U.S. FOOD & DRUG ADMINISTRATION

PATIENT-FOCUSED DRUG DEVELOPMENT
GUIDANCE PUBLIC WORKSHOP

Methods to Identify What is Important to Patients & Select, Develop or Modify Fit-for-Purpose Clinical Outcomes Assessments

Workshop Date: October 15-16, 2018

Discussion Document for Patient-Focused Drug Development Public Workshop on Guidance 2:

METHODS TO IDENTIFY WHAT IS IMPORTANT TO PATIENTS

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I. INTRODUCTION

FDA recognizes the need to obtain meaningful ***patient input***[1] to understand their experience with their disease and its treatment to inform development of endpoint measures to assess clinical outcomes of importance to patients and caregivers in medical product development. To ensure a ***patient-focused*** approach to medical product[2] development and regulation, FDA will develop guidance on methods to identify what matters most to patients to be measured in clinical trials, specifically, how to design and implement studies to capture the patient's voice in a robust manner. This document has been developed to support the Patient-Focused Drug Development Guidance: Methods to Identify What is Important to Patients and Select, Develop or Modify Fit-for-Purpose Clinical Outcome Assessments public workshop[3] discussions that will inform guidance development.

This workshop will address the second in a series of four methodological ***patient-focused drug development*** (PFDD) guidance documents[4] that FDA is developing to describe in a stepwise manner how stakeholders (patients, researchers, medical product developers and others) can collect and submit ***patient experience data*** and other relevant information from patients and ***caregivers*** for medical product development and regulatory decision making.

Guidance 1[5] covers the selection of patients from whom to collect information (e.g., sampling methods for collecting representative information on patient experience. Guidance 2 will focus on methods to elicit relevant information from patients[6], in particular how their disease affects their daily lives, what they find most troublesome, and the challenges, problems, and burdens of the treatments for the disease. Some of these issues were introduced in Guidance 1, but will be covered in greater depth in Guidance 2.

The discussion document for the Guidance 2 workshop presents a more in-depth discussion of:

- Methods for eliciting information from patients and other stakeholders, specifically gathering information about what aspects of ***symptoms***, impacts of their disease, and other issues are important to patients;
- Common pitfalls in collecting information from patients that can lead to results that inadequately or incompletely identify what is important to patients; and

[1] The Glossary defines many of the terms used in this discussion document. Words or phrases found in the Glossary appear in bold italics at first mention.
[2] A drug, biological product, or medical device.
[3] https://www.fda.gov/Drugs/NewsEvents/ucm607276.htm
[4] The four guidance documents that will be developed correspond to commitments under section I.J.1 associated with PDUFA VI under Title I of the FDA Reauthorization Act of 2017. The projected timeframes for public workshops and guidance publication reflect FDA's published plan aligning the PDUFA VI commitments with some of the guidance requirements under section 3002 of the 21st Century Cures Act. https://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm563618.pdf
[5] *Draft Guidance for Industry, FDA, and Other Stakeholders Patient-Focused Drug Development: Collecting Comprehensive and Representative Input*
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM610442.pdf
[6] When referencing patients, we are including other stakeholders.

- Operational details including development of interview guides, selection of types of survey questions, and considerations for collecting demographics and survey information, which are provided in appendices to this document.

A. OVERVIEW AND SCOPE

For ease of navigation through this document, the content is organized into three parts:

- Methods to identify what is important to patients
- Approaches to asking the right questions (in qualitative and quantitative research settings)
- Best practices in how to do qualitative and quantitative research (operationalization)

An overview of the content presented in this document is shown in **Table 1**.

Table 1. Overview of Content

	Topic	Section
Methods to Identify What Is Important to Patients	What types of research methods can be used to identify what is important to patients?	Section IIA
	How do you identify what is important to patients?	Section IIA.1
	How do you frame questions to capture patients' experience with the burden of disease and/or treatment?	Section IIB.1
	How do you frame questions to capture patients' experience on treatment benefits and risks in the management of their disease?	Section IIB.2
	What types of qualitative methods can be used to talk to patients?	Section IIIA
	What types of quantitative methods can be used to obtain patient input?	Section IVA Appendix7
Asking the Right Questions	How to avoid inappropriate framing of questions when talking to patients (e.g., leading/judging questions)?	Section IIIA.1(i)
	What types of questions do you ask in a survey?	Section IVA.1(i)
	How to avoid inappropriate framing of questions in surveys (e.g., priming)?	Section IVA.1(i)
	How to talk to special patient populations (pediatrics, cognitively impaired, rare diseases) and different cultures?	Appendix 2
	How to survey special patient populations and different cultures?	Appendix 5
Best Practices in How to Do Qualitative and Quantitative Research	How to design and implement qualitative studies?	Appendix 1
	What are the relevant study materials needed for: • Qualitative studies (e.g., interview/discussion guides)? • Survey studies?	Appendix 1 Appendix 4

	Topic	Section
(Operationalization)	How to design and implement studies for different types of settings (observational, screening/exit interviews)? • Qualitative studies • Quantitative studies	Appendix 3 Appendix 6
	How to design and implement quantitative studies (e.g., surveys, other technologies)?	Appendix 4 Appendix 7

B. QUESTIONS FDA HAS IDENTIFIED FOR THE OCTOBER WORKSHOP

With this discussion document FDA seeks input from patient stakeholders, researchers, medical product developers, and others on how best to communicate FDA's current thinking on approaches to collecting patient experience data. Questions for readers to consider for Guidance 2:

1. Identify best practices (qualitative and quantitative methods) for eliciting information about what aspects of symptoms, impacts of disease, and other issues important to patients that are-representative of the target population of patients and caregivers. What level of detail of the methodology do you think is appropriate for this guidance?

