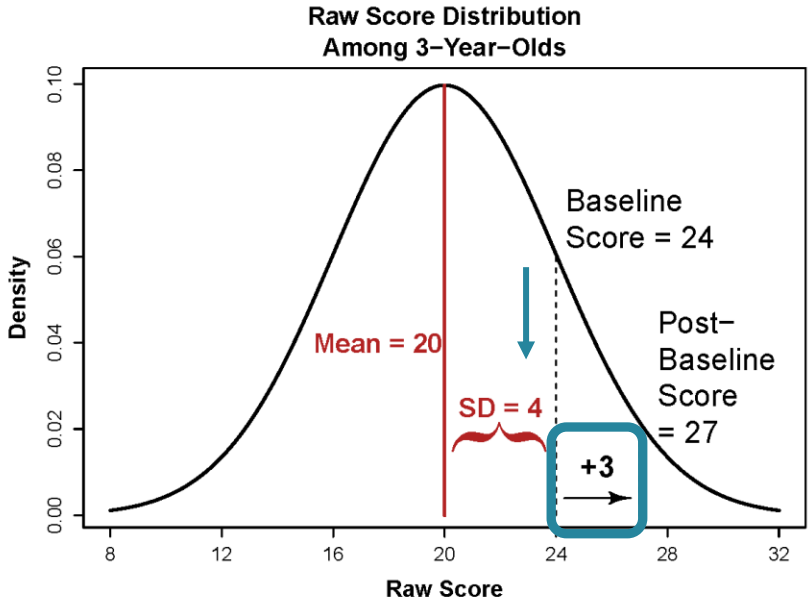
What Are Age-Normed Scores?

Age-norming scores usually involves:

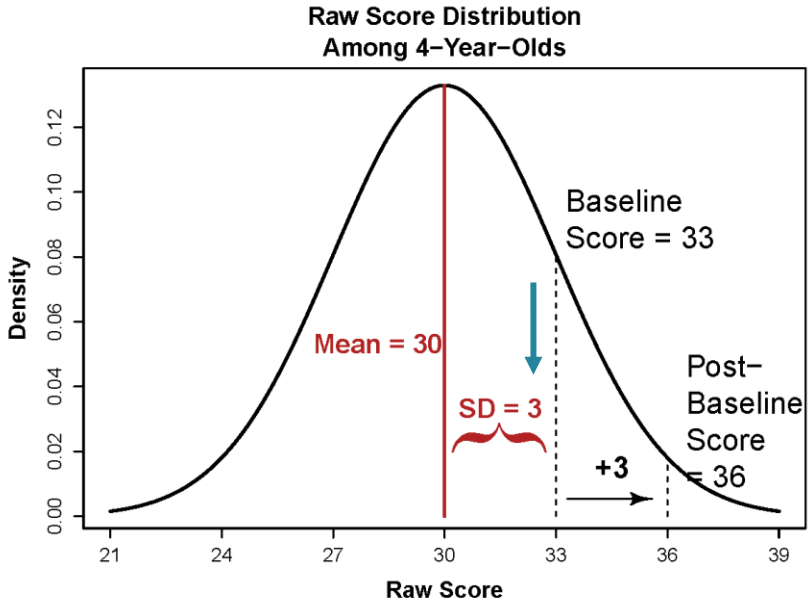
1) **Adjusting** raw scores (e.g., sum scores, Item Response Theory [IRT] scores) for the raw score mean and standard deviation ***within each age group*** in the normative sample
2) **Transforming** these age-adjusted scores ***within each age group*** to have some desired mean (e.g., 50, 100), standard deviation (e.g., 10, 15), and sometimes also shape (e.g., normal distribution)



Additional Consideration #1: Age-specific variability in raw scores *changes* the apparent treatment effect quantified by age-normed scores.



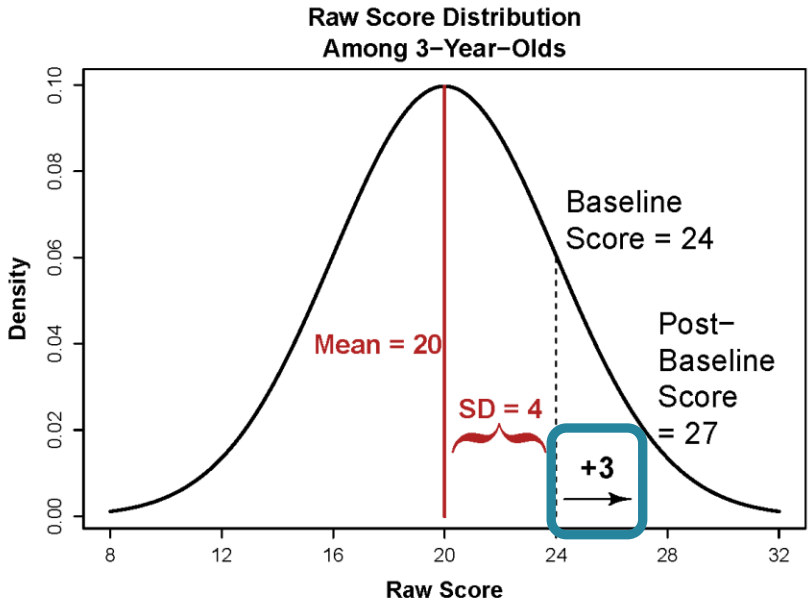
Investigational therapy improves the raw score for two patients, one 3 years old and one 4 years old, by 3 points

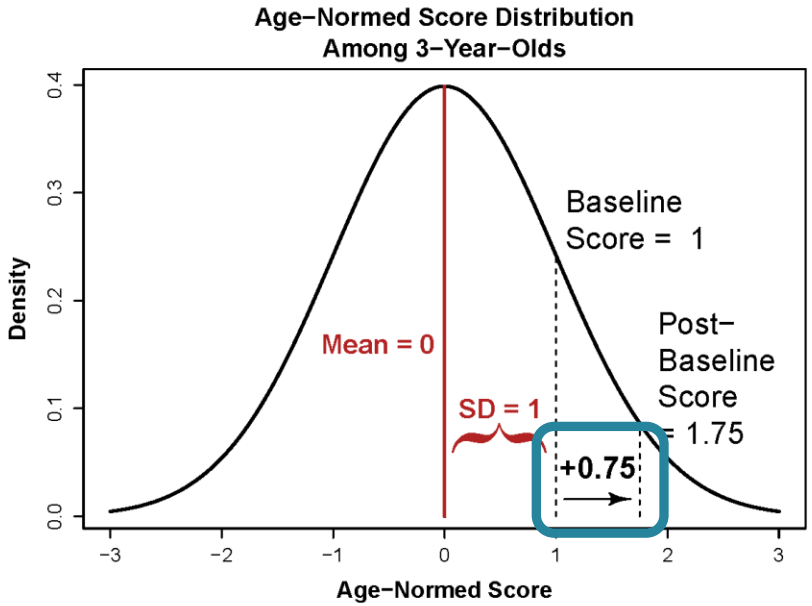


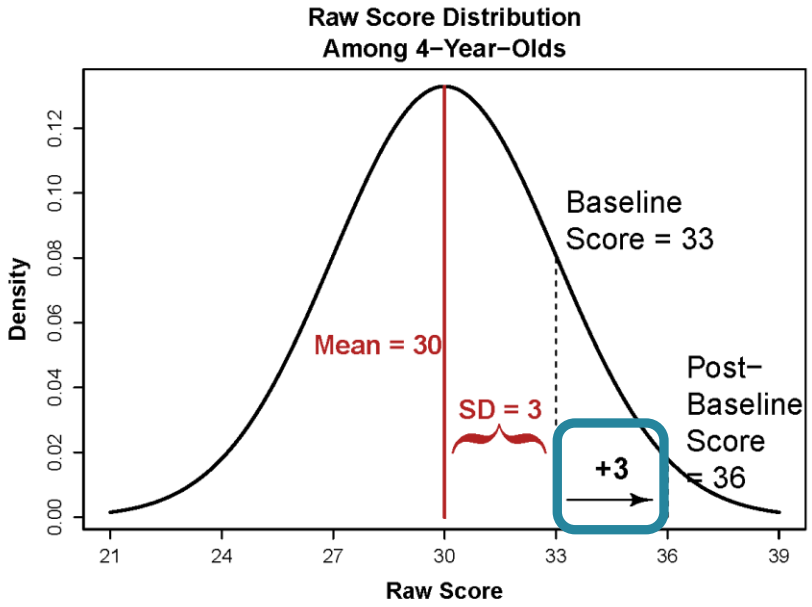
The variability, or standard deviation (SD), among 3-year-olds = 4

