# *Qualitative Methods in Clinical Trials: Opportunities and Challenges*

***14th Annual***
***Patient-Reported Outcome Consortium Workshop***

**April 19-20, 2023 • Silver Spring, MD**

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# Session Outline

- Foundations of qualitative research in the context of clinical outcome assessment (COA) selection or development
- Qualitative interviews to elicit patient experience data in clinical studies
- How longitudinal qualitative interviews embedded at key timepoints in a clinical study can add context
- Use of qualitative research to obtain important perspectives outside of a clinical trial setting
- Panel discussion
  - Patient perspective
  - FDA perspective
- Question and Answer

# Session Participants

## Moderator

- *Maria Mattera, MPH* – Scientific Director, Patient-Reported Outcome Consortium, Critical Path Institute

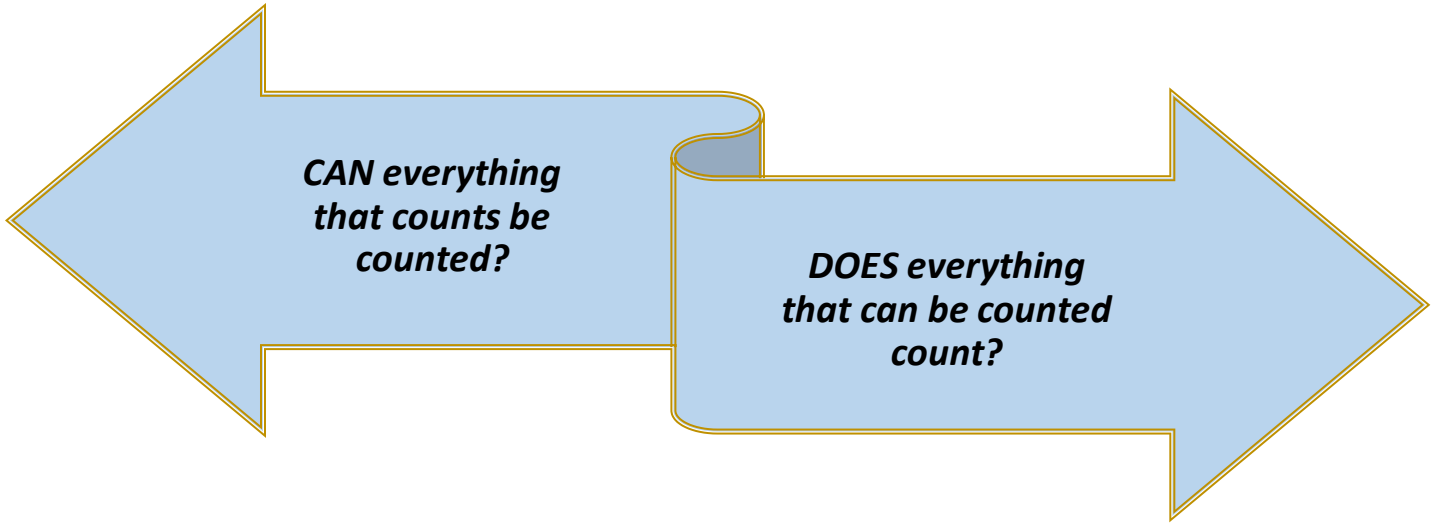
## Presenters

- *Asha Hareendran, PhD* – Patient Centred Outcomes Research Excellence Lead, UCB Biopharma Srl
- *Nicola Williamson, MSc* – Associate Director, Patient-Centered Outcomes, Adelphi Values
- *Jane Wells, MSc* – Clinical Outcomes Assessment Lead, Sanofi
- *Calvin N. Ho, PhD* – Associate Director, Patient Centered Science, AstraZeneca
- *Bellinda King-Kallimanis* – Director of Patient-Focused Research, LUNGevity Foundation

## Additional Panelists

- *Marc Yale* – Advocacy and Research Coordinator, International Pemphigus Pemphigoid Foundation
- *Naomi Knoble, PhD* – Associate Director of Rare Disease Measurement Science, Division of Clinical Outcome Assessment, Office of Drug Evaluation Sciences, Office of New Drugs, Center for Drug Evaluation Research, U.S. Food and Drug Administration

# Foundations of Qualitative Research in the Context of COA Selection or Development



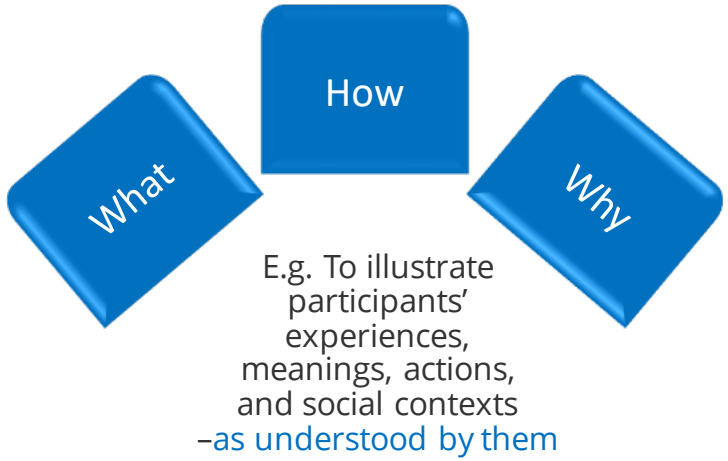

Asha Hareendran
Patient Centred Outcomes Research (PCOR) Excellence Lead
UCB Biopharma Srl, UK

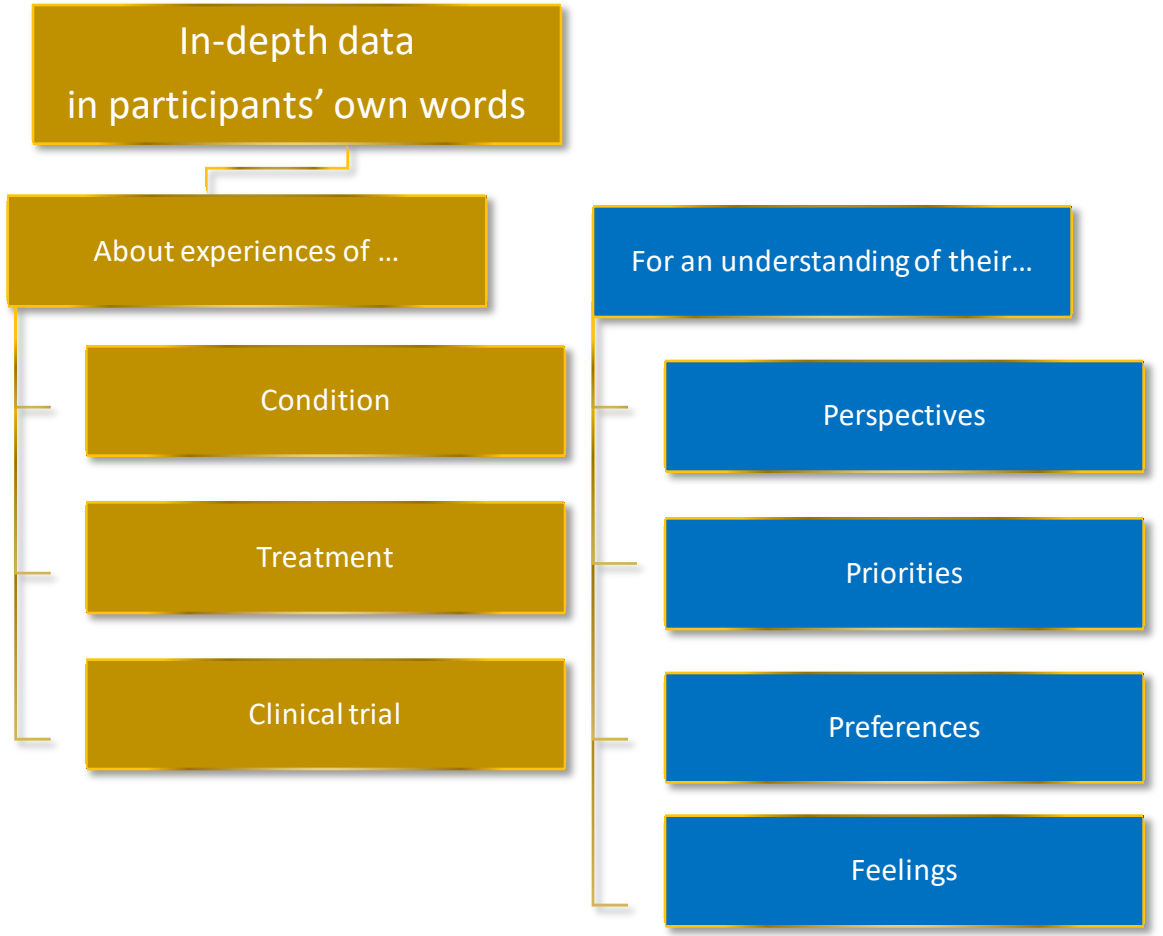
# Agenda

- What is Qualitative Research?
- Types of Qualitative Research - Data Collection
- Opportunities for Use in Drug Development
- Illustrative Example
  - Example case study : Qualitative research used for the development of a patient reported outcome (PRO) measure

# Qualitative Research

"…..the study of the *nature* of phenomena …especially appropriate for answering questions of *why* something is (not) observed, assessing complex multi-component interventions, and focussing on intervention improvement"



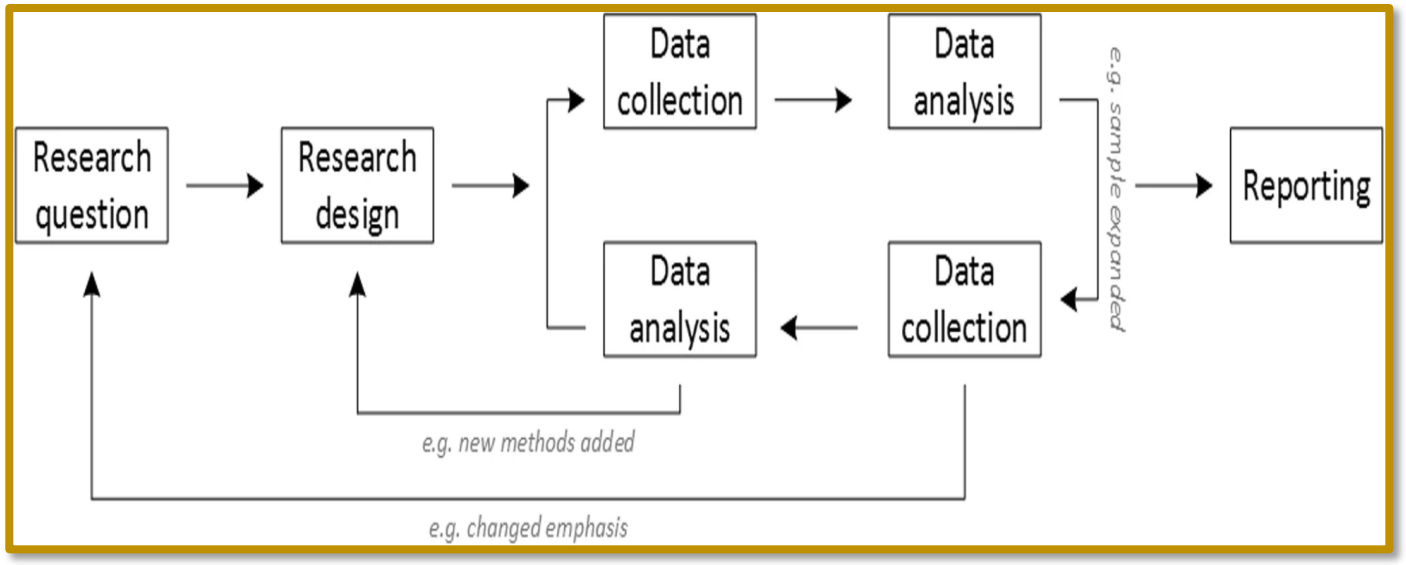



1. Methods of data collection in qualitative research: interviews and focus groups | British Dental Journal (nature.com)

# Qualitative Research Methods are Unique

## Research Methods are Not Completely Separate and Consecutive as in Quantitative Research

*"Sampling, data collection, analysis, and interpretation are related to each other in a cyclical (iterative) manner, rather than following one after another in a stepwise approach"*
(Fossey et al, 2002)