2. What sample size will elicit sufficient information about the patient experience to assure ***representativeness*** but is feasible?

3. What other data (e.g., data from social networks, accelerometry, room surveillance) can be used to elicit or derive information about the patient experience in a feasible manner?

4. Use of social media is recognized as a potential data collection method to elicit information regarding patient experience.
    a. Will information collected from social media sources meet the goals of Guidance 2 (e.g., collecting representative information on important symptoms, burdens, and related issues)? If yes, how do we determine the adequacy of data from social media sources?
    b. Is there a need for patient verification if social media is the data collection method to elicit information about the patient experience?

5. Important considerations are needed for special populations, such as pediatrics, the cognitively impaired, and rare diseases. What other special populations (beyond pediatric, cognitively impaired, and rare diseases) should be identified for this FDA Guidance? Are there any other factors to consider when eliciting information from special populations?

6. The level of rigor needed for generating patient experience data can vary across studies and will depend on the intended use. However, there are certain elements common to all studies such as a protocol, structured data collection, and analysis. How much detail about each aspect would be useful in guidance? On a website? Elsewhere?

7. What document structure and content would be most useful for this guidance?

8. Many potential research methods are available and not all could be included in the discussion document. Is it clear the Agency is open to discussion of the methods described and other methods, both within medical product programs and in the pre-competitive space?

9. What are the most important timepoints when FDA input could be maximally helpful?

II. METHODS TO IDENTIFY WHAT IS IMPORTANT TO PATIENTS

A. Methodological Overview

What types of research methods can be used to identify what is important to patients? FDA recommends using ***qualitative***, ***quantitative***, or ***mixed methods*** to collect robust and meaningful patient experience data, which includes the ***disease and treatment burden*** and ***benefits*** and ***risks*** in management of the patient's disease. For details on the important distinctions between these methodological approaches refer to **Table 2 of Guidance 1**.

Qualitative and quantitative methods can be categorized by the depth of information (e.g., descriptive information) they provide and the extent to which they collect information that may be more generalizable to the ***target population***. When selecting an appropriate research method, you should ideally balance the importance of depth versus ***generalizability***, or use a mixed method approach to get a combination of both.

1. Concept Elicitation

Concept elicitation is a process to collect a holistic set of relevant ***concepts*** (e.g. disease and treatment symptoms and associated impacts) that are important to patients. Concepts can be elicited using qualitative, quantitative, or mixed methods (See **Sections III, IV** and **V**).

Concept elicitation should occur in a wide range of patients with the disease of interest and/or other stakeholders such as ***patient representatives***, caregivers and clinicians to represent variations in severity and in demographic characteristics such as age, sex, ethnicity, education, and language groups in accordance with the anticipated study design to obtain representative input from the underlying target patient population.

B. Developing the Research Objectives and Questions

Research objectives and questions should be clearly stated so that the data collected from patients meets the intended use of the information. Research objectives and questions should be specific, clearly defined and reflect the scientific and regulatory goals of the study. A discussion of how to define research objectives and questions can be found in **Section IIB of Guidance 1**.

The research objectives should determine the questions to be addressed to the patient group, the methods to be implemented, and the appropriate target population.

Questions to ask yourself when determining the target population include but are not limited to the following:

- What are the potential barriers for patients created by inclusion and exclusion criteria?
- What is the impact of exclusion criteria on the enrollment of particular subpopulations?
- Does the study design and methodology impact representation of subpopulations in a study?

1. Burden of Disease/Treatment and Benefits and Risks (Harms) in Disease Management

How do you frame questions to capture patients experience with the burden of disease/ treatment and benefits and risks in disease management? Table 2 lists some important considerations that can serve as the foundation for research objectives and questions intended to capture the patient experience related to disease/ treatment burden and benefits and risks in disease management.

Table 2. Considerations for Researchers for Framing Research Questions and Objectives Related to Disease/Treatment Burden and Benefits and Risks (Harms) in Disease Management

Patient Experience	Considerations	Example Questions/Objectives
Burden of Disease	• Patient perspective on burden of disease • Caregiver perspective on patient's burden of disease • Frequency and/or severity of symptoms • Impact of disease symptoms on functioning in patients' daily lives • Symptoms that require treatment or reaching out to doctor • Symptoms most important to improve with treatment	• Which disease symptoms are most important to patients? • Which impacts of disease symptoms are most important to patients? • Which symptoms are most burdensome to patients?
Burden of Treatment	• Patient perspective on burden of treatment • Impact on participation in activities (e.g., work and school) • Caregiver perspective on patient's burden of treatment • Patient experiences (positive/negative) with a mode of administration of a treatment (e.g., subcutaneous vs. intravenous infusion, oral vs. subcutaneous)	• Which aspects of treatment burden are most important to patients?