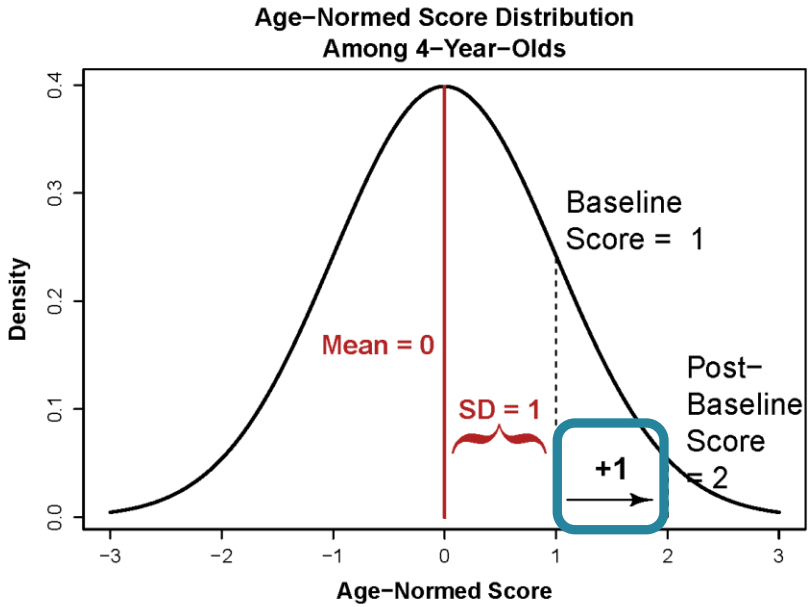
The SD is smaller among the 4-year-olds.

Additional Consideration #1: Age-specific variability in raw scores *changes* the apparent treatment effect quantified by age-normed scores.



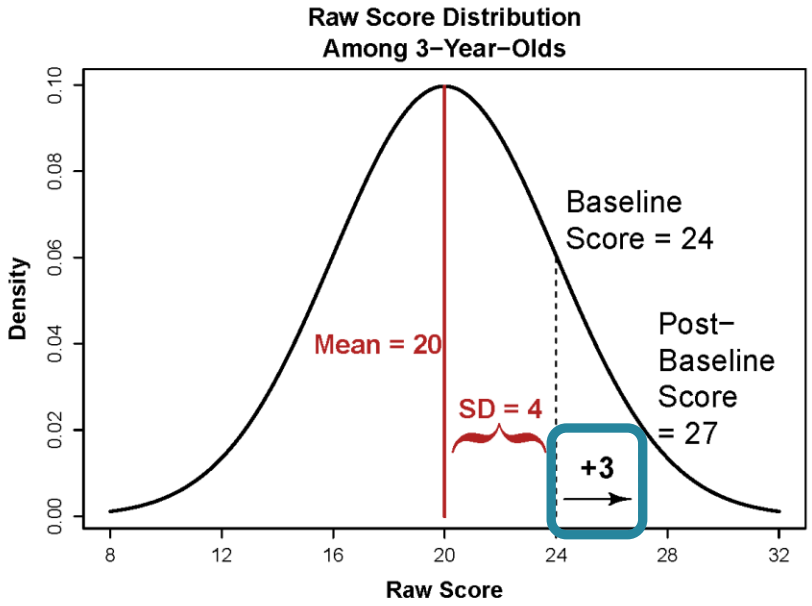


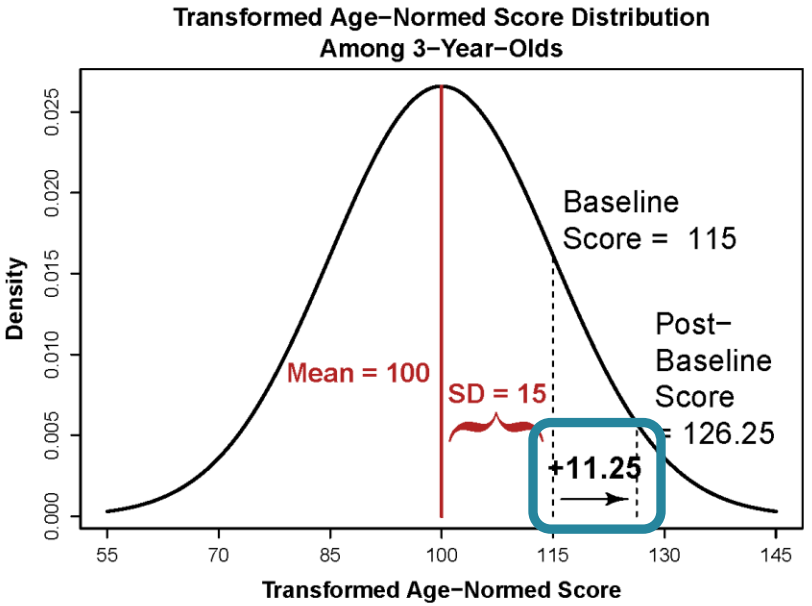




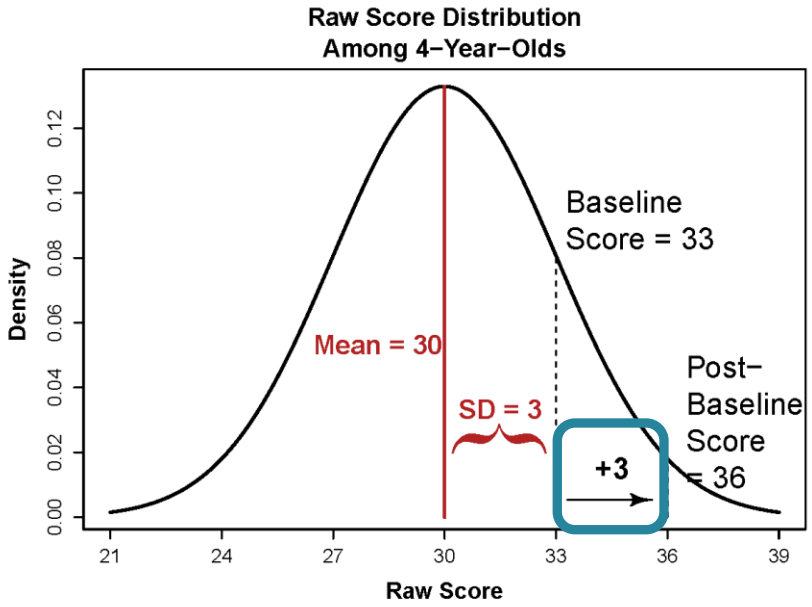
Because raw score variability is *higher* among 3-year-olds than 4-year-olds in the normative sample, the corresponding change in age-normed scores is <u>less</u> for the 3-year-old than the 4-year-old.

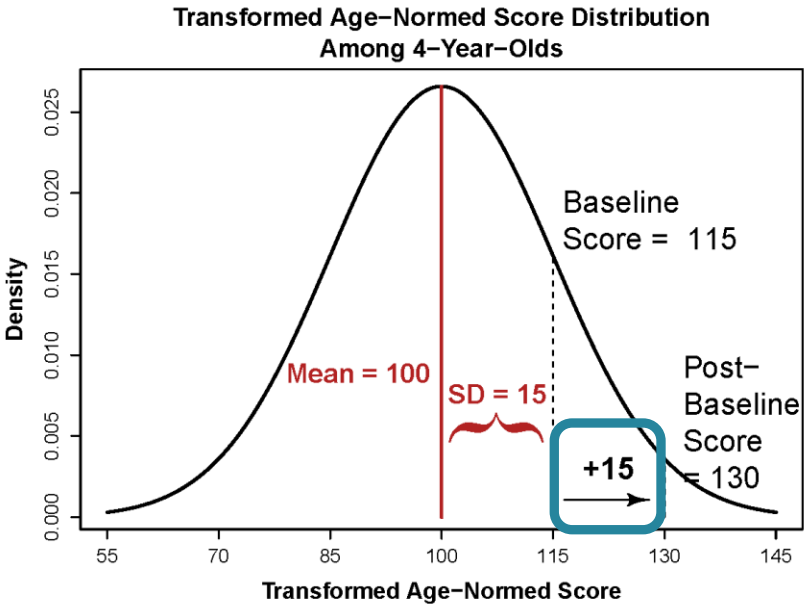
Additional Consideration #1: Age-specific variability in raw scores *changes* the apparent treatment effect quantified by age-normed scores.





Similarly, the change in transformed age-normed scores is less for the 3-year-old than the 4-year-old because raw score variability is higher among 3-year-olds than 4-year-olds in the normative sample.