2. Understanding and Evaluating Qualitative Research - Ellie Fossey, Carol Harvey, Fiona Mcdermott, Larry Davidson, 2002 (sagepub.com)
3. Figure Source: How to use and assess qualitative research methods | Neurological Research and Practice | Full Text (biomedcentral.com)
4. Qualitative research | Study Designs | EQUATOR Network (equator-network.org)

# Best Practices, Guidelines, and Standards Exist for Qualitative Research Too!

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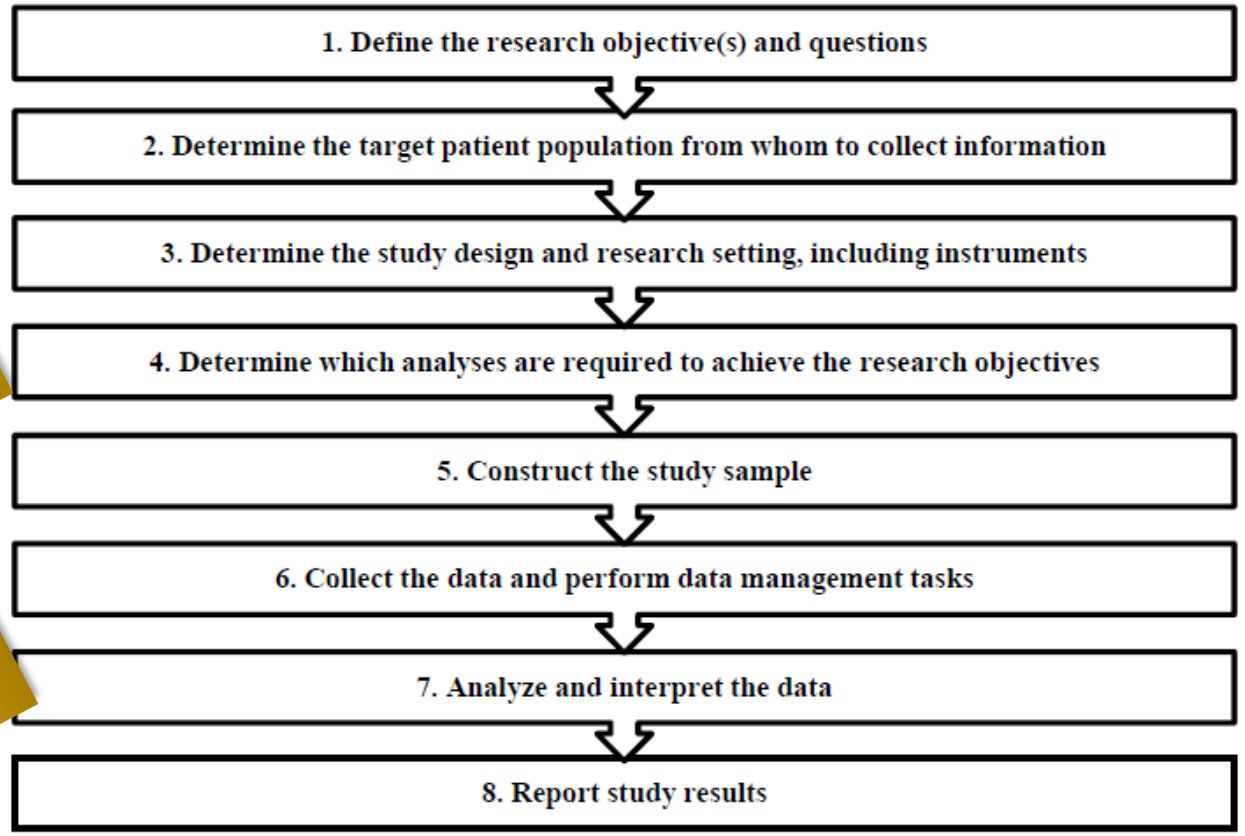
Selecting appropriate theoretical frameworks
Data collection, analyses, reporting

Involving patients/ caregivers as advisors, co-creators

Evaluating reliability of coding, saturation..

**Figure 1. General Steps for Conducting Studies About Patient Experience**




Ensuring representative sampling

For reporting*

5. Figure Source : Guidance 1 Patient-Focused Drug Development: Collecting Comprehensive and Representative Input | FDA

6. Beyond study participants: a framework for engaging patients in the selection or development of clinical outcome assessments for evaluating the benefits of treatment in medical product development

*7. https://www.equator-network.org/

# Types of Data Collection in Qualitative Research

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| | | |
|---|---|---|
| One to One Interviews | Structured, semi-structured, unstructured; in-person, telephone, web-based | DREAMM-1 Patient perspectives from the first-in-human study of single-agent belantamab mafodotin for relapsed and refractory multiple myeloma (RRMM). | **Embedded Interviews**: Symptoms, treatment-related adverse events (AEs), treatment burden, and overall treatment satisfaction (N=17) |
| Focus Groups | In person, tele/video conference, Online – synchronous, asynchronous | The Impact of a Digital Intervention (Happify) on Loneliness During COVID-19: Qualitative Focus Group | A **3-day asynchronous focus group**: Experiences with loneliness, with Happify Health, and with social distancing (N=11) |
| Case Studies | | Using continuous sedation until death for cancer patients: A qualitative interview study of physicians' and nurses' practice in three European countries | Qualitative **case study design** : 84 patient cases: interviews with 57 physicians 73 nurses; |
| Qualitative Surveys | | Chronic pain concepts of pediatricians: a qualitative survey | **Online survey**: **responses to a case vignette-** What caused pain, how they would explain it to patient and family (N=233) |
| Observations, Ethnography | | An Ethnographic Investigation Tracking the Experience of Chronic Myeloid Leukemia (CML) Patients on Tyrosine Kinase Inhibitor (TKI) Therapies | **In-home interviews/7 day photo journal and debrief**: Adherence, disease knowledge, disease management, relationship with HCPs (n=50); 5 countries |
| Social Media Analyses | | Comparison of Literature review, social media listening (SML) vs interviews for Concept Elicitation in Presbyopia | SML conducted using publicly accessible social media sources with focus on ophthalmologic diseases (N= 270 of 4456 posts) |

# References for Examples of Data Collection Methods


- Eliason, L., Correll, J., Martin, M., Cardellino, A., Opalinska, J., Piontek, T., ... & Popat, R. (2020). Patient-Reported Experiences During and Following Treatment With Belantamab Mafodotin (Belamaf) for Relapsed/Refractory Multiple Myeloma (RRMM) in the DREAMM-2 Study. Blood, 136, 1
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- Findley, A., Sharma, G., Bentley, S., Arbuckle, R., Patalano, F., Naujoks, C., ... & Chiva-Razavi, S. (2022). Comparison of Literature Review, Social Media Listening, and Qualitative Interview Research Methods in Generating Patient-Reported Symptom and Functional Impact Concepts of Presbyopia. Ophthalmology and Therapy, 1-16.

# Qualitative Research Opportunities for Use in Drug Development

## Early Development up to Proof of Concept (PoC)

**To understand and describe natural history of a disease**

**Concept Elicitation Studies**

- *To identify what to measure: To develop patient-relevant target product profiles; to evaluate potential candidates*

**Cognitive Interview Studies**

- *To test measures of the concept(s) of interest in the context of use (early trials): for development of de novo instruments or the adaptation of existing instruments for new context of use; testing linguistic adaptations; testing usability of electronic data capture*

**Clinical Trial Experience**

- *To design future studies to enhance participant experiences in clinical trials*

## PoC to Registration

- **Develop attributes for preference studies**
- **Embedded/exit interviews**
  - Patients' experience of proof of efficacy on the concept of interest- efficacy, tolerability, convenience
  - To inform interpretation of results
  - Meaningfulness/relevance to patients/caregivers

## Beyond Approval

- **Patient experience studies** to support submissions to decision makers- HTA, payers
- **Translate meaning of trial outcome** about patient experiences to support clinical decision making



8. Finding Qualitative Research Evidence for Health Technology Assessment

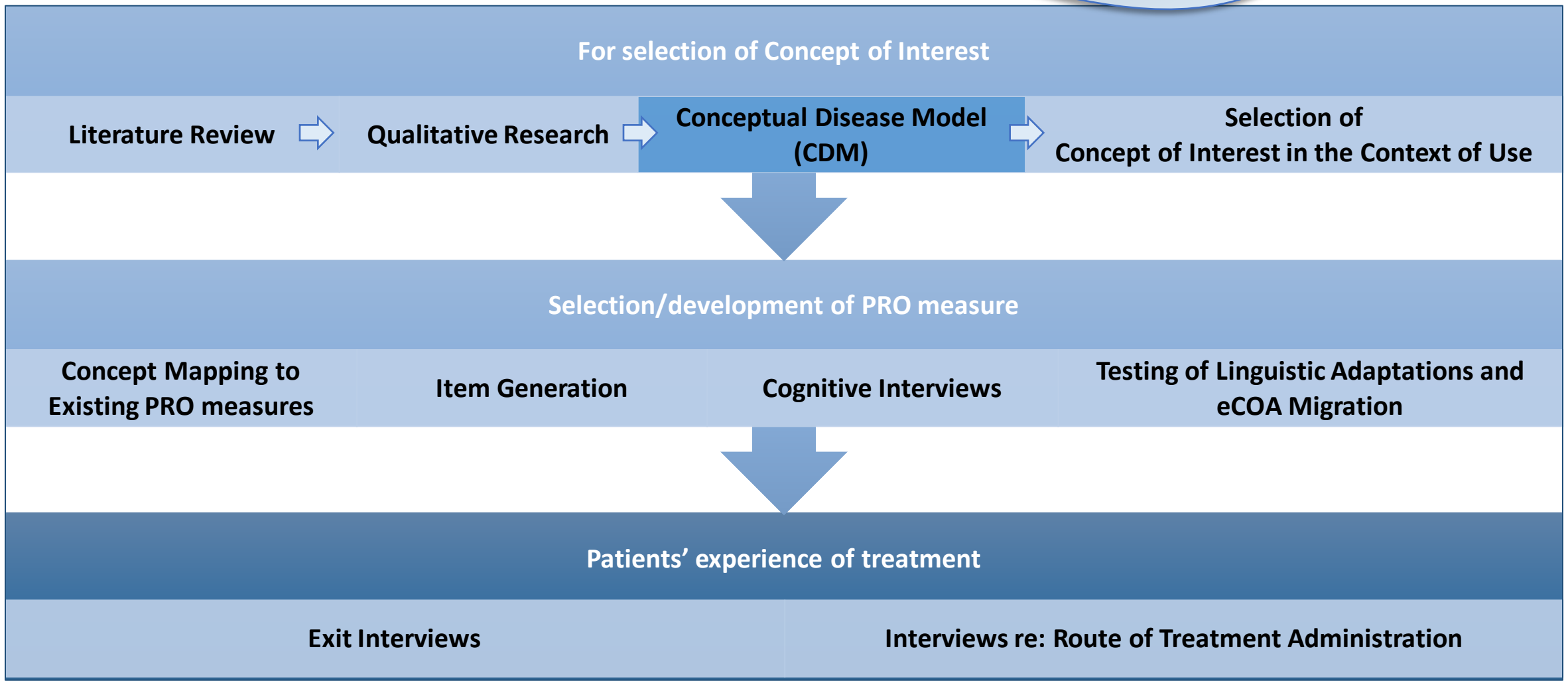
# Example Case Study

Uses of Qualitative Research Methods in Drug Development – for development of a PRO measure

# Example Case Study

## Uses of Qualitative Research Methods

**Context of Use**
To evaluate Patient Reported Outcomes in clinical trials of a prophylactic (preventive) treatment for **migraine**