Patient Experience	Considerations	Example Questions/Objectives
	• Treatment frequency (e.g., daily vs. weekly) • Time to administer treatment • Treatment storage (e.g., refrigeration, room temperature) • Special treatment administration (e.g., treatment administered only at hospital/clinic)	
Benefits and Risks	Patient perspective on: • Frequency of treatment side effects • Severity of treatment side effects • Ideal ***treatment outcome*** (resolution of symptoms, relief of symptoms, increased survival) • Efficacy of prior treatment(s) (***treatment effects***) • Ideal treatment • Convenience of treatment (including frequency of dosing regimen, ease of use, route of administration) • Treatment satisfaction • Treatment adherence • Impact on participation in activities (e.g., work and school)	• How much did a patient improve in their symptoms or impacts while on treatment? • What treatment benefits are most important to patients? • What treatment benefits did the patient expect to experience? Did the patient's experience align to what he/she expected? • What treatment side effects (risks/harms) are of most concern to patients? • Are patients willing to experience the treatment side effects to achieve treatment benefit?

III. QUALITATIVE RESEARCH METHODS

KEY MESSAGES

- Identify the appropriate participants to talk to (i.e., patients with condition of interest)
- Determine a sufficient number of participants to talk to
- Use an experienced and well-trained facilitator (e.g., interviewer, moderator) to lead interviews or discussions
- Use a semi-structured interview/discussion guide with well-designed questions to get better insights from participants, as the facilitator's choice of words can affect the participants' input or behavior.
- Use a balanced mix of open-ended and structured/pre-determined probing questions

A. Sources of Qualitative Data to Elicit Burden of Disease and Treatment Benefits and Risks

What types of qualitative methods can be used to talk to patients? Qualitative research methods can generate in-depth information about the experiences, perspectives, and feelings (including needs and priorities) of patients and other individuals (e.g., clinicians, caregivers), in their own words. These include but are not limited to:

- Interviews (**Section III.A.1(i)**)
- Focus groups (**Section III.A.1(ii)**)
- Consensus panels (Delphi) (**Section III.A.1(iii)**)
- Observations (**Section III.A.1(iv)**)
- Social Networks (**Appendix 7**)
- Patient-focused drug development (PFDD) meetings (FDA or externally-led)[7]

Qualitative methods can be useful for achieving the following research goals:

- Eliciting information regarding which disease-related concepts (e.g. signs, symptoms and impacts) are important to patients
- Determining research and drug development program priorities based on the patient experience
- Gaining a more in-depth understanding of disease or treatment burden in order to develop clinical trial ***endpoints***

Table 3 lists some advantages and disadvantages of using different methods of gathering qualitative data. **Section III.A.1** will provide further detail on each method.

Table 3. Advantages and Disadvantages of Different Qualitative Data Collection Methods

Qualitative Research Method	Advantages	Disadvantages
One-on-One Interviews	• Can gain in-depth information on the topic of interest and/or understanding of how a respondent interprets a question • Flexible – can tailor interviews to generate more or less detailed information based on research needs • Interviews can generate can	• Timing (e.g., length of interviews; number of patients interviewed) • Data interpretation can be influenced by subjective interpretation • Studies can be expensive

[7] https://www.fda.gov/drugs/developmentapprovalprocess/ucm579400.htm

Qualitative Research Method	Advantages	Disadvantages
	generate rich, nuanced data about an individual's experience and perspectives robust data for analysis	
Focus Groups	• Can gain in-depth information on the topic of interest and/or understanding of respondents' question interpretation • Saturation can be obtained sooner with focus groups than with one-on-one interviews. • Elicit feedback from multiple participants at one time • Participants more likely to provide candid responses • Participants can build on each other's ideas • Relatively inexpensive	• Individual data might not be available from each participant • May not be efficient in covering maximum depth on a particular issue • Distractions or peer-pressure may emerge within the group • Single individuals might dominate the conversation and multiple perspectives may not be shared • Group setting may inhibit some individuals from providing sensitive information • Large volumes of qualitative data might be difficult to analyze • Data analysis can be influenced by subjective interpretation • Less flexibility in scheduling can present recruitment challenges
Consensus Panels (Delphi)	• Acceptable method for reaching consensus among appropriate experts and stakeholders on important issues and topics • Anonymous process, when appropriate, reduces the role of ego and interpersonal issues in reaching consensus	• Lack of universal guidelines for process • Size of expert panel should be considered as it is difficult to achieve consensus among a larger group • Implications for lack of anonymity in the case of modified Delphi panel methods • Definitions of "expert" opinion is variable • No clear standards for the most acceptable level of consensus

Qualitative Research Method	Advantages	Disadvantages
Observations of Patient Behavior or Events (rating from a video observation)	• Low burden for participants as the observation is non-invasive and does not require active participation • Advantages of naturalistic settings/real-world context	• Less common because it may be time-consuming and logistically cumbersome to execute if conducted in natural settings (e.g., study environments may vary across locations) • Some concepts and experiences are not observable • Can be expensive • Participant behavior may be affected by observer presence • Observational environments, if in naturalistic settings, may be variable and affect the reliability and generalizability of the results
Social Networks	• See **Table 6 of Appendix 7** for advantages of social networks	• See **Table 6 of Appendix 7** for disadvantages of social networks
PFDD Meetings	• See advantages of focus groups	• Input is limited to patients who can attend the meeting which may minimize generalizability of findings to the target population • See disadvantages of focus groups

You should consider various factors when selecting the source of qualitative data to use, including but not limited to:

- Research purpose
- Target population
- Sample size (projected based on knowledge of the target patient population and in consultation with expert stakeholders)
- Study design
- Feasibility factors (e.g., research environment, cost of execution within the context of study budget, willingness and ability of patients to participate)
- Time
- Geography

Table 4 lists some other participant factors to consider when selecting the most appropriate qualitative method.