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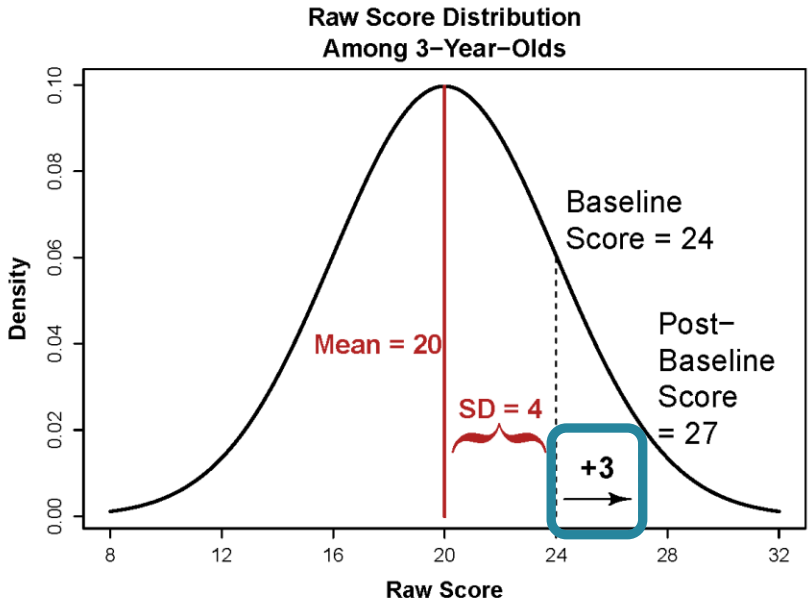
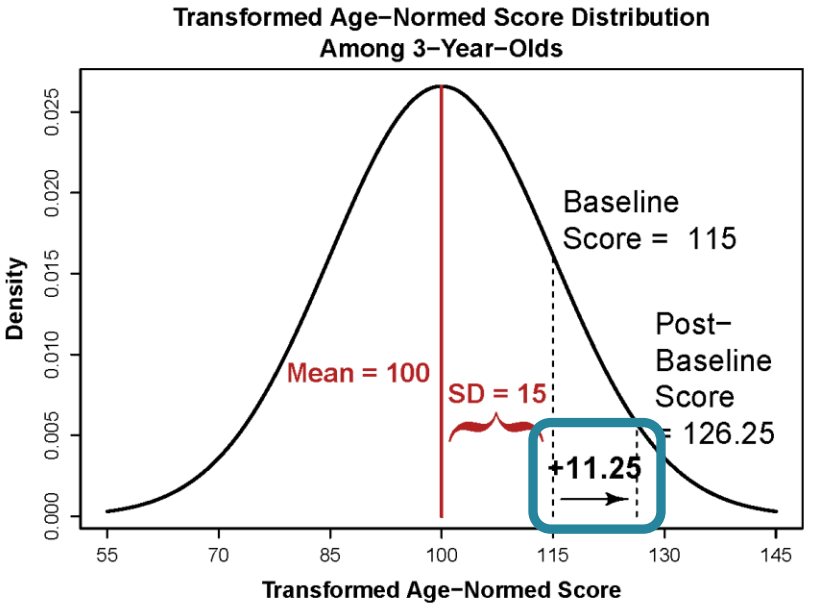
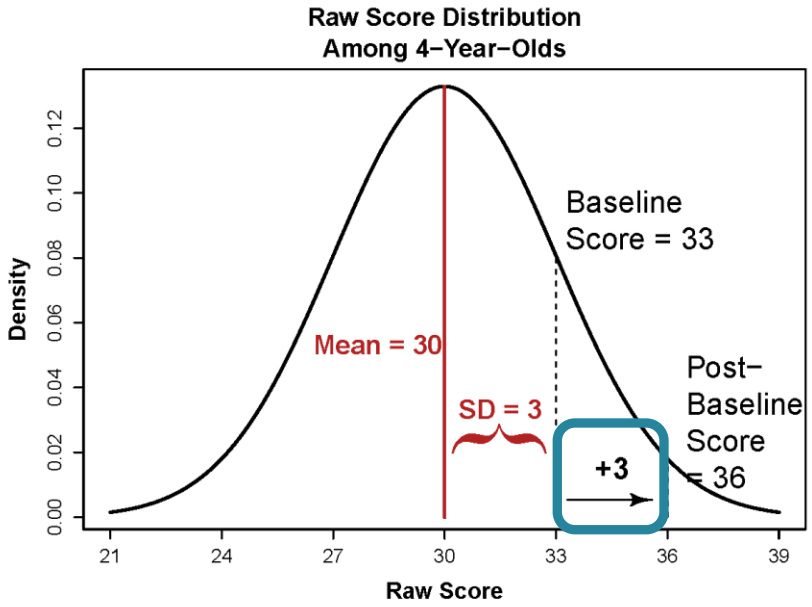


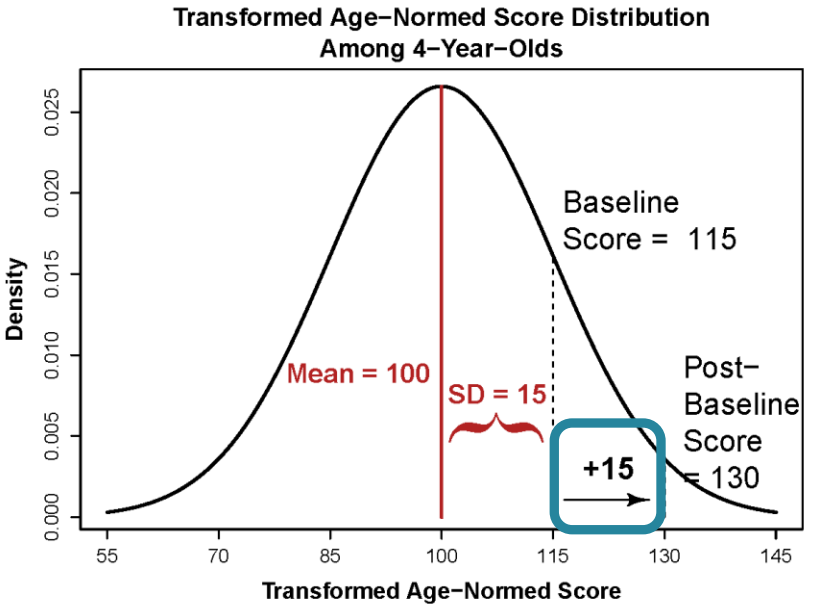


This makes it challenging to compare changes in age-normed scores among normative age groups.

The children had the same raw score improvement.

The change in their age-normed and transformed age-normed scores are not the same.