9. Dodick, D.et al . (2018). *Cephalalgia*, *38*(6), 1026-1037. 8
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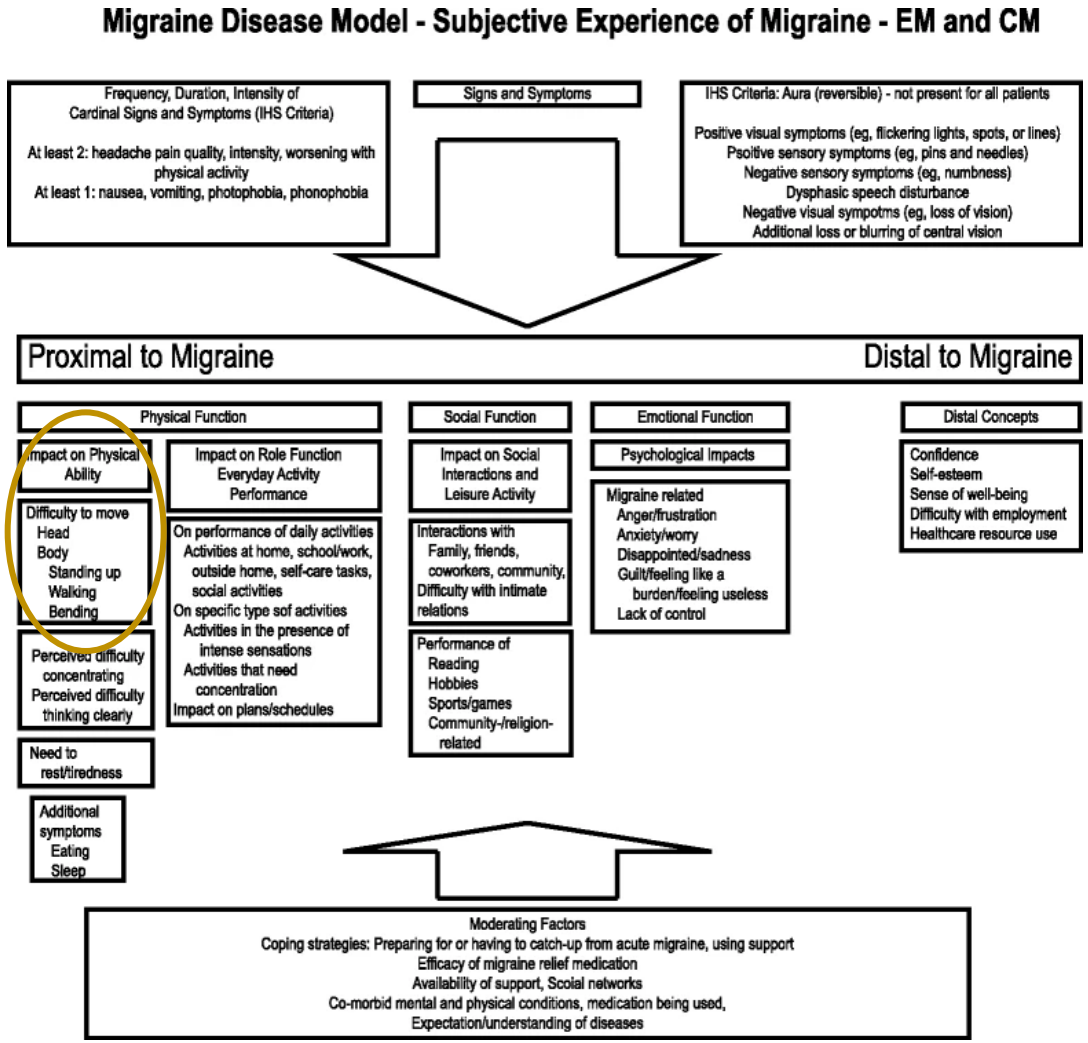
11.Mannix S, et al. 2016 Dec;14:1-1

# The CDM Developed Based on Qualitative Research

## was used as a visual aid to help identify the concepts of interest (COI) in the context of use




CDM-Conceptual Disease Model; EM-episodic migraine; CM-chronic migraine

**Impact on physical functioning** selected as the COI that would be most important to evaluate the *immediate benefits of interventions that prevented migraines.*

- Direct impacts of preventing migraines would be experienced in terms of changes in impact on physical functioning
- Likely to be observed over a shorter duration of time (approximately 6 months)

11.Mannix S, et al. 2016 Dec;14:1-1.

# Qualitative Research Underpinned the Development of the PRO Measure

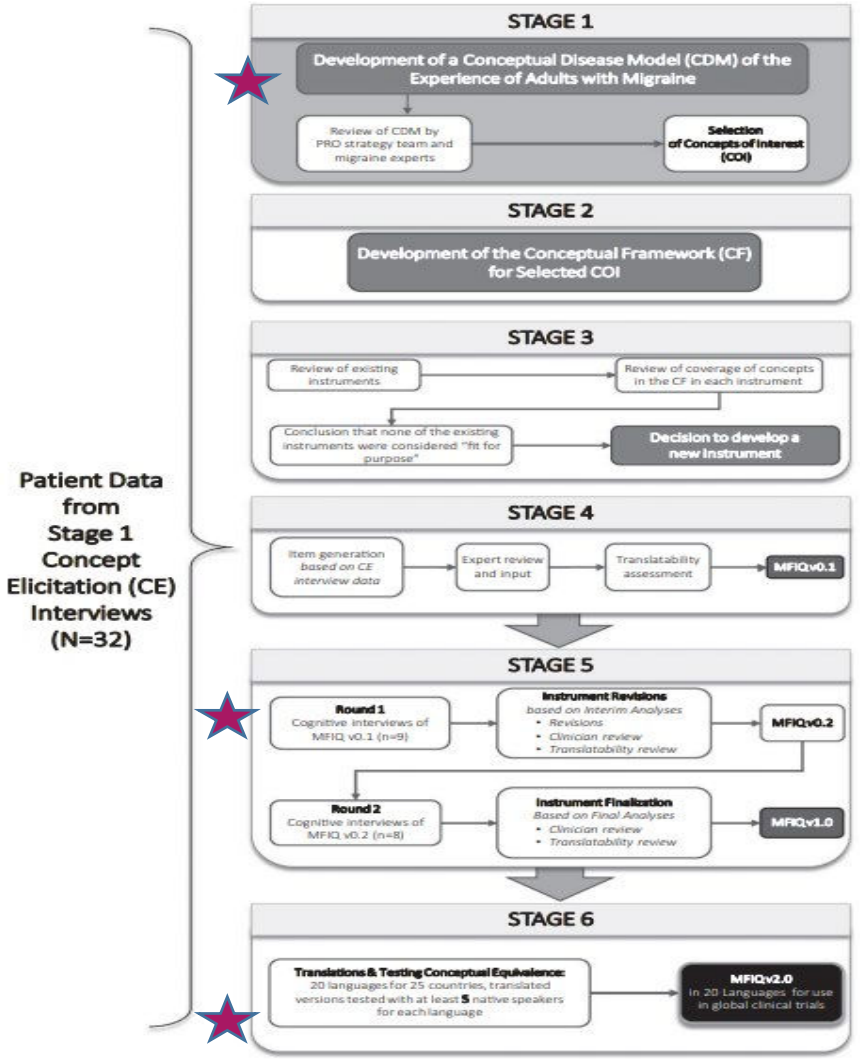
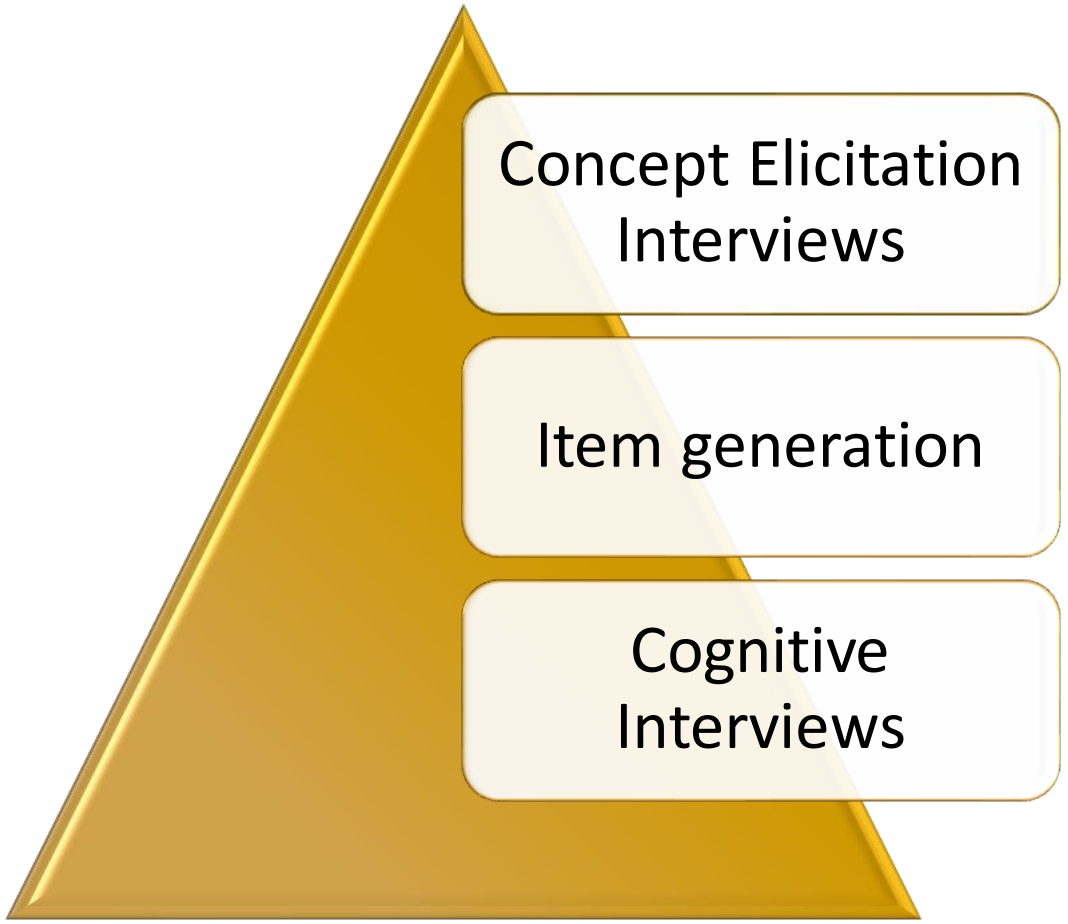



Fig. 1.—Stages in the development of the new PRO instrument. *CE interviews and Stage 1 has been described in detail by Mannix and colleagues[20] and only summarized in this paper.

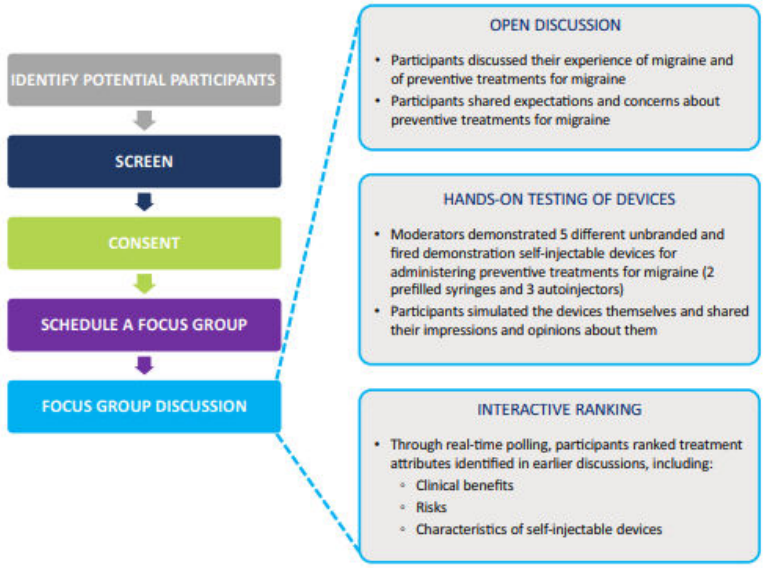



12. Development of a New Tool for Evaluating the Benefit of Preventive Treatments for Migraine on Functional Outcomes – The Migraine Functional Impact Questionnaire (MFIQ) (wiley.com).