Table 4. Considerations for Selecting Qualitative Methods for Participants

Respondent Burden

• **Length of discussion**
  ○ Consider sessions that are shorter in duration (e.g., 30-90 minutes each), when possible.
• **Travel**
  ○ Determine whether remote alternatives (e.g., video-conferencing or telephone conferencing) can be used in lieu of in-person sessions.
• **Access to technology**
  ○ Consider respondent accessibility to technology during study design; accommodations should be made accordingly to the extent possible to those with limited access.

Disease Progression
• **Patient and caregiver availability**   ○ Consider patient's disease status and level of care required when determining recruitment targets as this may impact study recruitment and retention.

1. Best practices for use of qualitative sources

The following sections outline general considerations related to each qualitative method. Additional details regarding considerations for special populations and different cultures can be found in **Appendix 2**.

i. Interviews

Interviews are the most common source of qualitative data in which a conversation between a research participant and interviewer is directed toward producing information about participants' experiences, feelings, and opinions and subsequently deriving meaning out of what participants say. Interviews are useful for gathering in-depth information around a topic or to further investigate the meaning attributed to questionnaire responses.

There are different types of interviews, which include:

- Semi-structured interviews
- Structured interviews
- Open-ended interviews

Table 5 outlines different types of interview methods that can be used to generate qualitative data on the patient experience.

Table 5. Types of Interview Methods

Type of Interviews	Description
Semi-structured interviews	• Most common method. • Using a semi-structured interview guide, the semi-structured interview allows the same general areas of information to be collected from each interviewee while still allowing a degree of flexibility and adaptability to help generate in-depth information from each participant based on their responses. • Interviewer sets the discussion agenda; the participant's responses help guide the level of information generated about the predetermined topics and their relative importance (Johnson and Christensen 2017).
Structured interviews	• Less common method. • Require the same open-ended questions to be asked of all participants, with no deviation. This approach facilitates faster interviews that can be more easily analyzed and compared. • A closed, fixed-response interview is a type of structured interview that requires each participant to be asked the same questions and asked to choose answers from among the same set of alternatives. This format is useful for those not practiced in interviewing; however, this method does not allow room for exploration and additional probing based on participant responses.
Open-ended Interviews	• Less common method. • Not led by predetermined questions. In order to remain as open and adaptable as possible, the dialog between the interviewer and participant remains open to the emergent priorities of the participant within the conversation. During the discussion, the interviewer provides little direction toward an *a priori* research agenda. • Although useful for generating in-depth responses, this type of interviewing is more time consuming in the analysis phase than other methods and may not be ideal for capturing information targeted toward specific research questions.

You should select an interview type to meet the needs of your study, taking into account the following:

- Target population, including disease characteristics (disease severity, rate of progression), clinical characteristics (phenotype, genotype), and demographics (e.g., age)
- Topic sensitivity (e.g., patients may be less open to discuss topics related to sexual functioning or mental health)
- Topic complexity (e.g., complex concepts might require more structured probes)

For sensitive topics, it will be important to use a trained and seasoned qualitative interviewer who can:

- Create a safe environment
- Build rapport
- Be patient and allow the respondent to gather their thoughts, control their emotions, and find the words to describe their experience.
- Use creative qualitative interventions or techniques

Once you have selected the interview method, you should also consider the mode or method of interview administration. Interviews can be administered in different modes/methods, which includes administration by:

- In-person
- Telephone
- Video Conference/Online [including web-based or webcam]
- Audio Computer-Assistance

The advantages and disadvantages of each interview mode/method are listed in **Table 6.**

Table 6. Advantages and Disadvantages of Different Interview Modes

Interview Mode	Advantages	Disadvantages
In-Person Interviews	• Researchers can conduct each interview in a controlled environment (e.g., central facility) or in a location convenient to participants • Allows for collection of both verbal and non-verbal responses to help inform data interpretation	• Time-consuming • Studies can be expensive • Scheduling and other logistical constraints (e.g., travel expenses) can limit participation
	• Can be implemented more rapidly than in-person interviews • Can provide an opportunity for including patients who	• Unable to assess non-verbal cues (e.g., eye contact, body language, and level of distraction) to help inform an

Interview Mode	Advantages	Disadvantages
Telephone Interviews	would otherwise not be able to participate in an in-person interview due to location, disease/condition, or level of impairment • Participants may be more comfortable providing more personal information when they are not face-to-face with the interviewer	interviewer's interpretation of participant responses • May be difficult to establish rapport between the interviewer and participant • Some participants have limited access to telephones; this should be taken into account when determining if telephone interviews are appropriate • Participants may dislike the intrusion of a call to their home or personal telephone line; may not have a private space to feel comfortable completing the interview • When telephone interviews are being conducted in a participant's home, disruptions (e.g., background noise and presence of family members) can interfere with sound quality and cause distractions
Video Conference or Online Interviews (e.g., web-based or webcam)	• Can be implemented more rapidly than in-person interviews • Can provide an opportunity for including patients who would otherwise not be able to participate in an in-person interview due to location, disease/condition, or level of impairment • Allows the interviewer to collect verbal and non-verbal responses	• Some participants have limited access to computers and other video or online conferencing equipment (e.g., web cams) and software; studies should supply participants with necessary video or online conferencing equipment and software when personal devices are unavailable • Participants might not feel comfortable with video or online interviews • When video or online conferencing is being conducted in a participant's home, disruptions (e.g., background noise and presence of family members) can interfere with sound quality and cause distractions