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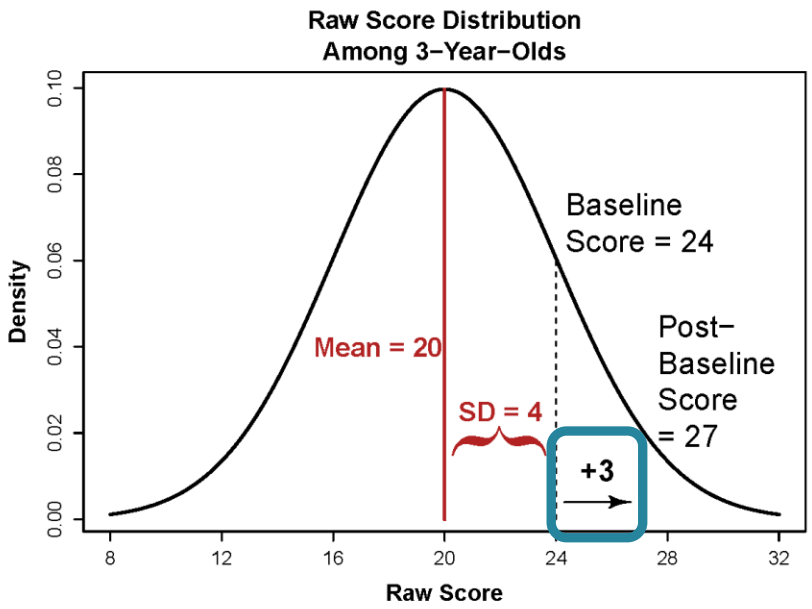
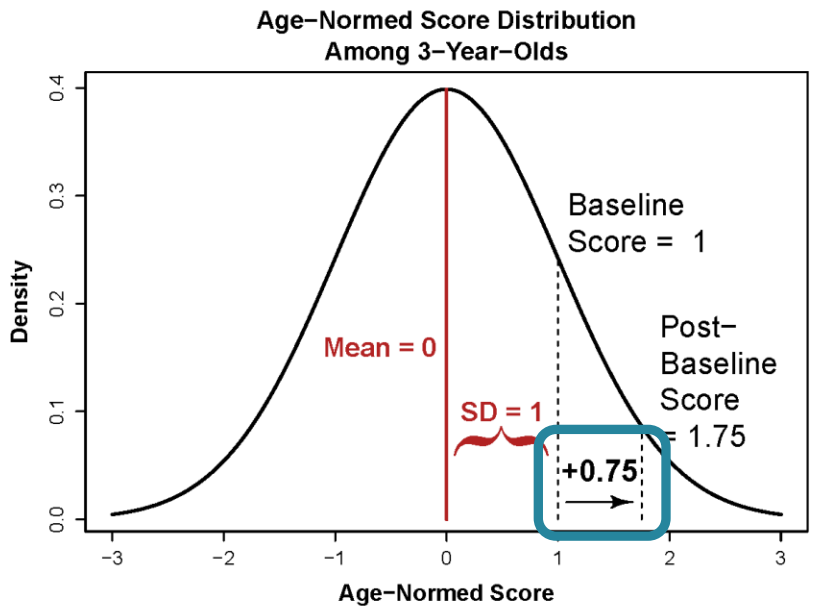
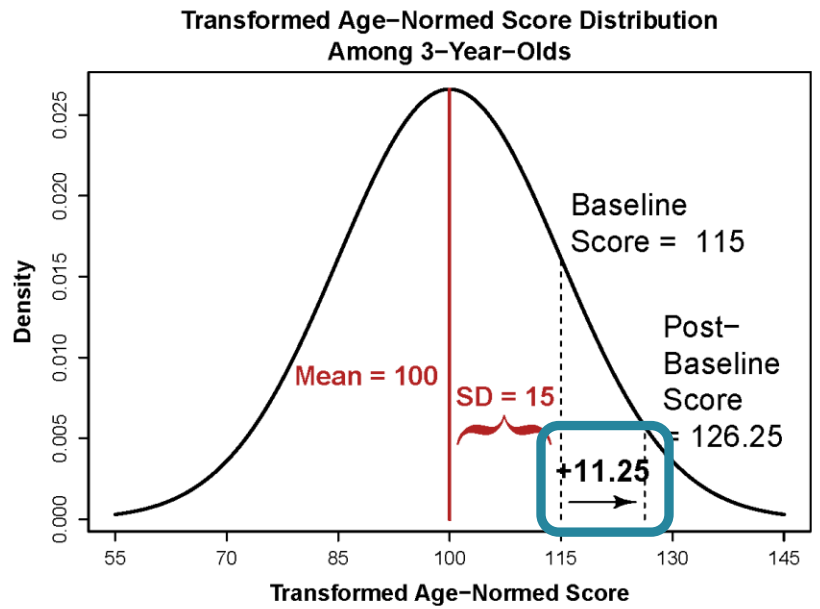
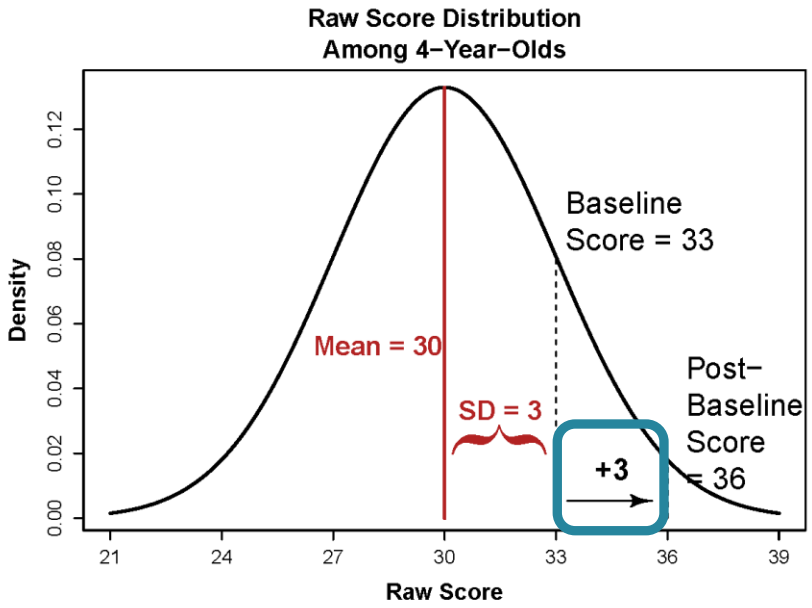
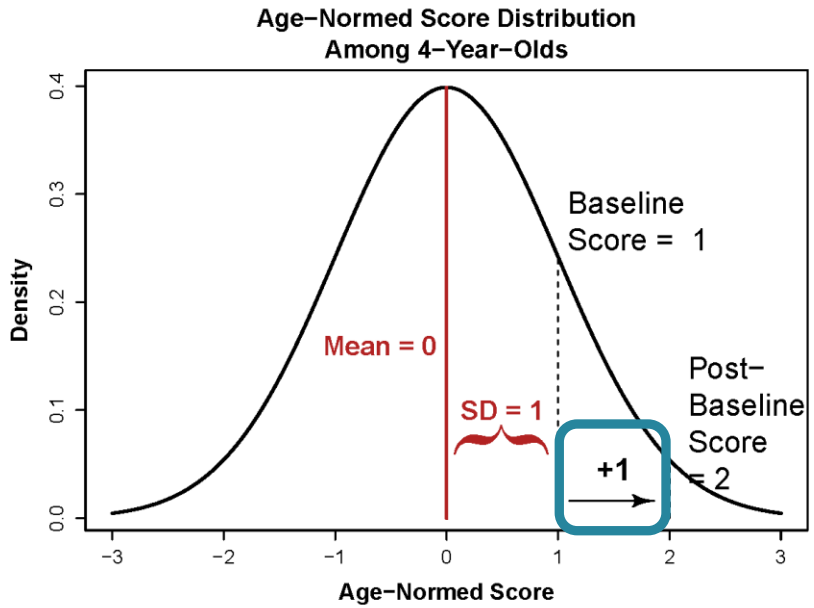
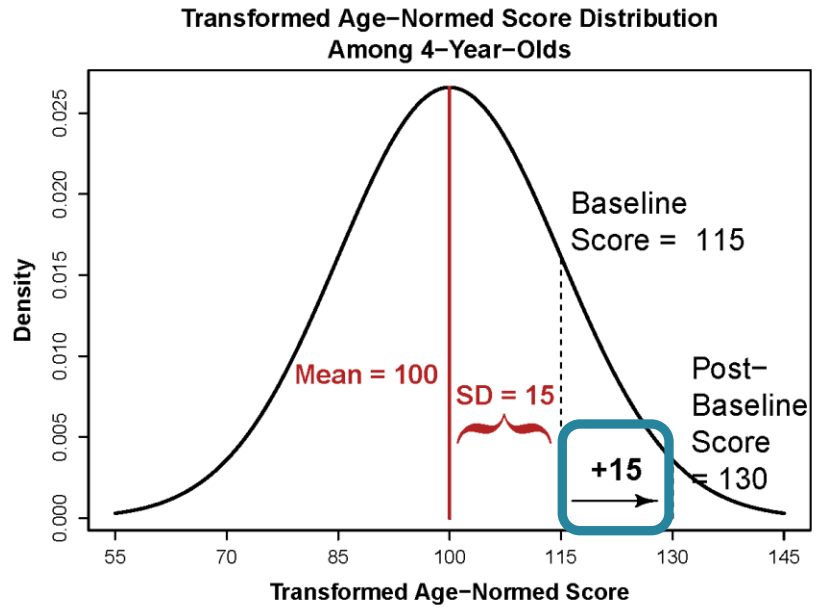




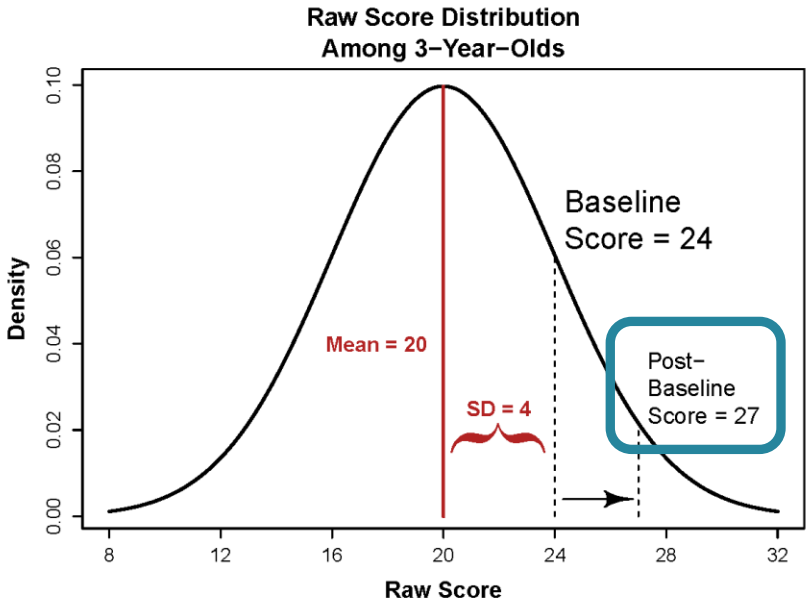








Additional Consideration #2: Because of differences among normative age groups in raw score distribution (e.g., mean, SD), aging out of one normative age group and into another can alter apparent treatment effects quantified by age-normed scores.