# Qualitative Research Helps to Characterize Patients' Experience of the Treatment

**Focus Groups re: patient perspectives of self-injectable devices**

Fig. 1 Overall study design and format of the focus group discussions




**Exit Interviews were requested and reviewed by the FDA DCOA**

**Reviews by the FDA Division of Clinical Outcome Assessment (DCOA) specifically note whether patient experience data was submitted with the Application**

Figure 1-1. Example of Patient Experience Data Table included in review documents for approved NDAs, BLAs, and supplemental applications

| **Patient Experience Data Relevant to this Application** (check all that apply) | Section of review where discussed, if applicable |
|---|---|
| ☐ **The patient experience data that were submitted as part of the application include:** | |
| ☐ 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 survey studies designed to capture patient experience data | |
| ☐ Natural history studies | |
| ☐ Patient preference studies (e.g., submitted studies or scientific publications) | |
| ☐ Other: (Please specify): | |
| ☐ **Patient experience data that were not submitted in the application, but were considered in this review:** | |
| ☐ Input informed from participation in meetings with patient stakeholders | |
| ☐ Patient-focused drug development or other stakeholder meeting summary reports | |
| ☐ Observational survey studies designed to capture patient experience data | |
| ☐ Other: (Please specify): | |
| **Patient experience data was not submitted as part of this application.** | |

12. Patient Perspectives and Experiences of Preventive Treatments and Self-Injectable Devices for Migraine: A Focus Group Study.

# EXAMPLE: FDA's Use of Interview Data from Clinical Trial Participants for Xermelo- DCOA Review

**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use XERMELO safely and effectively. See full prescribing information for XERMELO.**

**XERMELO® (telotristat ethyl) tablets, for oral use**
**Initial U.S. Approval: 2017**

**----------RECENT MAJOR CHANGES----------**

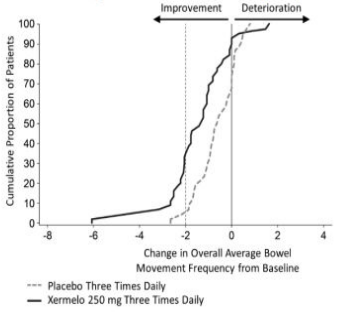
| | |
|---|---|
| Contraindications (4) | 9/2022 |
| Warnings and Precautions, Constipation (5.1) | 9/2022 |

**----------INDICATIONS AND USAGE----------**

Xermelo is a tryptophan hydroxylase inhibitor indicated for the treatment of carcinoid syndrome diarrhea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by SSA therapy. (1)

To aid in the interpretation of the bowel movement reduction results, the proportion of patients reporting any particular level of reduction in overall average bowel movement frequency is depicted in Figure 1 below. For example, 33% of patients randomized to Xermelo and 4% of patients randomized to placebo experienced a reduction in overall average bowel movements from baseline of at least 2 bowel movements per day.

**Figure 1: Cumulative Proportion of Patients with Carcinoid Syndrome Diarrhea Reporting Change in Overall Average Bowel Movement Frequency**




Page 12

Reference ID: 5051099

Extracts from Approved Product label (fda.gov)

"The Clinical Outcomes Assessment (COA) reviewers analyzed data from various anchor measures that were captured in the clinical trial and concluded that the observed impact of Xermelo on bowel movement frequency in this trial resulted in a clinically meaningful within-patient change in Study LX301"
Extract from summary review 208794Orig1s000SumR.pdf (fda.gov)

"The Applicant has provided substantial evidence of effectiveness to support the approval. The durable responder-analyses show that more than 20% of CS patients who had SSA-refractory diarrhea at baseline had greater than 30% reduction of the BMs/day for over 50% of the 12-week treatment period. Although this was not the primary analysis and was not statistically valid from (redacted text) the clinical reviewer standpoint, these results in treating drug-resistant diarrhea are clinically meaningful".
Extract from: Medical Review : 208794Orig1s000MedR.pdf (fda.gov)

Telotristat etiprate (Xermelo)
BM Question in DiaryPRO

## B. Suggested Comments to Sponsor/Applicant

No questions were submitted by the sponsor/applicant. In response to the Review Division's request for review, we have the following comments:

- Reduction of two BMs or 30% from baseline per day is considered meaningful by the patients interviewed in the patient-reported outcome sub-study (patient exit interviews conducted in study LX1606.301). However, this responder definition was not proposed as a study endpoint.

- "Durable response" defined as "reduction of at least 30% in BM frequency from Baseline for at least 50% of the days of participation in the double-blinded trial period" was not appraised by the patients during the exit interviews. In addition, statistical testing of "durable response" was conducted as other efficacy analysis without controlling for multiplicity (i.e., Type I error).

Extract from publicly available DCOA review: 208794Orig1s000OtherR.pdf (fda.gov)

# Qualitative Research …….

Helps to scientifically translate and document participants insights into evidence of patient experiences that can be used to inform health care decisions

Following best practices ensures that the evidence is scientific, meaningful, valid, and reliable

# References


1. Gill, P., Stewart, K., Treasure, E., & Chadwick, B. (2008). Methods of data collection in qualitative research: interviews and focus groups. British dental journal, 204(6), 291-295.
2. Fossey, E., Harvey, C., McDermott, F., & Davidson, L. (2002). Understanding and evaluating qualitative research. Australian & New Zealand journal of psychiatry, 36(6), 717-732.
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6. Wilson, H., Dashiell-Aje, E., Anatchkova, M., Coyne, K., Hareendran, A., Leidy, N.K., McHorney, C.A. and Wyrwich, K., 2018. Beyond study participants: a framework for engaging patients in the selection or development of clinical outcome assessments for evaluating the benefits of treatment in medical product development. Quality of Life Research, 27, pp.5-16.
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9. Dodick, D. W., Ashina, M., Brandes, J. L., Kudrow, D., Lanteri-Minet, M., Osipova, V., ... & Lenz, R. A. (2018). ARISE: a phase 3 randomized trial of erenumab for episodic migraine. Cephalalgia, 38(6), 1026-1037. 8
10. Lanteri-Minet, M., Goadsby, P. J., Reuter, U., Wen, S., Hours-Zesiger, P., Ferrari, M. D., & Klatt, J. (2021). Effect of erenumab on functional outcomes in patients with episodic migraine in whom 2–4 preventives were not useful: results from the LIBERTY study. Journal of Neurology, Neurosurgery & Psychiatry, 92(5), 466-472.
11. Mannix S, Skalicky A, Buse DC, Desai P, Sapra S, Ortmeier B, Widnell K, Hareendran A. Measuring the impact of migraine for evaluating outcomes of preventive treatments for migraine headaches. Health and Quality of Life Outcomes. 2016 Dec;14:1-1
12. Seo J, Smith CA, Thomas C, Tervonen T, Hareendran A, Ford JH, Stauffer VL, Nicholson RA, Duffy KH, Tockhorn-Heidenreich A. Patient perspectives and experiences of preventive treatments and self-injectable devices for migraine: a focus group study. The Patient-Patient-Centered Outcomes Research. 2021 Jun 16:1-6

# Qualitative interviews to elicit patient experience data in clinical studies

Nicola Williamson, Associate Director, Patient-Centered Outcomes, Adelphi Values

Jane R Wells, Clinical Outcomes Assessment Scientist Lead, Patient Informed Development and Health Value Translation, Sanofi

# Agenda

1. Introduction to in-trial interviews
2. In-trial interview methodology
3. Operational challenges and considerations
4. Case study and learnings
5. Key messages and conclusions

# Disclaimer

- The views expressed in this presentation are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of companies the authors are affiliated with.

- Content of this presentation was previously presented at a workshop at ISOQOL 29th annual conference 2022[1] and is based on personal and organisational experiences leading and working on in-trial interview studies and thought leadership and publications.[2-8]

# What are in-trial interviews?

In-trial interviews are a means to collect qualitative data with participants or persons involved in a **clinical trial**.

- Qualitative interviews to elicit patient experience data in clinical studies may be called screening, embedded, in-trial, integrated, incorporated or exit interviews, often depending at what point within the trial they are conducted. They may be conducted:

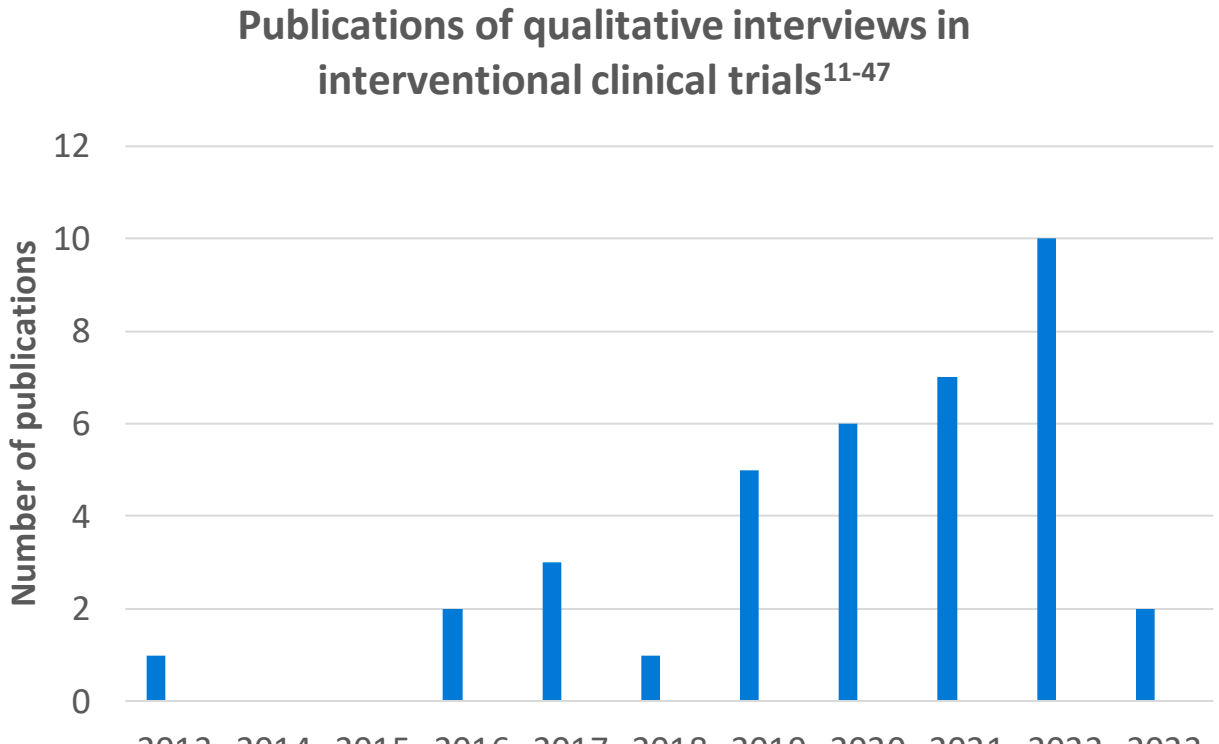

- Interviews are mostly conducted when participants **exit the efficacy phase of a trial**.
  - Ideally interviews are conducted with participants who are still blinded, to minimize bias.
  - Similarly, in-trial interviews may not be recommended in open-label trials and open-label phases of trials, due to the risk of bias, undermining trial integrity and/or data quality concerns.
- Such interviews are usually conducted with **clinical trial participants** but can also be with observers of participants (i.e., caregivers/parents, clinical investigators, or site staff).[2]

# In-trial interview data can be valuable to a range of stakeholders

- In clinical trials, the value of collecting **additional patient experience data from trial participants** beyond that provided by clinical outcome assessment (COA) endpoints is increasingly recognized.[1-5, 10]
- The Food and Drug Administration (FDA) Patient Focused Drug Development guidance outline that screening or exit interviews can be a **valuable method** to obtain **important feedback from participants**.[9]
- While qualitative interviews are not a new methodology, the **application of them in clinical trials is still relatively new** and emerging and there is not yet consensus on best practice methods or how these interview data may be used.[2]