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When the interview type and mode/method of administration is determined, you should consider the following:

- Number of interviews to conduct
- Design interview questions and interview guide
- Interviewer training and expertise
- Sites to recruit participants (number of sites, geographic and patient representation)

Number of interviews is dependent upon multiple factors, including but not limited to:

- Study design
- Disease or condition (e.g., rare disease, heterogenous disease)
- Study population (e.g., demographics)
- ***Concept saturation***

The study setting can also vary in which an interview is administered. The interview can be administered outside of a clinical trial (observational study) or within a clinical trial (screening or exit interview). See **Appendix 3** for considerations for these different types of qualitative studies.

How do you avoid inappropriate framing of questions when talking to patients? The way interview questions are framed is critical to ensure unbiased ***patient input***. When you ask questions to patients you want to learn more about the patient's experience with their disease and treatment. Leading questions (e.g., questions that includes or implies the desired answer to the question in the phrasing of the question itself) are problematic as they result in biased or false/misleading answers (results). It also is a missed opportunity to hear an unexpected insight.

Some ways to avoid asking leading questions include:

- Use a semi-structured interview guide with set of prepared questions (do not rephrase questions in your own words)
- Design neutral questions to the extent possible
- Do not suggest an answer
- Do not assume you know how the participant is feeling

Other types of questions that may cause challenges to reliability of participants' responses include:

- Questions that cast judgment on a participant's belief or choice
- Questions that are too broad, particularly, when asking about an abstract/complex concept(s)

While follow-up/probing questions can help explore a topic further and provide clarification and more details on participants' responses, the frequent use of probing questions, specifically unstructured probing questions, can potentially introduce bias (e.g., mining data to affirm interviewer's own ideas).

A good probing question includes but is not limited to the following:

- Is clear and concise
- Allows for multiple responses
- Avoids yes/no responses
- Stimulates reflective thinking

Examples:

Example of a leading question

"Do you consider it important to engage in daily exercise?"

This question guides the respondent to respond in a more favorable or preferred answer. To prevent any misleading, this question could be changed to ask:

"How often do you think you should exercise in a week to maintain a healthy lifestyle?"

Example of a question that casts judgment

"Could you tell me why you are not treating your child's autism?"

This question implies that the interviewer is potentially casting judgment on the participant's beliefs or choices. To minimize any perceived judgment, this question could be changed to ask:

"Tell me what you think is the ideal course of treatment for your child's autism."

Qualitative interviewers should adopt a non-judgmental attitude to avoid interviewer bias and maintain a positive relationship with the interviewee.

Example of a question asking about an abstract or complex concept

"How satisfied were you receiving treatment through infusion?"

Satisfaction is an abstract or complex concept since it is multidimensional. To obtain more meaningful information about this concept, direct specific questions may need to be asked to understand what elements go into an individual's satisfaction:

"Think about the last time you were at the clinic receiving your infusion. Please describe your infusion experience."

"What did you like or not like about your infusion experience?"

"What parts of the infusion experience do you feel impacts your satisfaction rating for the treatment?"

Examples of probing:

Scenario: A participant is being asked about benefits and risks of their treatments. The initial questions from the interviewer is:

What specifically about this treatment makes it the best?

The participant provides a very ambiguous response. Pre-determined focused probes may be needed to further explore the participant's thoughts on the treatment. For example:

- Method of administration for the treatment
- Treatment dosing regimen
- Treatment side effects.

Some examples of how to frame probing questions for qualitative research interviews can be:

- *"Tell me more about that."*
- "And how did you feel about that?"
- "What do you mean when you say [xxx]?"
- "What was your expectation for the treatment?"

ii. Focus Groups

Focus group interviews are carefully planned discussions conducted among a small group of participants, led by a trained moderator. Focus group discussions are designed to elicit information regarding participants' experiences, feelings, and perspectives on a certain topic. Group dynamics in focus groups can facilitate additional insights that one-on-one interviews cannot; participant responses often prompt additional dialogue that would not otherwise occur between an interviewer and participant in a one-on-one setting. Similar to interviews, framing of questions for focus group discussions are important (see **Section IIIA.1(i)**).

Special considerations for focus groups include the following:

- Number of focus groups to conduct
- Sample size

As a general guideline, you should plan to conduct 3-4 focus groups, initially. However, the number of focus groups may vary based on the following:

- Complexity of the topic(s) being discussed (e.g., all versus some impacts of a disease on multiple dimensions of a patient's quality of life);
- Heterogeneity of the participant sample, and
- Number of ***subgroups*** you plan to elicit information from (e.g., different age groups, disease severity groups).

After conducting your focus groups, you should evaluate the data and determine whether additional sessions are necessary to cover topics sufficiently (i.e., saturation) given the heterogeneity of the patients.