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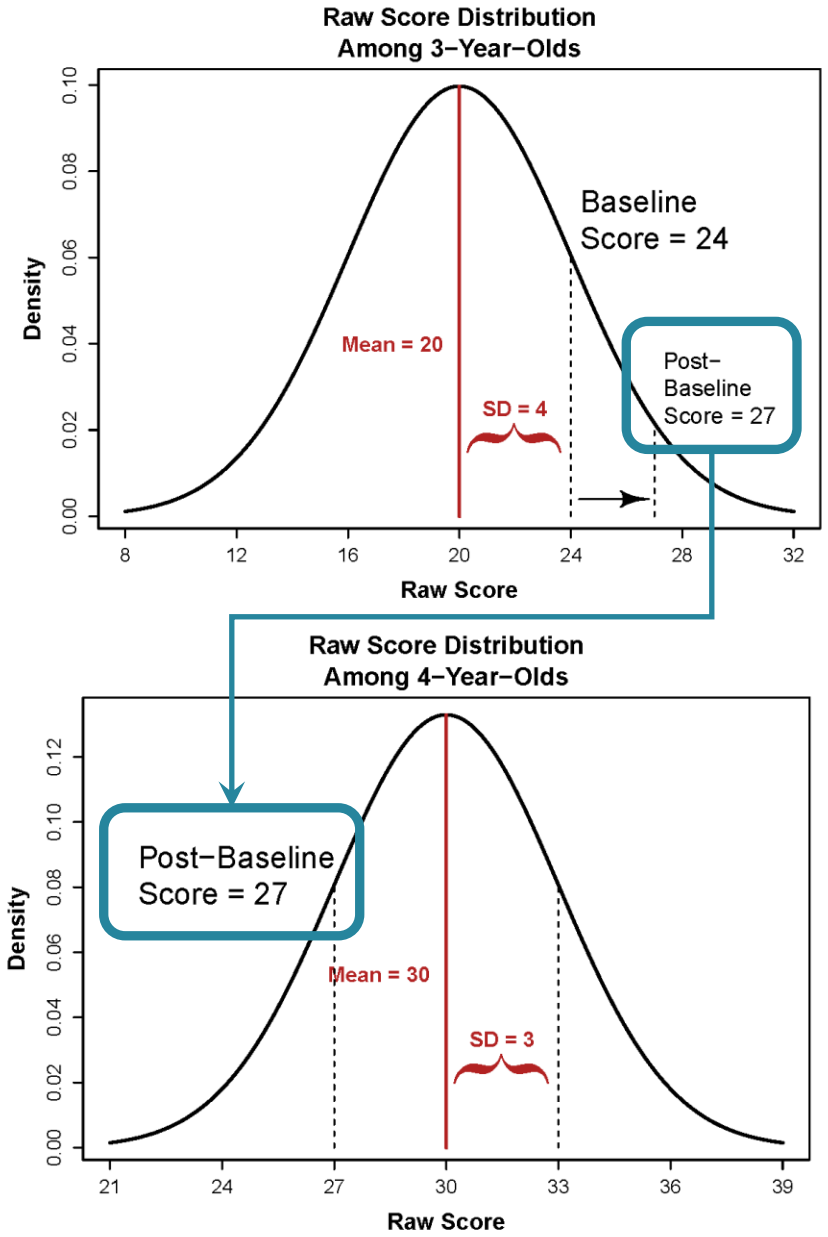
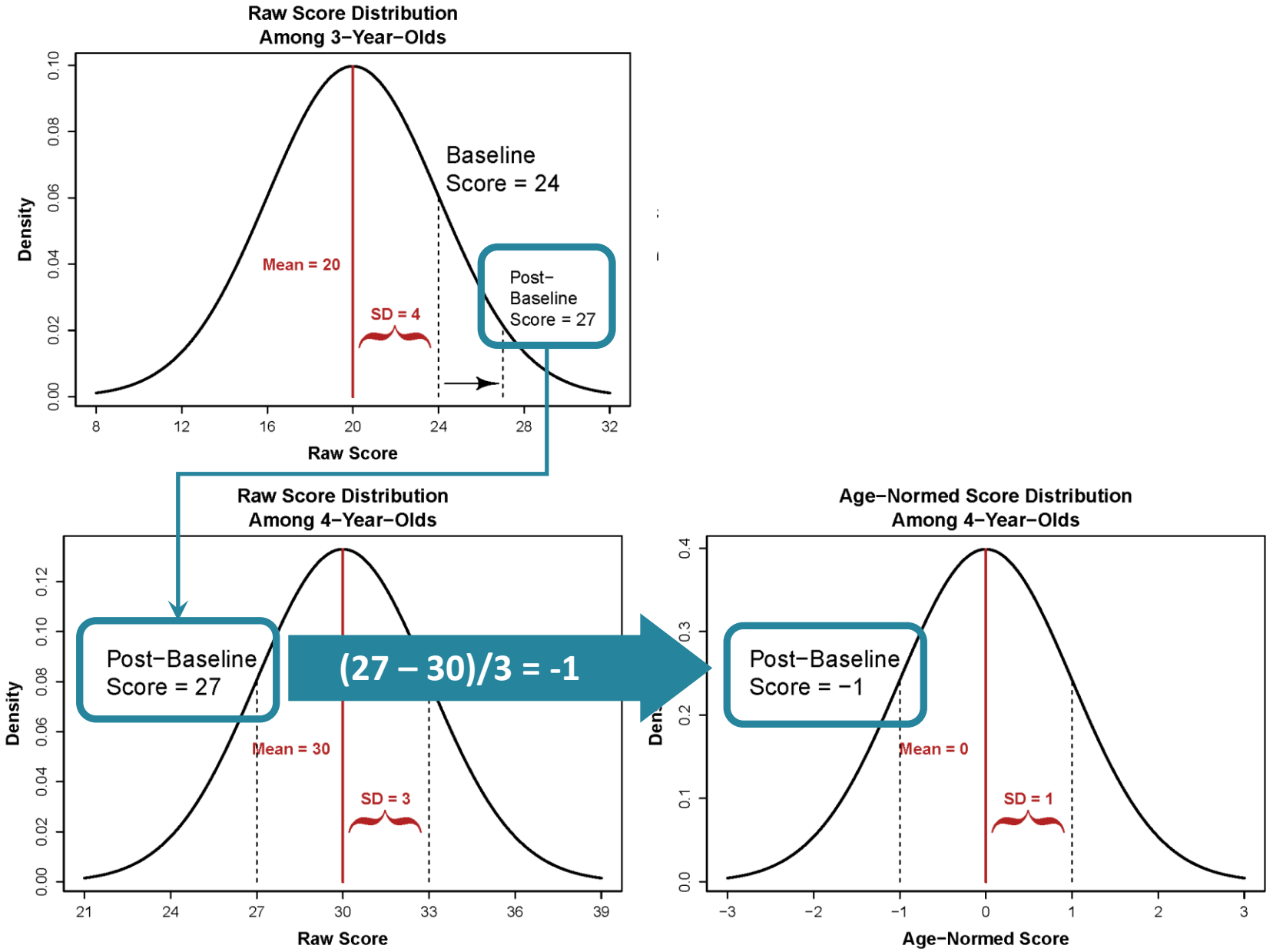


By the time of the post-baseline score, the child turned 4.

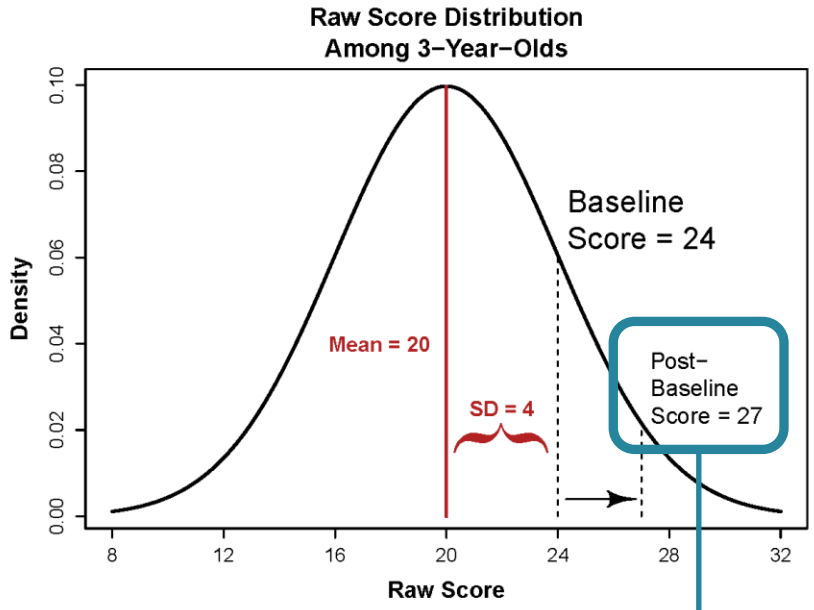
Among 4-year-olds, the score is below the mean.

Additional Consideration #2: Because of differences among normative age groups in raw score distribution (e.g., mean, SD), aging out of one normative age group and into another can alter apparent treatment effects quantified by age-normed scores.