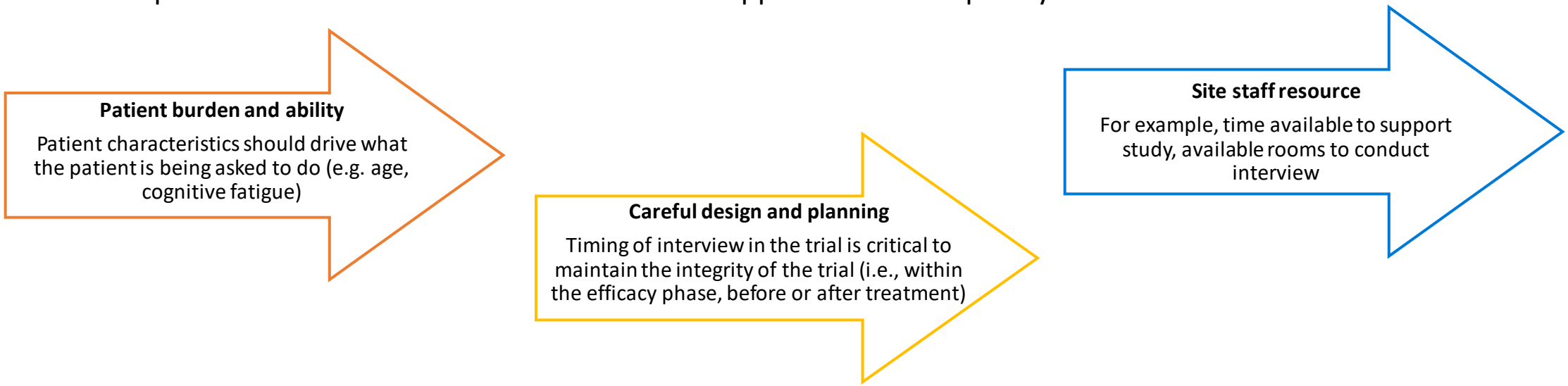

1. Interviews can be used to ensure patient experiences and needs are meaningfully incorporated into decisions. Patients can provide input into study designs, patient-relevant outcomes, and unmet needs.
2. Data generated can be used to build knowledge of the disease and treatment, foster patient informed differentiation of products, and improve future trial recruitment and procedures.
3. Evidence can be used to supplement, support and help interpret trial data. Regulators may request to conduct this methodology to generate evidence in specific contexts of use.
4. Provide insights into treatment benefit to demonstrate value of treatment and consider risk vs benefit to inform reimbursement and regulatory decision-making.
5. Showcase a patient-centred approach in drug development programs, and inform value communications and messaging for products.
6. Further understand disease experience from the patient perspective, improve patient-clinician communication, and support individualized treatment decisions.

# There is a growing body of in-trial interview literature and thought leadership

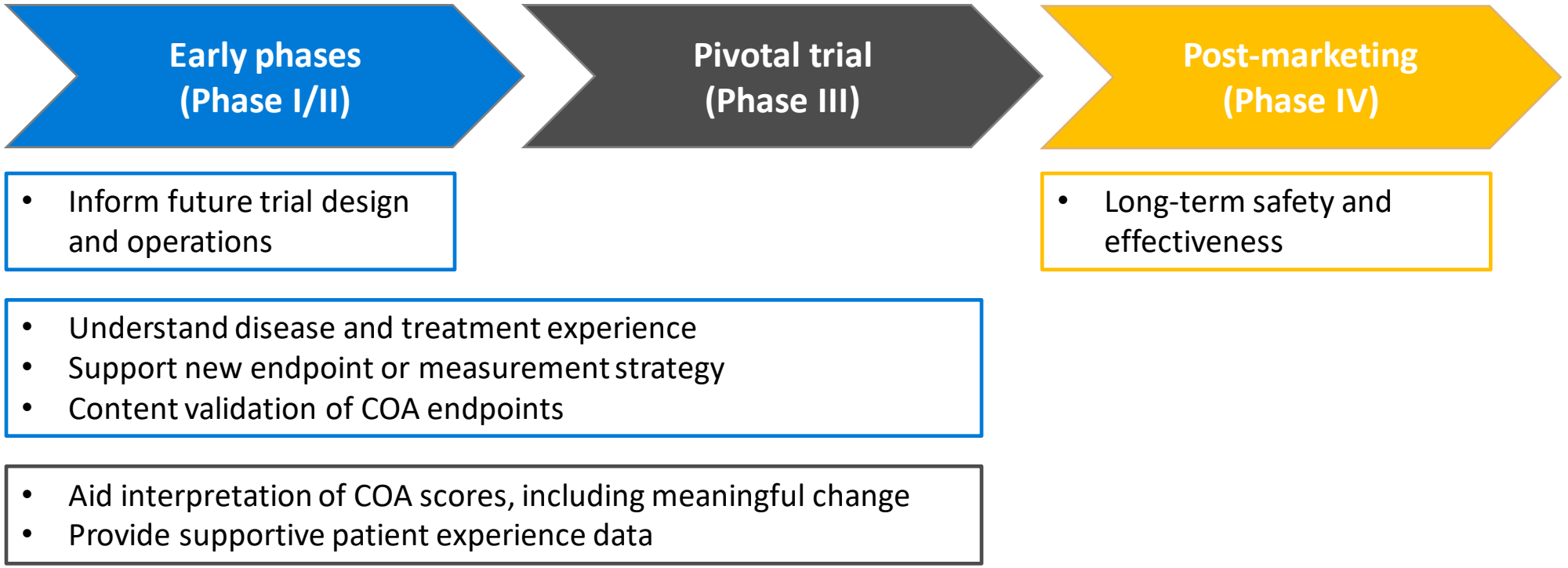



# Overview of in-trial interview methodology

- The methodology follows standard approaches for qualitative interviews and will be **driven by the research aims and objectives**.
- An interview is typically **30-60 minutes in length** using a semi-structured interview guide with **open-ended and closed-ended questions**.
- One-to-one interviews with participants, conducted by **expert interviewers** and not site staff to reduce bias.
- Generally easier to conduct **interviews remotely** via telephone/a teleconference software due to disparate nature of interview scheduling and trial sites.
- It is critical that the **same level of rigour** and careful **planning of the design** of qualitative interview studies is applied when planning an in-trial interview study, and that it makes sense with where you are in the development program.
- Interview methodology **must balance scientific rigor with logistical feasibility** of implementing within the clinical trial in a manner acceptable to internal stakeholders. Selection of approach and complexity should consider:



# What research questions can in-trial interviews help answer?




- The figure shows the research questions most suitable for each phase of clinical development. However, broadly topics can be explored at any time regardless of trial phase, though some topics may be more or less important depending on phase and disease area.

# Early phases can be the most useful time to obtain insights from trial participants

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**Early phases (Phase I/II)**

*"How did you find taking part in the trial?"*

*"How did you feel about the study procedures that you did during the study?"*

**Inform future trial design and operations**

- Inform study design to improve recruitment and retention
- To hone the logistics of a trial to ensure smooth-running and feasibility for sites and participants

**Understand disease and treatment experience**

- Explore current disease experience including symptoms and impacts most important to improve
- In novel treatments, first opportunity to explore and document the patient perspective of treatment acceptability, benefits, burden and satisfaction, such as new product features and how these meet unmet treatment needs
- Compare patient experience with previous treatments and study treatments

*"How satisfied or dissatisfied are you with the ability of the treatment to control your symptoms?"*

**Support new endpoint or measurement strategy**

- Identify concepts of importance to patients, supporting endpoint selection
- Develop and refine new measures
- Usability testing to assess appropriateness of the eCOA, digital health technology or performance outcome measures, to inform any modifications or additional training needed prior to use

**Content validation of COA endpoints**

- Generate COA content validity evidence by evaluating the appropriateness of a COA in the intended trial population

*"Since the start of the trial, have you experienced any changes in the symptoms you experience? Tell me about that."*

*"Can you describe what, if any, symptoms you experience now?"*

*"What is most important for the treatment to improve?"*

*"What does this question mean to you?"*

*"How did you find using the handheld device?"*

*"Have you ever experienced [concept]?"*

# Pivotal trials may be last opportunity to obtain insights from the trial population prior to approval

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**Pivotal trial (Phase III)**

**Aid interpretation of COA scores**

- Obtain patient input on meaningful change (improvement, worsening, stabilization) on COA scores or concepts supporting primary or secondary endpoints
  1. Qualitative discussion of change in COA concepts, but not directly linked to COA scores. For example, magnitude of change, expectation, type of change (frequency of symptom, duration, severity…etc)
  2. Discussion about change in COA scores, directly linked to trial COA(s) scores. Exploring why a patient selected or would select a response and what that change means to the patient. Can be accomplished with or without actual patient scores

- This qualitative score interpretation data can be triangulated with quantitative score interpretation data (i.e., anchor-based meaningful change analysis) for patient-informed meaningful change scores

**Provide supporting patient experience data:** Can provide supporting context to other efficacy endpoints when evidence of patient benefit is lacking. **It is critical evidence in small samples sizes to inform patient-centric evaluation**, where COAs are insufficient or lacking in power

*"At the start of the study you answered X. Why did you choose that answer?"*

*"What bothered you most about [symptom]?"*

*"Is this improvement important/meaningful to you? Why?"*

*"If you had changed from [baseline response] at the start of the study to [2 point difference], would this improvement still be important to you? Why?"*

# Longer term outcomes can be explored in post-marketing studies

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**Post-marketing (Phase IV)**

**Long-term safety and effectiveness**

- Similar to interviews in phase III, interviews in phase IV can enable better understanding of treatment outcomes, with focus on longer term outcomes where change/slowed decline cannot be easily shown in shorter clinical studies
- Data can support and provide context for interpretation of longer term COA data
- Sponsors may want to extend the use of a treatment and learn about additional benefits from the patient perspective
- Explore adherence and compliance to treatment in the longer term
- Ability to collect targeted evidence if needed for payer negotiations in specific countries/markets

*"You mentioned at the start of the study that you had difficulty with XX. How has this changed if at all?"*

*"How did you feel after you received the treatment?"*

*"What are your thoughts on how often you need to take the treatment?"*

*"Would you be interested in taking the study treatment in the future if it were available?"*

*"How did you feel about the number of visits you made to the site?"*

*"How did your expectations for the treatment match your experience?"*

# Operational considerations when planning an in-trial interview study

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**Getting internal buy in**

- Address the **concerns of internal stakeholders** upfront through careful planning
- Important to have the **budget available** – studies can be costly
- Request **regulatory input early** – regulators may request the methodology

**Incorporated vs standalone**

- Studies **incorporated** into the clinical trial **maximize efficiencies and minimize timelines**
- Standalone studies require **separate protocol**, **separate ethics**, **contracting** with sites, etc. Site engagement may also be a challenge

**Sample (subset of trial sample)**

- Typically conducted with a **subset of the clinical trial sample** (~n=20-40). Sample sizes need to be large enough to adequately represent **key demographic and clinical characteristics** of the target population and ensure sufficient numbers of patients **receiving active treatment**

**Country selection**

- Selection of certain countries to be involved in the interview study may be driven by **disease prevalence** and satisfying regulatory authority requirements in **key markets** and generating **country-specific data**
- Ethics and translation requirements may also be a factor

**Site training and communication**

- Important to have a **sufficient number of sites** that have sufficient **pools of potential participants** and have site staff resource to support the interview study
- Participation of sites that are anticipated to be **engaged and willing to be involved** in the study

- **Training** of site personnel involved in the interview study activities will ensure all parties have clearly **defined roles and responsibilities**.
- This includes setting expectations for when each party should perform activities (i.e., consent, sending reminders, scheduling interview)

- Clear **communication channels** should be established between the site, sponsor and interviewers to avoid duplications, for example sponsor can keep interviewer updated on recruitment to minimise need to contact sites