In addition to determining the number of focus groups to conduct, you should consider the sample size for each focus group to ensure you include the appropriate number of participants. While it has been suggested that a reasonable number of participants in a focus group lies between 5 and 10 patients they often range from 4 to 12 patients, although a larger group (e.g., between 10 and 12 patients) may make it difficult to generate rich responses from each participant (Krueger & Casey, 1988). Ultimately, it is important to keep the group small enough to enable the elicitation of in-depth responses from each participant but large enough for you to get a wide variety of perspectives across different severity levels and demographic representation within the target disease. A group may become fragmented (e.g., multiple, simultaneous conversations occur) when it exceeds 12 participants, decreasing the likelihood of engagement and responses from each individual.

Factors to consider when determining the appropriate sample size for a focus group include:

- **Study purpose.** If the purpose of your focus group is to elicit information regarding symptoms and disease characteristics, more participants may be useful in a highly heterogeneous condition for a detailed discussion and to adequately cover the concept. If the purpose of the focus group is to cognitively debrief on a measure or pilot test a measure, more participants will be required to generate sufficient data.

- **Complexity of the topic.** The more complex the condition or topics you want to discuss, the fewer participants you want to enroll per group.

- **Number of probing questions you want to cover.** More questions, fewer people per group.

- **Participant characteristics.** Focus group participants ought to be representative. Participants should reasonably represent the target patient population intended for a planned clinical trial or appropriate referent group so that results from the focus group interviews can be as generalizable as possible.

iii. Consensus Panels (Delphi)

The Delphi Panel technique is a multi-stage survey process with the intent to achieve consensus among experts on an important topic or issue; they can provide valuable data to help describe a phenomenon. There are many different Delphi methods that can generate consensus data. Different Delphi panel techniques and characteristics are presented in **Table 7**.

Table 7. Types of consensus panels

Delphi Panel Technique	Characteristics
Classical Delphi	• Uses an open first round to facilitate idea generation to elicit opinion and gain consensus • Uses three or more rounds • Can be administered by paper (by postal mail), email, or online (see eDelphi below)
Modified Delphi	• Modification usually takes the form of replacing the first round with face-to-face interviews or a focus group or having a face-to-face meeting for the last session. • May use fewer than three rounds • Can be administered by paper (by postal mail), email, or online
Decision Delphi	• Usually adopts the same process as Classical Delphi • Focuses on making decisions rather than coming to consensus
Policy Delphi	• Uses expert opinion to come to consensus and agree on future policy related to a given topic
Real Time Delphi	• Usually adopts a similar process to Classical Delphi except experts may be in the same room • Consensus is reached in real-time rather than by postal mail • Sometimes referred to as a consensus conference
e-Delphi	• Usually adopts a similar process to Classical Delphi but is administered by email or online web survey
Technological Delphi	• Similar to the Real-time Delphi but uses technological devices (e.g., handheld keypads) allowing experts to respond to questions immediately while the technology calculates the mean or median response among panel members. This allows for instant feedback and a chance for experts to recast their votes in light of the group opinion when moving toward consensus
Online Delphi	• Usually adopts the same process as Classical Delphi however, questionnaires are completed and submitted online.
Argument Delphi	• Focused on the production of relevant factual arguments • A derivative of the Policy Delphi • A form of Delphi where there may be no consensus
Disaggregative Delphi	• Goal of consensus is not adopted • Conducts various scenarios of the future for discussion • Uses cluster analysis to process the data and facilitate interpretation

Source: Keeney et al., 2010

iv. Observations

Observational research methods, while not common, can also be used to generate meaningful patient experience data. These methods could be useful in the following scenarios:

- Patients who experience episodic behavior that cannot be observed in a controlled environment.
- Assessment of event and behavioral progression over extended periods of time (e.g., document changes in irregular behaviors that deviate from the norm – like aggressive behaviors or confusion and behaviors observed in elderly Alzheimer's patients).

In these cases, researchers can observe patients in real-time to generate data related to symptoms or daily life functioning.

The different types of observations that are relevant to evaluating burden of disease and treatment, as well as management of patient's disease and burden of treatment include:

- **Participant as observer**. The researcher is a member of the group being studied, and the group is aware of the research activity. For example, a researcher who is a patient advocate and also a patient themselves, who observes naturalistic behaviors of fellow patients in a community setting. Disclosure of their role as a researcher to participants is given in advance for transparency.

- **Observer as participant**. The researcher is not a member of the group being studied and identifies his/her researcher role to the group. For example, a researcher collecting data without direct involvement with participants.

- **Complete observer**. The researcher is neither seen nor noticed by the group under study and the group is unaware of being observed. For example, a researcher observing an interview at a research facility (via two-way mirrors) or through live-streamed video.

Observations of individuals or groups often can be done to supplement interviews (individual or group) by documenting cues from the environment and behaviors. Data from observations can be useful in generating confirmatory evidence, used to complement more common elicitation methods (e.g., one-on-one interviews) in the following ways:

- Confirm definitions of terms that participants use in interviews.
- Capture non-verbal cues (e.g., facial expressions, gestures, tone of voice, and other non-verbal indicators) that are important for conceptual interpretation.
- Provide contextual information for specific disease or treatment experiences.
- Observe events that participants may be unable or unwilling to share (e.g., socially unacceptable behaviors like aggression).
- Observe the duration of episodic events reported by patients in interviews or focus groups.

Some disadvantages of observations can be that they are time consuming and may require observers to receive special training on discerning significant from trivial observations. Refer to **Appendix 3** for additional details regarding considerations for observational data collection.