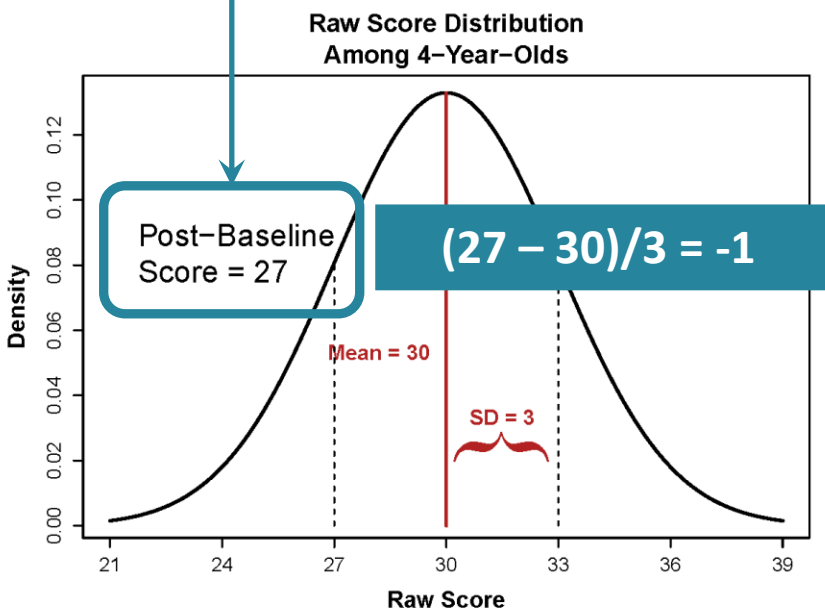


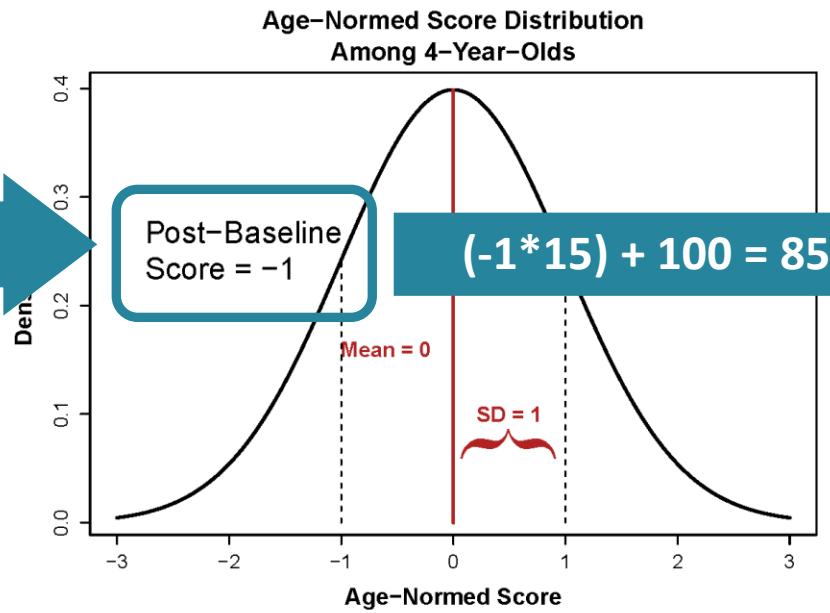
1 standard deviation (SD) below the mean for 4-year-olds

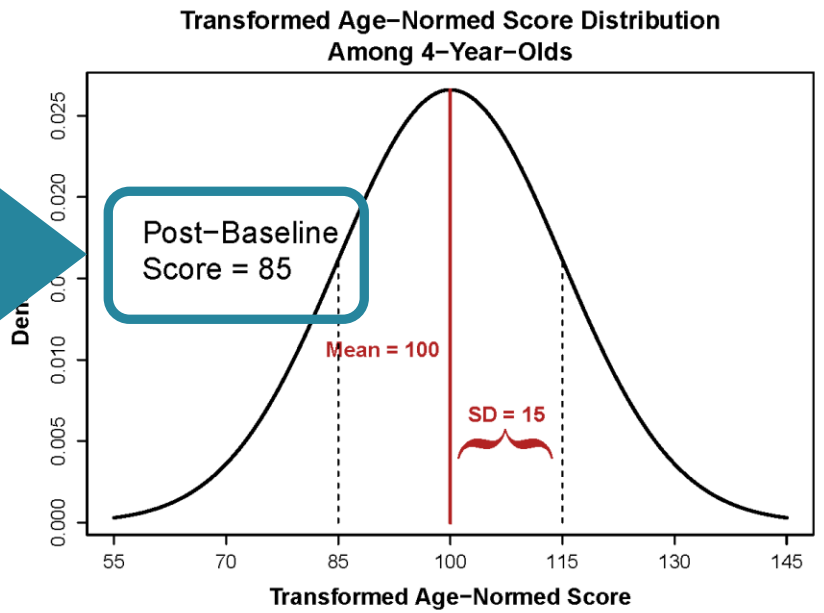
Additional Consideration #2: Because of differences among normative age groups in raw score distribution (e.g., mean, SD), aging out of one normative age group and into another can alter apparent treatment effects quantified by age-normed scores.



The transformed age-normed score is 85 for the (now) 4-year-old.