# Operational considerations when planning an in-trial interview study

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| | | | |
|---|---|---|---|
| **AE and safety reporting** | • AE reporting is a key consideration for these interview studies, as they may be reported by participants **during the interview** or identified **during analysis**<br>• There is a need to **avoid duplication of AEs** already reported in the clinical trial | • Reporting procedures depend on the **clinical trial AE reporting procedures** and **sponsor requirements**<br>• **Typical approach to take is reconciliation of AE reports** with sites **throughout the study** and at the **end of the study** | • If **COA scores** are discussed during the interviews, ensure it is agreed how that data will be **separate from AE reports**<br>• Ensure that AE reports **do not risk unblinding of treatment allocation** depending on who has access to the AE report |
| **Data management and handling** | • **Data management plan** can be used to detail how data will be **securely managed**, **stored**, **processed** and **transferred** to different parties during the course of the study, including how, where and when data will be shared and in what format | • Ensure that the study is using **secure methods for data transfer** (i.e., secure file sharing platform rather than by email)<br>• Ensure that data are stored according to **retention periods** | • Consider who will **retain copies of documents** in accordance with the Trial Master File<br>• A data transfer agreement may be needed between the vendor and sponsor to outline what data will be transferred and when (i.e., sharing demographic data following database lock) |
| **Analysis of blinded or unblinded data** | • Ensure analysis of interview data is considered in relation to wider trial data and **timing of database lock** and unblinding of data. Blinded interim analysis could be performed and an unblinded full analysis following database lock | • Depending on research objectives it may not be necessary to analyse data unblinded (i.e., disease experience, feedback on trial procedures).<br>• **Unblinded analysis** could provide **useful insights** into **treatment experience** and **exploration of meaningful change** | |

# Case study: Exit interviews to generate evidence of meaningful change (improvement)

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## CONTEXT

- **Therapeutic area:** Acute and less common dermatology condition
- **Population:** Adults and adolescents
- **Development:** Phase 3 double-blind, placebo controlled RCT (direct from Phase 2a)
- **Trial sample size:** n=78
- **COA endpoints:** Primary and key secondary

## CHALLENGE

**Regulatory feedback** indicated that PRO measures lacked evidence of meaningful score improvement

**Small trial sample size** and **no suitable anchors** indicated that generating sufficient quantitative evidence of meaningful change with trial dataset was not possible

## SOLUTION

- **60-minute telephone** interview at trial exit
- **20 to 30 trial participants** aged 12+ years
- Semi-structured guide **to explore meaningful within patient change**
- **Standalone protocol** study design
- Up to **15 clinical sites** in North & South America and Europe

FDA U.S. FOOD & DRUG ADMINISTRATION

conducting exit interviews/surveys within your phase 3 study may be an approach to evaluate meaningful scores changes by interviewing patients regarding:

a) Their thoughts on what they believe constitutes a meaningful improvement from baseline in their symptoms in terms of each item
b) What they consider to be a meaningful improvement in terms of anchor scale(s) category changes (e.g., 1-category change, 2-category change, "a little better," "moderately better", etc)
c) Whether they believe they experienced a meaningful improvement from baseline.

# Case study: Feasibility challenges when exploring meaningful change in trial participants

## CONTEXT

- **Therapeutic area:** Acute and less common dermatology condition
- **Population:** Adults and adolescents
- **Development:** Phase 3 double-blind, placebo controlled RCT (direct from Phase 2a)
- **Trial sample size:** n=78
- **COA endpoints:** Primary and key secondary

## CHALLENGE

**Challenge 1.** Not possible to obtain PRO measure scores ahead of exit interview because of risk of unblinding

**Challenge 2.** Not all study participants will have experienced investigational treatment change because the trial is a placebo-controlled

There was no possibility of excluding placebo participants from the exit interview study because:

- This would risk unblinding to the patient and investigator and impacting rest of data collection
- All study participants needed to be eligible to achieve the interview study target sample size

## SOLUTION

Patients were given **hypothetical scenarios** about score changes rather than discussing actual trial scores

This approach including interview guide was **FDA reviewed and supported**

Exit interview data to be positioned as **supportive of meaningful change** data derived from trial using anchor-based analyses

Accept risk that exit interview **result interpretation will be challenging** as effect of investigational drug is unknown

Exit interview data will be **included in the COA dossier**

# Key messages and conclusions

- In-trial interviews can provide **in-depth qualitative insights** into the experience of patients in a clinical trial, in addition to traditional clinical outcome assessments, providing evidence in the specific **trial context of use**.

- However, there are numerous **challenges and considerations** when designing an in-trial interview study which should be carefully thought out and planned for in advance.
  - There is a need to **streamline** the **operational challenges** when planning an interview study to facilitate **internal endorsement** and **continued implementation** within clinical trials.

- We will continue to learn how best to design, analyse and report these data and the value it can add to various stakeholders in providing evidence to **inform measurement strategies, selection of endpoints** and **future trial designs** and to **support product approvals**.

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# Using qualitative interview studies embedded in multi-country clinical trials to evaluate rare disease patient experiences

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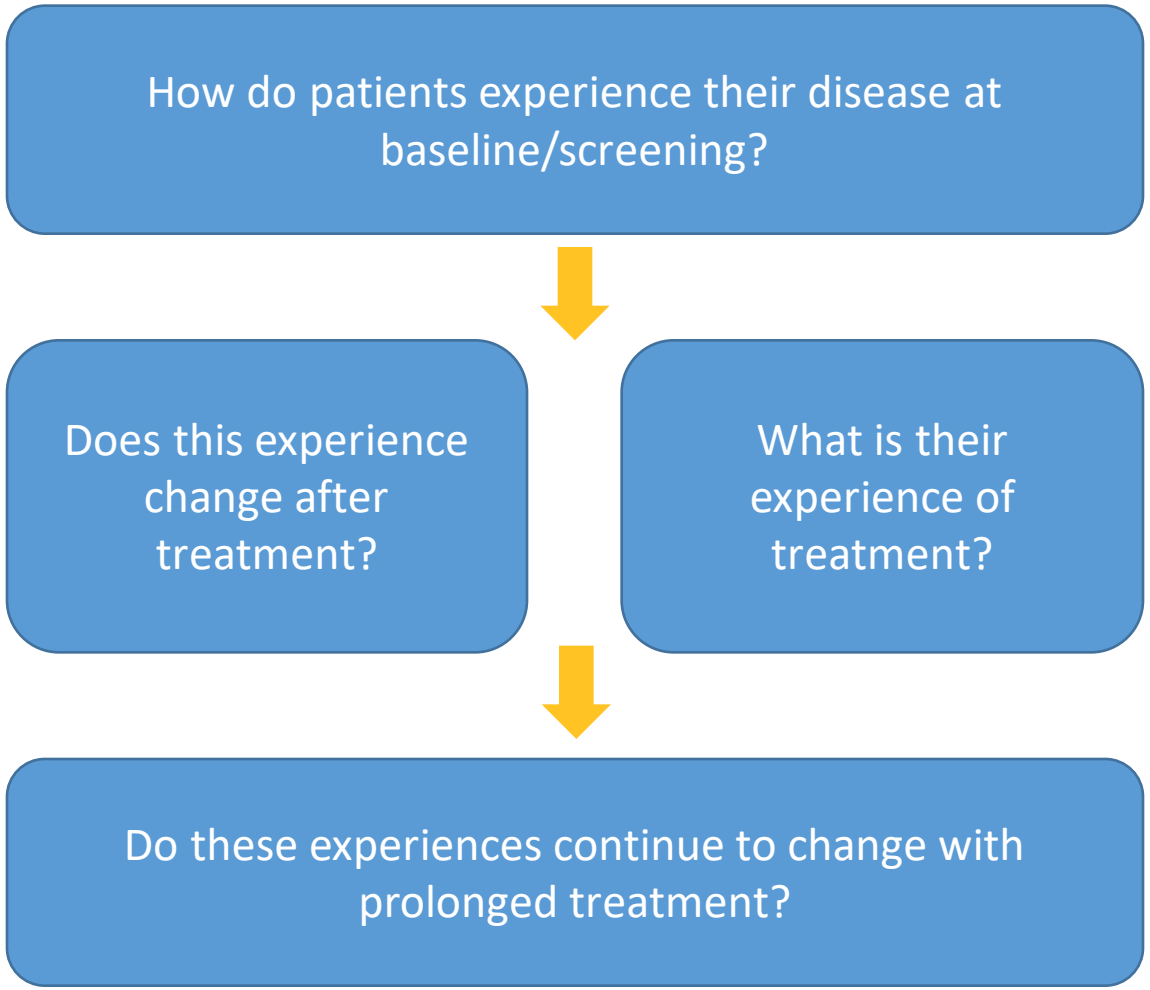
# Introduction

- This presentation covers in-trial interviews conducted in collaboration with the Patient Centered Solutions team at IQVIA.

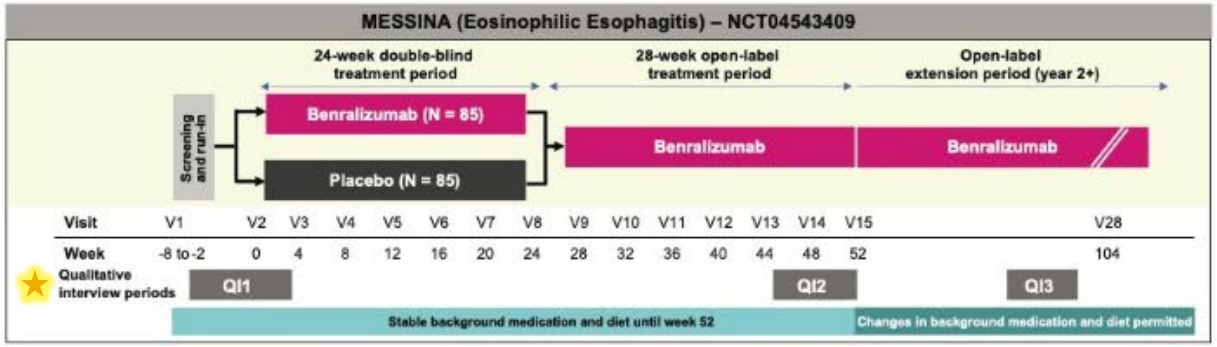
- Because the trial results have not been reported, the focus will be on methodology, research questions, and potential uses for the evidence.