IV. QUANTITATIVE RESEARCH METHODS

KEY MESSAGES

- Identify the appropriate participants to survey (i.e., patients with condition of interest)
- Determine a sufficient number of participants to survey
- Design a survey with specific, well-designed, and well-understood questions and adequate response options

A. Sources of Quantitative Data to Elicit Burden of Disease/Treatment and Benefits and Risks

What types of quantitative methods can be used to obtain patient input? Quantitative research methods are characterized by the collection of quantifiable data (e.g., numerical data) and the application of statistical methods to summarize the collected data. There are different quantitative approaches or sources to gather information related to the burden of disease and treatment; and benefits and risks in patients' disease management, which include but not limited to:

- Surveys/questionnaires
- Other technologies (e.g., social networks, accelerometry, room surveillance) (**Appendix 7**)

The use of surveys/questionnaires can be a quantitative approach to gather information related to the burden of disease and treatment and benefits and risks in patients' disease management. However, surveys/questionnaires can also be a qualitative approach depending on the type of questions being used (see **Section IVA.1(i)(b)**).

1. Best practices for use of quantitative sources

The following sections outline general considerations related to survey methods. Details regarding considerations for special populations and different cultures can be found in **Appendix 5**.

i. Surveys/questionnaires

There are two components in designing a survey/questionnaire:

- Deciding what to measure
- Designing and testing questions including instructions and response options

a. Deciding what to measure

What types of questions do you ask in a survey? For the assessment of burden of disease and treatment and benefits and risks in patients' disease management, you will need to consider what aspects of these objectives that you want to measure in a question. See **Section IIB**.

b. Designing and testing questions

How to avoid inappropriate framing of questions in surveys?

Designing a good survey/questionnaire involves:

- Selecting or designing questions that match the research objective(s) (see **Section IIB**)
- Designing clear questions specific to the content of interest (e.g., disease symptoms and impacts, current treatment, past treatments, treatment side effects)
- Designing questions that are interpreted and understood well by participants (e.g., questions should be designed for an appropriate reading level and use minimal clinical terminology)
- Testing questions to make sure they can be answered as intended
- Placing the questions in a format to maximize the ease of use for respondents and interviewers

Questions for surveys/questionnaires can be generated from multiple sources, which include but not limited to the following (Streiner, Norman & Cairney, 2015):

- Literature
- Clinical observation
- Patients (e.g., focus groups, interviews)
- Expert opinion (e.g., interviews, Delphi panel)
- Theory
- Research

Patients living with the disease are the ideal source of information to generate questions for a survey/questionnaire to evaluate burden of disease and treatment benefits and risks.

When designing questions for surveys/questionnaires, you should design questions to be good measures to maximize the relationship between the answers recorded and what you are trying to measure. The goal of a good measure is to increase the reliability of the question to ensure consistent measurement across respondents (e.g., patients, caregivers, clinicians) (Flower, 2002).

A good question has the following characteristics:

- Questions mean the same thing to every respondent
- Questions are scripted, if administered by an interviewer

- Response options are appropriate and meaningful and communicated consistently to all respondents

Key considerations to increase the reliability of respondents' answers to questions:

- Identify potential respondents
- Use natural and familiar language
- Avoid using incomplete questions (e.g., Age?, Reason last saw doctor?)
- Avoid poor wording of questions (e.g., poorly defined terms)
- Avoid using double-barreled or multi-barreled questions (i.e., a question that asks two or more concepts at once)
- Avoid using double negatives (i.e., a sentence that includes two negatives)
- Avoid leading questions (see **Section IIIA.1(i)**)

Examples:

Example of a double-barreled sentence

How embarrassed or self-conscious have you been because of your condition?

This question is asking two different concepts or issues:

1. How embarrassed have you been because of your condition?
2. How self-conscious have you been because of your condition?

Each of these two concepts may offer a different feeling from a respondent, and combining them into one question makes it unclear which feeling is being measured. Once a respondent answers the question, it will be impossible to know which concept the respondent was thinking about when they answered the question (unless it was an interviewer-administered question).

Example of a double negative sentence

Do you agree or disagree with the following statement?

Doctors should never be allowed not to discuss urgent lab results with patients on weekends.

If you disagree, you are saying that you do not think that doctors **should not** discuss urgent lab results to patients on the weekends. In other words, you probably believe that doctors should discuss urgent lab results to patients on the weekends.

If a negative item is in fact needed for a survey/questionnaire, you should underline the negative word or words to catch the participant's attention.

Questions can elicit different types of data, which include:

- ***Nominal*** data (also known as categorical variables) (e.g. sex, race, ethnicity)
- ***Ordinal*** data (e.g. disease severity of none, mild, moderate, severe; symptom frequency of never, sometimes, always)
- ***Continuous*** data (e.g. age, BMI, fever temperature)

Questions used in surveys/questionnaires can be classified in two different groups, which also applies to questions being asked in interviews:

- Closed-ended questions (questions with fixed set of response options)
- Open-ended questions (questions without a fixed set of responses options, e.g., free text)

Table 8 lists examples of closed- and open-ended questions, as well as the advantages and disadvantages of using different question types.