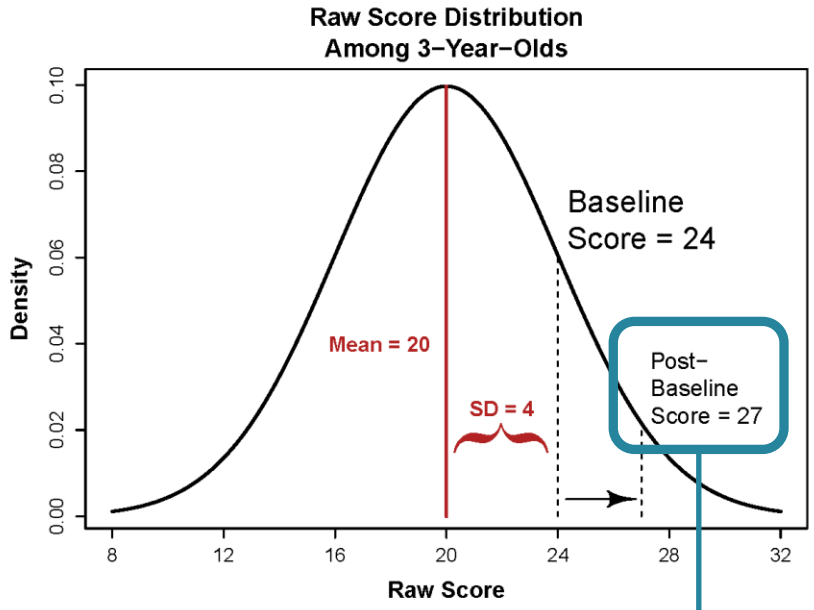




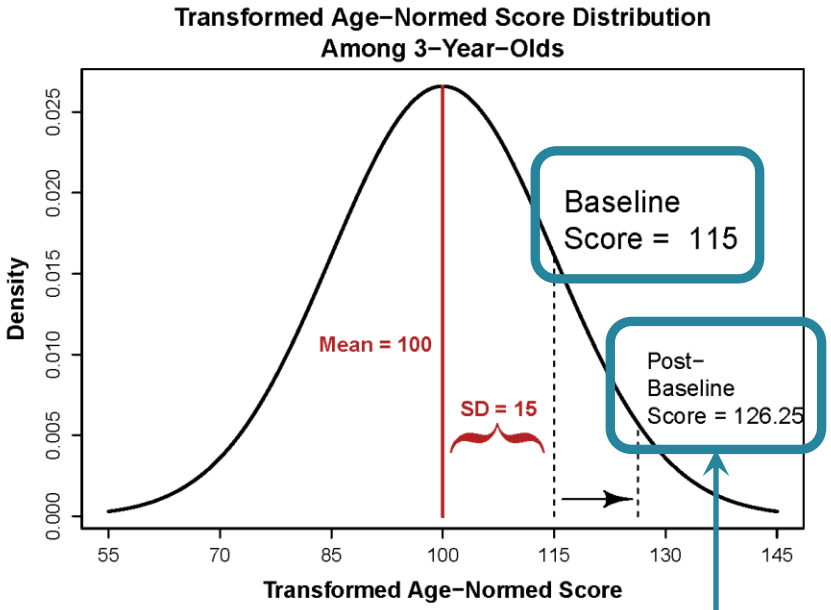
(27 – 30)/3 = -1

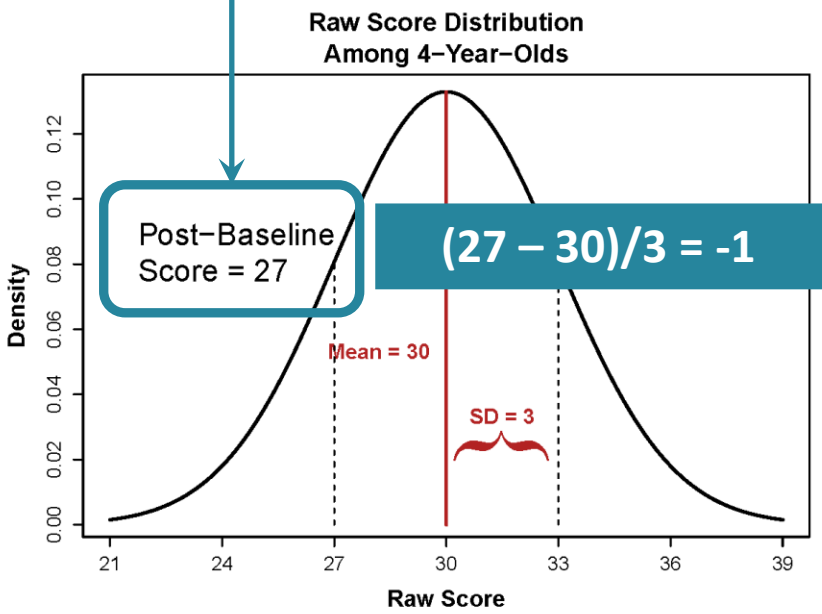
(-1*15) + 100 = 85

Additional Consideration #2: Because of differences among normative age groups in raw score distribution (e.g., mean, SD), aging out of one normative age group and into another can alter apparent treatment effects quantified by age-normed scores.

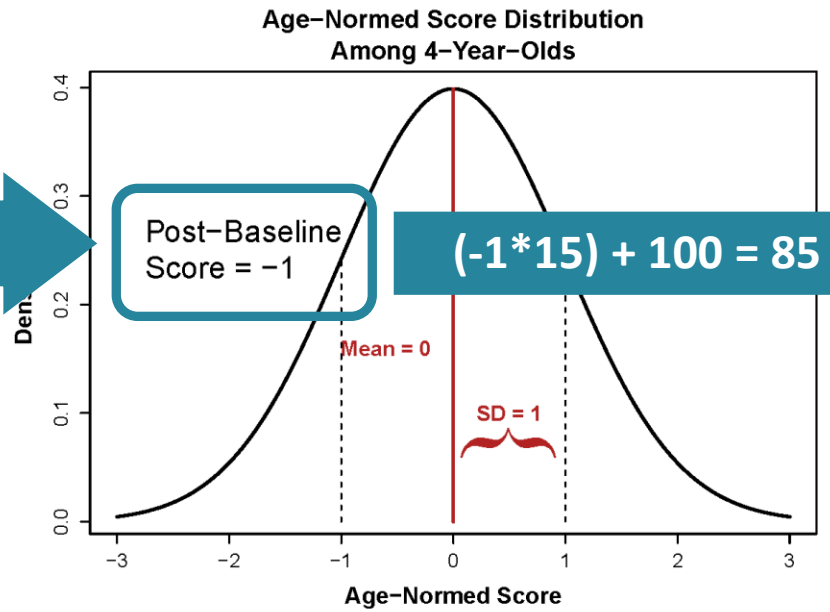


If the child was still 3, their transformed age-normed score would be 126.25.