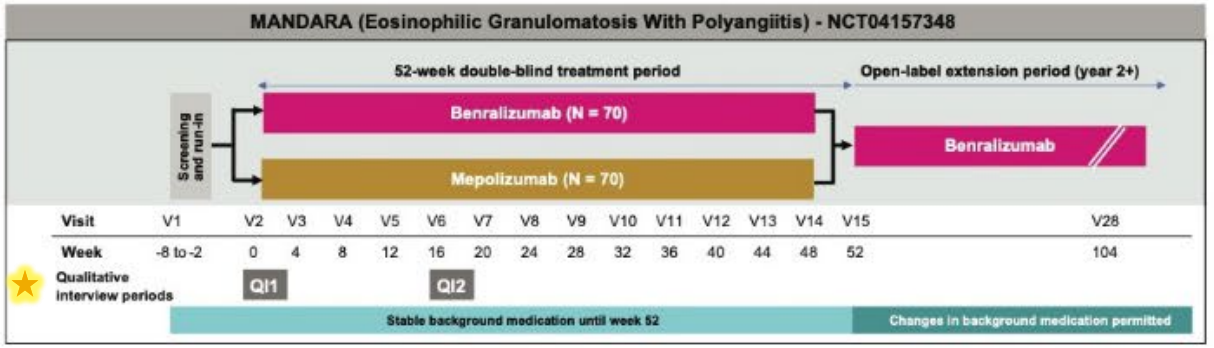
# Longitudinal qualitative research

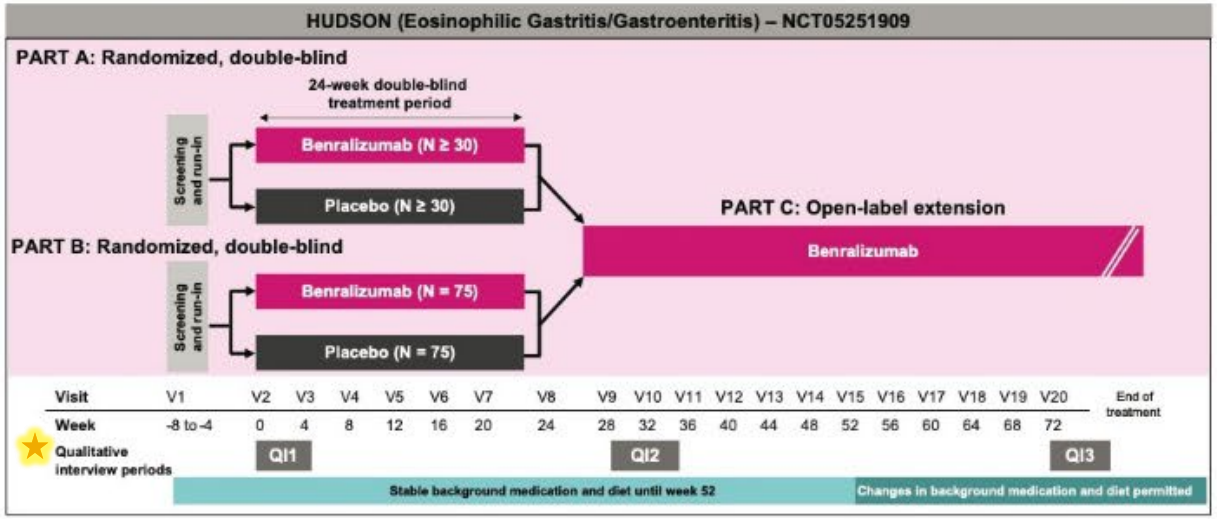
- Patients' experiences with their medical condition can change over time, as the condition progresses and/or gets treated
- Interventional clinical trials often use longitudinal designs to track changes over time
- Longitudinal qualitative research embedded in clinical trials can put these quantitative findings into context
- Analysis can be done at the level of individual patients or at the group level

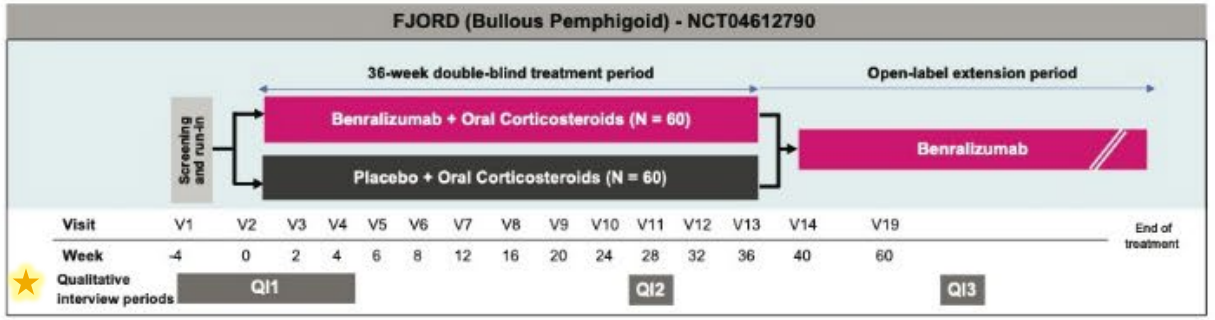


# Embedded interviews in the benralizumab program




Four straight-to-Phase 3 rare disease trials with few/no fit-for-purpose COAs to use as symptom endpoints

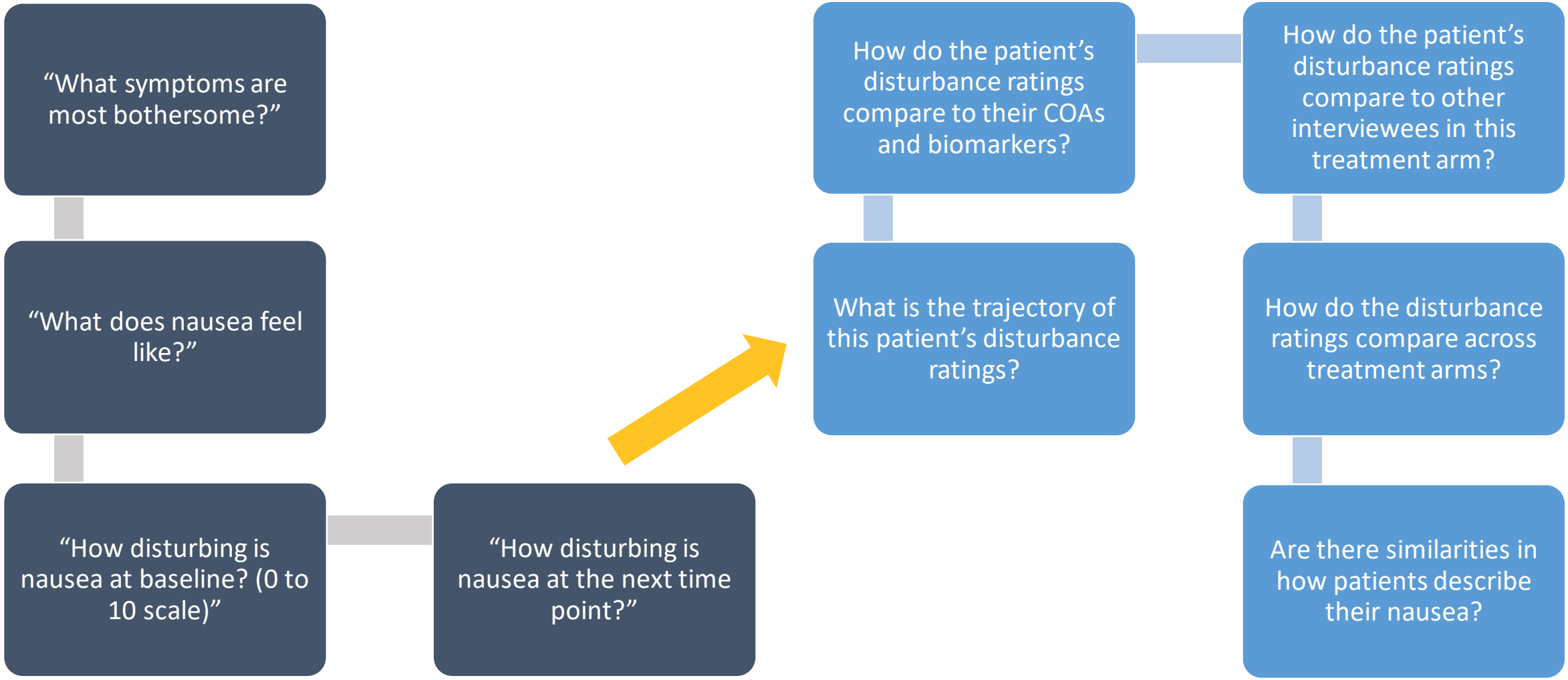
# Methods

- Semi-structured qualitative interviews are included as optional sub-studies within four Phase 3, randomized, double-blind, multi-country clinical trials
- Adult patients who opt into the interview sub-study will participate in telephone interviews at the beginning of the study, a mid-point in the study, the end of the study, and/or after several months of open-label treatment, depending on the study
- The interviews will be transcribed, translated into English, if necessary, and coded for themes
- The interview data will also be evaluated in the context of clinical and demographic data from each trial
- The analysis will incorporate patient-level efficacy data from each trial, including patient-reported outcome assessments

# What are we hoping to find out?

- Key symptoms and health related quality of life impacts
  - How do these change over time?
  - How do these change with active treatment?
  - How do these compare to the concepts measured in the COAs in the trials?
- Differences between subgroups of patients (e.g., disease severity, comorbidities, gender, geography)
- Meaningful change on certain PRO measures (added per FDA recommendations)

# Example questions and analysis flow



# Meaningful change

**VERBATIM:** How severe has your nausea been over the past 14 days?
I am going to read you a list of the possible answers.

- No nausea
- Very mild nausea
- Mild nausea
- Moderate nausea
- Severe nausea
- Very severe nausea

How would you answer this question right now?

Moderate nausea

# Meaningful change

Would a change to “mild nausea” seem to you a meaningful improvement in your nausea?

How would you characterize this improvement in your own words?

What would be different in your life?

Alternatively:
- Worsening
- Stabilization

…

# Meaningful change

Would a change to “severe nausea” seem to you a meaningful worsening in your symptoms?

How would you characterize this worsening in your own words?

What would be different in your life?

Make sure the language used is appropriate for the patient!

…

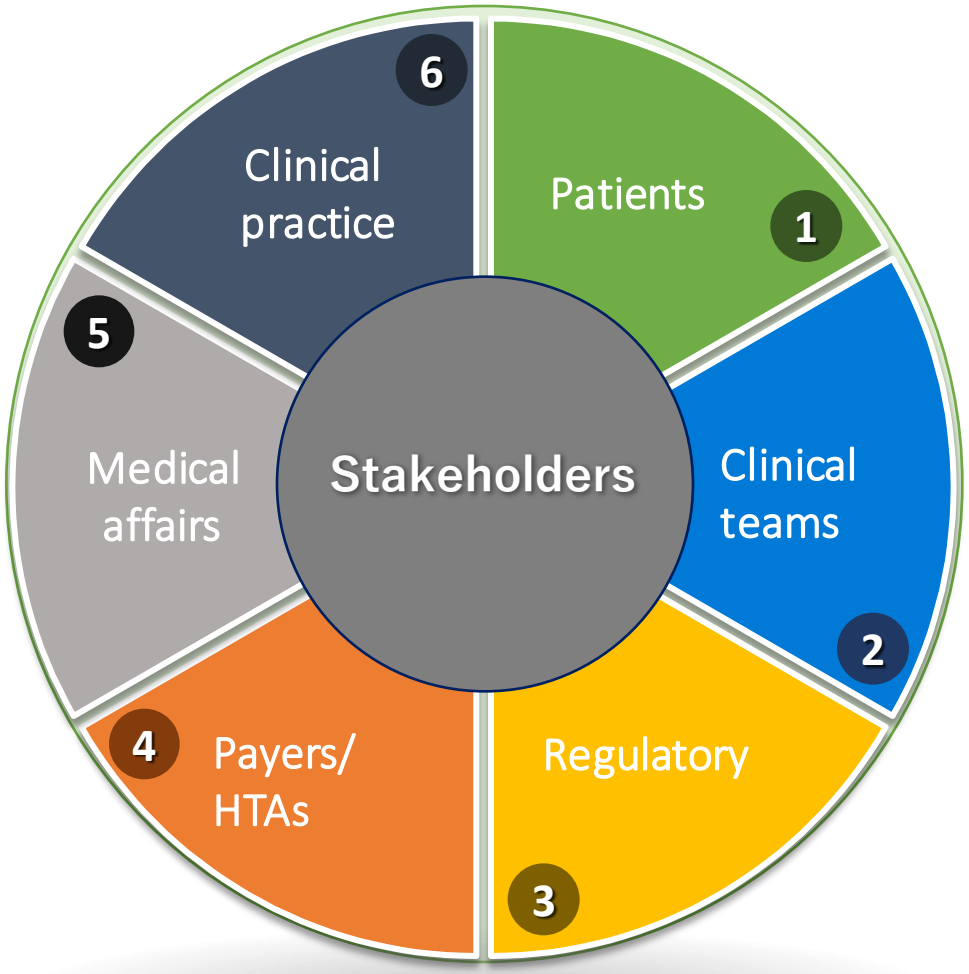
# Topics we are not (directly) addressing

- Tolerability and adverse events
- Patient experience in the trial
- Usability of eCOA devices
- Cognitive debriefing of COAs

All of these are potentially good topics, depending on your research goals

Consider including these topics in studies with rare, hard-to-reach populations

# What we can do with the evidence




1. Publish plain language articles/summaries and reference results in disease awareness programs.
2. Use data to inform the development of future studies, especially if interviews are conducted prior to Phase 3.
3. Compare interview data with other trial data during interpretation of results.
4. Interview data can elucidate treatment benefits and risks, and thus inform reimbursement recommendations and decisions.
5. Published interview data can be referenced in interactions with healthcare providers, congress booths, etc.
6. Results can help healthcare providers understand the true burden of disease and benefits of treatment.