Table 8. Advantages and Disadvantages of Open- and Close-ended Questions

Question Type	Examples	Advantages	Disadvantages
Closed-ended questions	*Which of the following health conditions do you currently have?* o *Asthma* o *Acne* o *High blood pressure* o *Glaucoma*	• Respondent can more reliably answer the question when response options are given • Researcher can more reliably interpret the meaning of answers • Easier and quicker for respondents to record answers	• May not provide respondent with a comprehensive list of response options • Response options may not be applicable to the respondent
Open-ended questions	*What health conditions do you have?*	• May obtain answers that were unplanned • May obtain more realistic answers • Provides opportunity for respondents to answer questions in their own words • May be more appropriate when the list of possible answers is lengthy	• May produce rare answers that cannot be analyzed in a useful manner

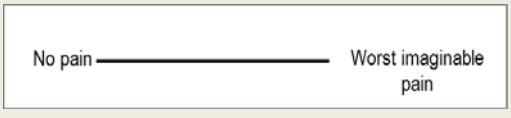
You should select the type of question for your survey/questionnaire based on the type of data you would like to have for the results of your study. In some instances, it may be valuable to use both open and closed-ended questions to collect both qualitative and quantitative data.

When considering responses to questions, it is important to consider the kinds of possible responses that may arise. You should provide acceptable response options for the question being asked (e.g., method by which responses will be obtained). The response options for the questions may be determined by the content of question asked.

Table 9 lists some examples of the different types of response options and their potential limitations.

Table 9. Different Types of Response Options

Response Option Type	Examples	Potential Limitations
Checklist	*Please check to indicate if you have ever had the following conditions (check all that apply):* o *Diabetes* o *Kidney disease* o *Stroke* o *High blood pressure* o *Asthma* o *Heart attack*	• Provides limited information • Checklists may not cover all the possible responses; in these instances, free text may be needed • The use of checklists can impact data analysis, so careful consideration is needed when analyzing data from a multi-option variable
Dichotomous (two response options)	*Have you ever been diagnosed with glaucoma?* o *Yes* o *No* *I have been diagnosed with glaucoma* o *True* o *False*	• May force respondents to choose between options that may not be that simple, resulting in a response that doesn't completely capture their experience/feelings • Limits the analysis that can be performed
Rankings	*Please rank the importance of the following characteristics of a treatment for lung cancer. (Fill in your rank order in the spaces provided using the numbers 1 through 5, with 1 indicating most important and 5 indicating least important.)*	• Ranking can be a difficult task for respondents, particularly if there are several response options (e.g., >5) • Rank order items can be

Response Option Type	Examples	Potential Limitations
	___ *Treatment relieves symptoms* ___ *Treatment has few side effects* ___ *Treatment will increase survival* ___ *Treatment can be taken as a pill* ___ *Treatment can be taken monthly*	difficult to analyze statistically and relate to other variables
Rating scales	<u>Numerical</u> *Please rate your pain at its worst in the last 24 hours.* o *0 (no pain)* o *1* o *2* o *3* o *4* o *5* o *6* o *7* o *8* o *9* o *10 (worst imaginable pain)* <u>Verbal</u> *Please rate your pain at its worst in the last 24 hours.* o *None* o *Mild* o *Moderate* o *Severe* *How often have you had pain during the past week?* o *Not at all* o *A little* o *Quite a bit* o *All the time*	• Decreased validity with extremes of age, e.g., young children (numerical) • Limited number of response categories (verbal) • Decreased validity in illiterate patients (verbal) • Although distances between verbal descriptors on verbal rating scales appear equidistant, the actual observed distances may vary (verbal) • Only rank-order inferences can be made about the relative differences between two or more ratings (verbal)
Visual analog scale	*How severe has your abdominal pain been today? (Place a mark(l) on the line below)* 	• False sense of precision • Cannot be administered verbally • Higher rates of missing data (Dworkin et al., 2005; Hawker et al., 2011) • Inconsistencies with the length of VAS line

You should consider the following factors to improve the validity of the respondents' response to questions:

- Comprehension of question
- Knowledge to answer the question
- Social desirability (e.g., questions are administered in an appropriate setting in relation to the sensitivity of the topic)
- Applicability of the content (although sometimes a not applicable response is also needed for the question)
- Relevant response options (e.g., if a question is asking about pain medication but does not include a response option for those who are not taking pain medications)

The ordering of questions in a survey/questionnaire is also important. The way a person responds to a question can be influenced by earlier questions (e.g., priming or the respondent is carrying over thoughts from the previous question to interpret the next question).

Priming can be problematic in survey research. Some ways to avoid priming include:

- Order questions deliberately
- Appropriate spacing of questions (separate topics into different pages or electronic screens)
- Use clearly defined questions (provide instructions on what the question is to address)
- Randomize the order of questions

Once you have drafted questions and determined the order of questions, it may be helpful to have them reviewed in a small subset of your study population prior to pre-testing them, if resources are available, to identify any potential problematic questions.

When the survey/questionnaire is designed and nearly ready for use, pre-testing the questions is an important step to find out if the data collection protocols and ***instrument*** can work realistically.

V. MIXED METHODS

Mixed methods research is where both qualitative and quantitative methods are used. Refer to **Sections III and IV** for how best to operationalize the respective method. For additional details on mixed methods, refer to **Section IIIC of Guidance 1**.

VI. CONCLUSIONS

This document has provided an overview of best practices of methods to collect what is most important to patients related to the burden of disease and treatment, and benefits and risks in patients' disease management to inform medical product development and regulatory decision making. The proposed best practices presented serve only as a basis for dialogue in the evolving and growing area of the ***science of patient input***.

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