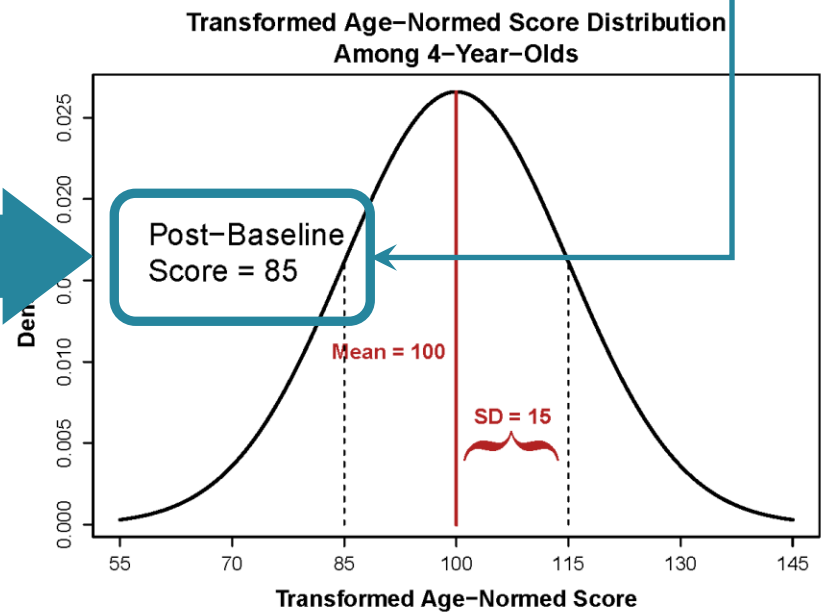




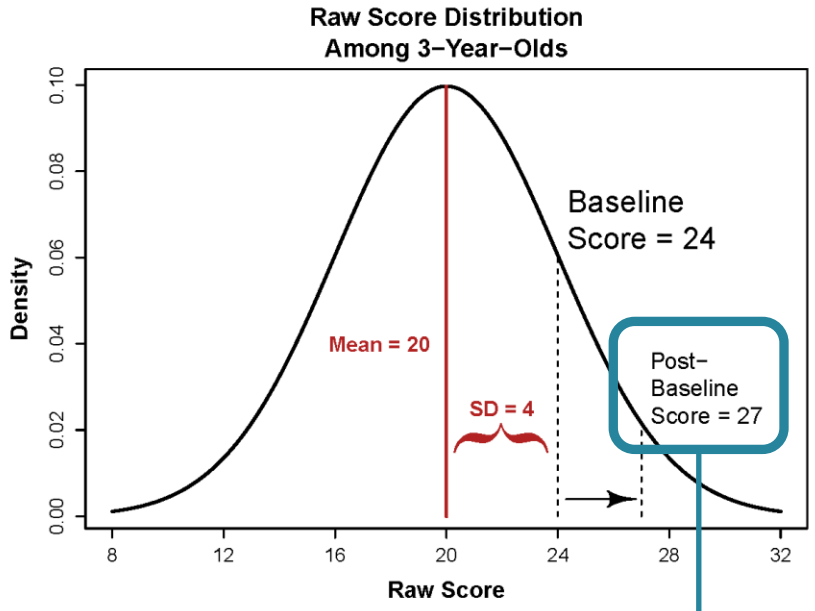
(27 – 30)/3 = -1

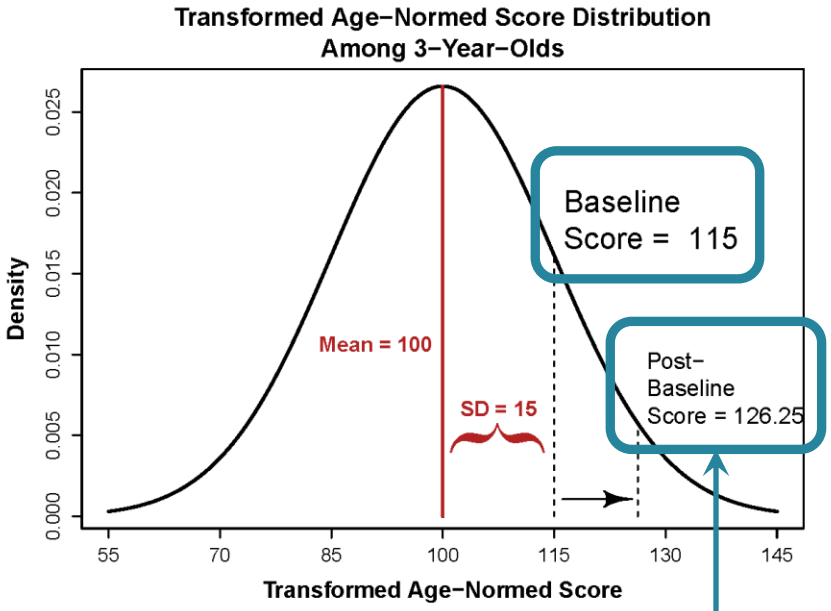


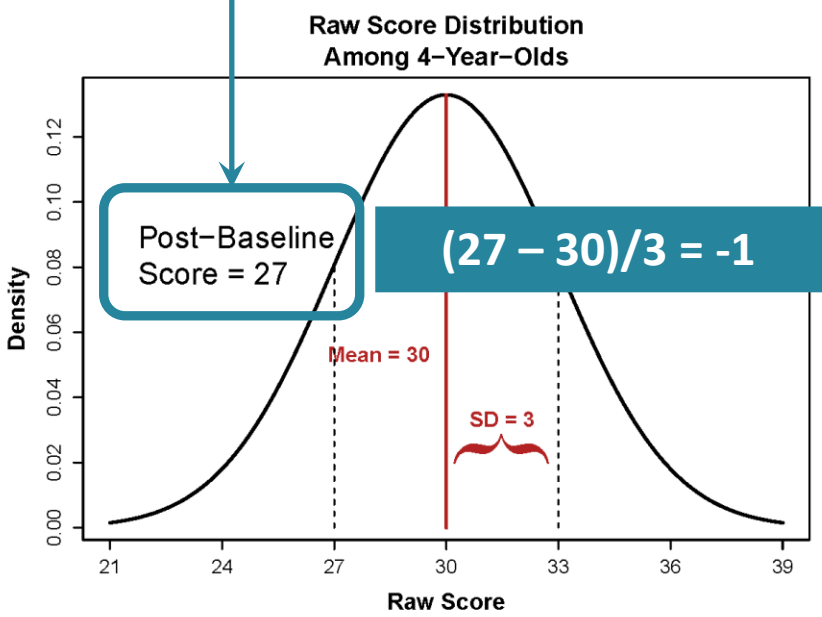
(-1*15) + 100 = 85



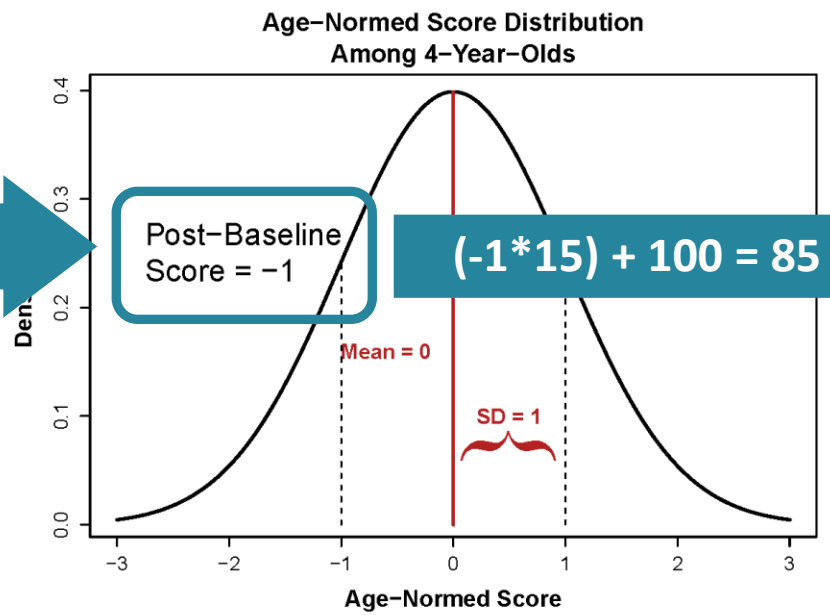
Because the child turned 4, the child's transformed age-normed score decreased approximately 30 points, making it appear the 3-year-old lost substantial oral expression skills when in fact the individual experienced gains.



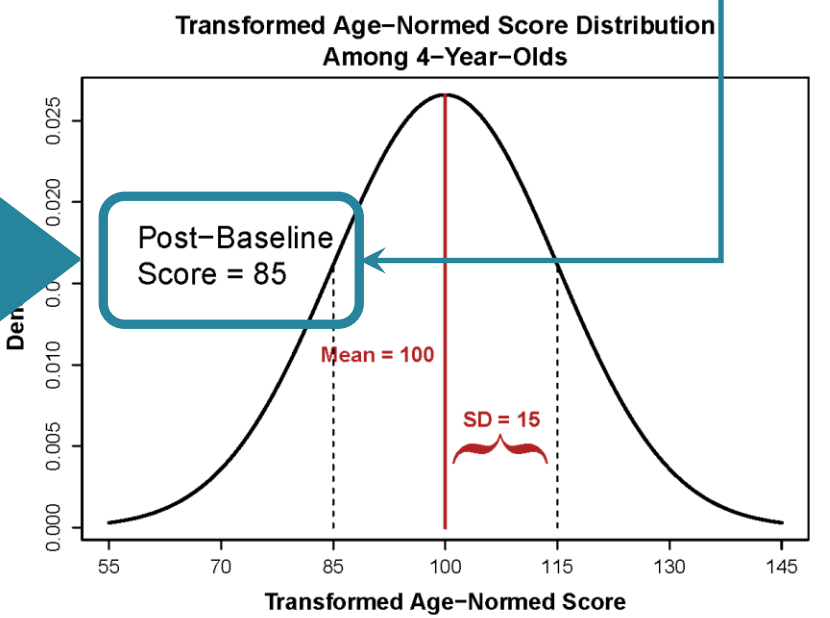




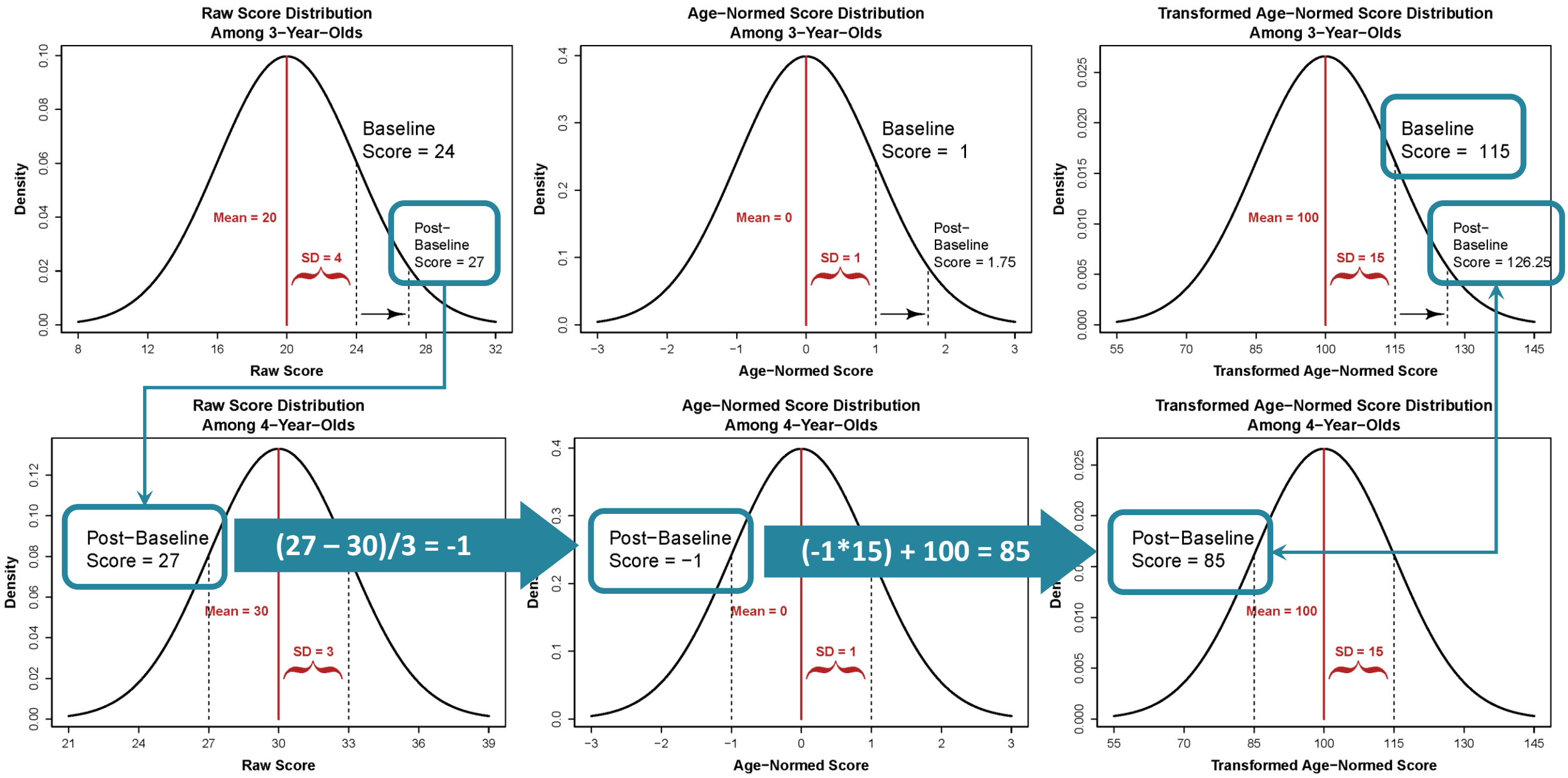
(27 – 30)/3 = -1



(-1*15) + 100 = 85



Additional Consideration #2: Because of differences among normative age groups in raw score distribution (e.g., mean, SD), aging out of one normative age group and into another can alter apparent treatment effects quantified by age-normed scores.




Panel Discussion
followed by
Q+A

Closing Remarks

Robyn Bent, RN, MS

Director, Patient-Focused Drug Development Program

Office of Center Director

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

U.S. FOOD & DRUG ADMINISTRATION

Thank you!