# Learnings we can share

## Best to get started as early as possible

- Well before Phase 3 if you can
- At the beginning of protocol development, rather than adding in later

## Can we get patients to pick up the phone?

- Cold calls get ignored as our relationship with telephones change
- Must take new technologies and patient preferences into account

## Informing patients and getting consent is key

- Informed consent must be easy to understand
- Site staff must be aware of study and on board with recruitment

# Special thanks


- Shehan McFadden, Oren Meyers, Keena Roberts, Pamela Delgado, Julie Bailey and the whole IQVIA Patient Centered Solutions team for execution and thought partnership in the development of these interview studies

- Sean O'Quinn, Vivian Shih, Erik Bark, Catherine Datto, and Margaret Melville at AstraZeneca for supporting the design and business case

- EoE, EG/EGE, BP, and EGPA patients from around the world who have contributed their time and their stories to this endeavor

# To learn more

## Posters describing interview methodology

- Ho, Calvin N., Oren Meyers, Julie Bailey, Vivian H. Shih, Erik Bark, Sean O'Quinn. Using longitudinal qualitative interviews embedded in multi-country clinical trials to evaluate rare disease patient experiences. Poster presented at: International Society for Quality of Life Research (ISOQOL) Annual Conference; October 19-22, 2022; Prague, Czech Republic.
- Ho, Calvin N., Oren Meyers, Julie Bailey, Erik Bark, Raquel Durban, Nirmala P. Gonsalves. Assessment of change in food-related behaviours and anxiety in EoE and EG/EGE clinical trials using longitudinal qualitative interviews. Poster presented at: European Academy of Allergy & Clinical Immunology (EAACI) Congress 2022; July 1-3, 2022; Prague, Czech Republic.

# Initial steps in creating a patient-centric addendum to clinical trial informed consent forms

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# Background

**In theory ->** The purpose of the informed consent form (ICF) is to outline the risk and benefits of the clinical trial to the person considering enrolling in a clinical trial

**In reality ->** It appears that generally ICFs:

- Are written using complex language and scientific jargon
- Are 25-30 pages long
- Have a lot of extraneous information not pertinent to the patient

**Solution ->** A multi-phase project involving both patients and caregivers, trialists (i.e., those who consent patients onto a clinical trial), regulators, IRB chairs and clinical trial sponsors to help streamline the informed consent process

# Phased approach to our project

PRO CONSORTIUM
CRITICAL PATH INSTITUTE

## Phase 1

Audit of ICFs for Phase 1, 2, and 3 lung cancer trials to identify:

- What and how information is being presented
- Whether forms are written in a comprehensible fashion (8th Grade Reading level). Audit was guided by 45 CFR 46 requirements

## Phase 2

Conducted 2 focus groups (FG) and 4 one-on-one interviews in the US to learn what participants need to make an informed choice. One FG was with a trial-naïve group and the other with clinical trial experience. Of the 9 participants, 5 had clinical trial experience.


## Phase 3

Results from the audit and qualitative phase were presented at an industry stakeholder roundtable to prioritize best practices and discuss a 1-2 page template addendum to the ICF summarizing key points for people considering enrolling in a clinical trial.

United States Congress. "45 CFR 46." Department of Health and Human Services. http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.104

# What patients wanted included in a summary

## Content

- Note that the study is optional
- What is being tested and what can the patient expect as treatment
- Clear explanation of criteria for study inclusion
- Where is the trial happening? (Travel vs local administration)
- Brief privacy statement on identity protection
- How the drug is administered and how frequently
- Duration of study and what comes after

## Formatting

- Bullet point format, but especially for criteria to qualify
- Page number references for lookup of key detail in the form
- Collate all important contact information in one place
- Snapshot of most common side effects

> *"[I'd include] a one liner about this being optional, and a one liner about your privacy…[saying that] all of your information is confidential, and you're treated with a patient identification number."*
> (Prior CT experience, stage 3)

# What we heard when we presented our results to industry stakeholders

- What participants in phase 2 wanted was considered as too much information for two pages
- Possible issues around a master template that would need modifying by country
  - What design features could we use in designing the template to help streamline that process
- Where roundtable participants had conducted similar work, they had received internal feedback on
  - How the team would ensure they weren't "cherry picking" anything designated as key information
  - Difficulties in striking a balance between technical language and lay language

# Flexibility to iterate & evolve is critical

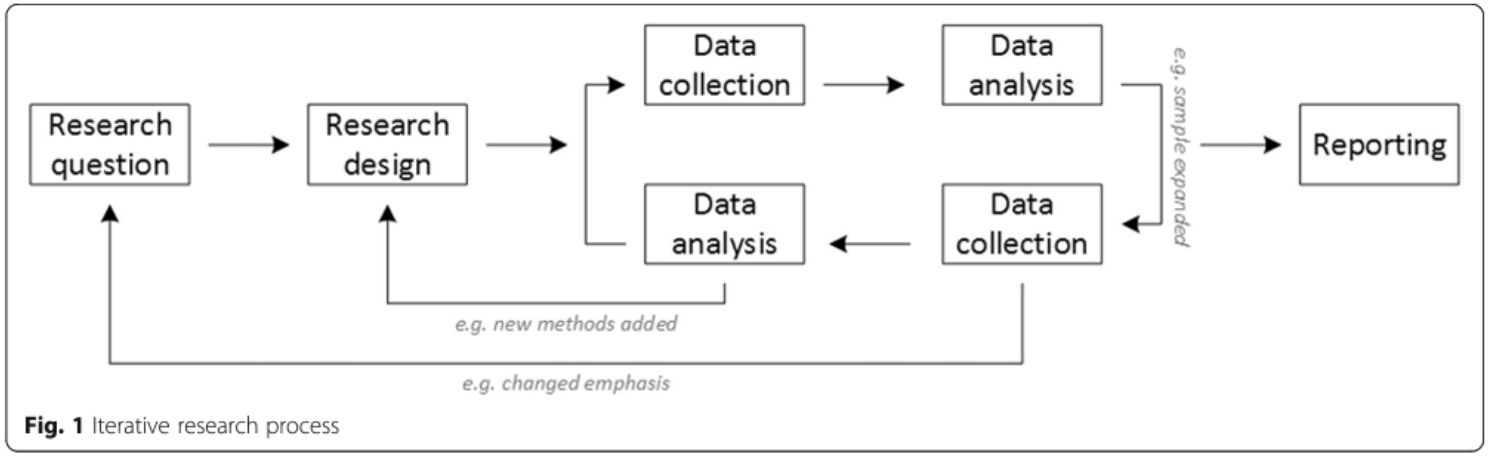


**Fig. 1** Iterative research process

- Insights gained in phases 2 and 3 led to us changing our research plan.
- Decades of work investigating the informed consent process had not led to change.
- We added an additional phase to our study.
- Hearing one side, the patient side, was not going to be sufficient to change the eco-system in which the ICF exists.

Busetto, L., Wick, W., & Gumbinger, C. (2020). How to use and assess qualitative research methods. Neurological Research and practice, 2, 1-10.

# Phase 4

**Phase 4**

Short survey (reviewed by patients & caregivers) to confirm priority of themes (~120 patients/caregivers)

To learn the challenges & barriers of ICF reform

Interview additional stakeholders, including:

- IRB Chairs
- Legal/compliance folks working in industry as well as independent experts
- Regulators
- Trialists (both principal investigators and staff who consent patients)

After 6 stakeholder interviews, we are back at the drawing board.

# Whole system view

- The patient's voice in our work is central.
- HOWEVER … to implement what those living with lung cancer have told us they need in terms of the ICF, we must listen to other voices to successfully navigate change.
- There are hidden barriers when trying to change complex systems- only by having structured conversations with a goal, have we been able to gain additional insights.
- The beauty of qualitative research is that you can consider the contexts in which individuals or groups function.

# Phase 4: Interview directions

"I'm thinking about the patient package insert that goes with labels. As an analogy... it's sort of almost an informed consent corollary to that, because that is also presenting risk information."

*Former legal consultant to pharma*

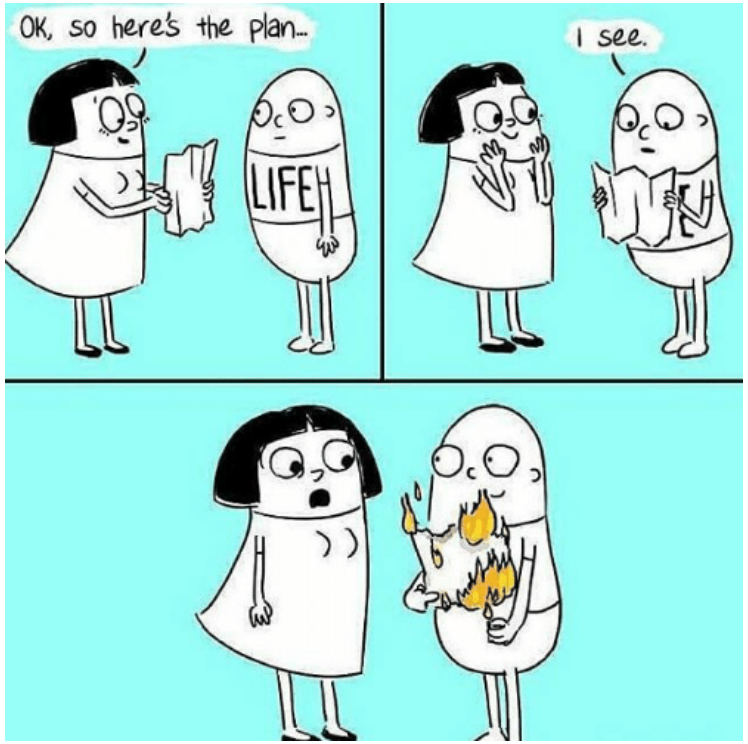
"The way I would look at it, I think it will be very hard to implement or require to have an IRB approved document… that's attached to the consent… just because the level of scrutiny and review this documents gets is, as we know, tremendous."

*IRB Chair and oncology trialist*

During our study, the FDA posted a Notice of Proposed Rulemaking regarding the informed consent form addressing a summary of key information to align with Health and Human Services Revised Common Rule. We are looking to align here and work with the FDA.

# Take aways

- We started with a plan to create a template addendum to the ICF.
- Emerging results required us to change and adapt.
- We are now reviewing our plan considering what we are hearing in our stakeholder interviews and the FDA's Proposed Rule Making.
- This is the opposite of a statistical analysis plan that requires researchers to carry out the proposed research plan.



# Thank you to my collaborators

- LUNGevity Foundation: Andrea Ferris, Tracey Grant, Tendai Chihuri, Upal Basu Roy
- EDGE Research: Lisa Dropkin, Mariel Molina, Lydia Redway
- UT Southwestern: David Gerber

# Panel Discussion and Q&A

**Moderator**

- *Maria Mattera, MPH* – Scientific Director, Patient-Reported Outcome Consortium, Critical Path Institute

**Presenters**

- *Asha Hareendran, PhD* – Patient Centred Outcomes Research Excellence Lead, UCB Biopharma Srl
- *Nicola Williamson, MSc* – Associate Director, Patient-Centered Outcomes, Adelphi Values
- *Jane Wells, MSc* – Clinical Outcomes Assessment Lead, Sanofi
- *Calvin N. Ho, PhD* – Associate Director, Patient Centered Science, AstraZeneca
- *Bellinda King-Kallimanis* – Director of Patient-Focused Research, LUNGevity Foundation

**Additional Panelists**

- *Marc Yale* – Advocacy and Research Coordinator, International Pemphigus Pemphigoid Foundation
- *Naomi Knoble, PhD* – Associate Director of Rare Disease Measurement Science, Division of Clinical Outcome Assessment, Office of Drug Evaluation Sciences, Office of New Drugs, Center for Drug Evaluation Research, U.S. Food and Drug Administration

# Thank you!