U.S. FOOD & DRUG ADMINISTRATION

PATIENT-FOCUSED DRUG DEVELOPMENT
PUBLIC WORKSHOP ON GUIDANCE 1

COLLECTING COMPREHENSIVE AND REPRESENTATIVE INPUT

ATTACHMENT TO DISCUSSION DOCUMENT APPENDICES

Workshop Date: December 18, 2017

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Appendix 1. Timelines for Development of the Four Guidances

Guidance 1: Approaches to collecting comprehensive and representative patient and caregiver input on burden of disease and current therapy. The guidance will address topics including: standardized nomenclature and terminologies, methods to collect meaningful patient input throughout the drug development process, and methodological considerations for data collection, reporting, management, and analysis.
Guidance 1 Projected time for public workshop: First Quarter, FY2018 Guidance 1 Projected time for publication of draft guidance: Third Quarter, FY2018
Guidance 2: Processes and methodological approaches to development of holistic sets of impacts that are most important to patients. The guidance will address topics including: methods for sponsors, patient organizations, academic researchers, and expert practitioners to develop and identify what are most important to patients in terms of burden of disease, burden of treatment, and other critical aspects. The guidance will address how patient input can inform drug development and review processes, and, as appropriate, regulatory decision making.
Guidance 2 Projected time for public workshop: First Quarter, FY2019 Guidance 2 Projected time for publication of draft guidance: Third Quarter, FY2019
Guidance 3: Approaches to identifying and developing measures for an identified set of impacts which may facilitate collection of meaningful patient input in clinical trials. The guidance will address methods to measure impacts (e.g., burden of disease and treatment), in a meaningful way, and identify an appropriate set of measure(s) that matter most to patients.
Guidance 3 Projected time for public workshop: First Quarter, FY2020 Guidance 3 Projected time for publication of draft guidance: Third Quarter, FY2020
Guidance 4: Methods and Technologies for Clinical Outcome Assessments—revising or supplementing the 2009 Guidance to Industry on Patient-Reported Outcome Measures. The draft guidance will also address technologies that may be used for the collection, capture, storage, and analysis of patient perspective information. The guidance will also address methods to better incorporate clinical outcome assessments into endpoints that are considered significantly robust for regulatory decision-making.
Guidance 4 Projected time for public workshop: Third Quarter, FY2019 Guidance 4 Projected time for publication of draft guidance: Third Quarter, FY2020

Appendix 2. Standards and Requirements Pertaining to Submission of Data

Regulations, guidances, standards, and requirements pertaining to capture/collection, transmission, processing, storage, archiving, retention, and submission of data from clinical studies include (but may not be limited to):

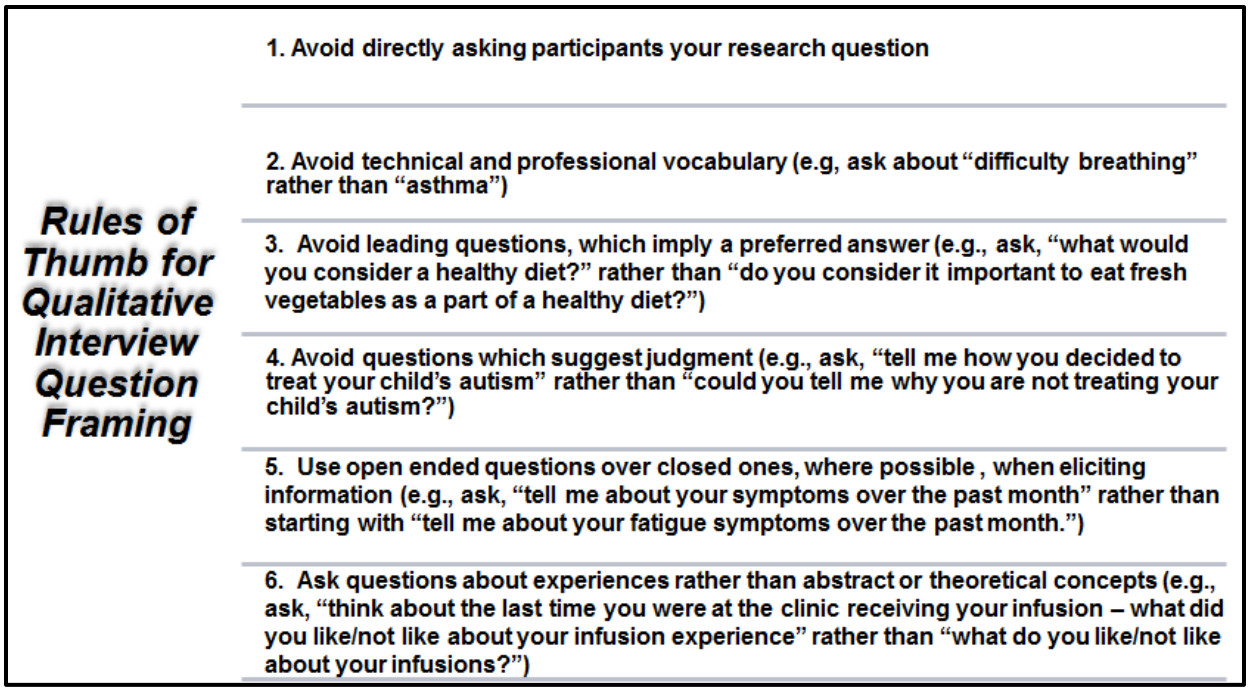
- FDA forms and submission requirements (https://www.fda.gov/drugs/developmentapprovalprocess/formssubmissionrequirements/)
- The International Council on Harmonisation (ICH) Guidelines[1], such as *ICH Harmonised Guideline for Good Clinical Practice: E6(R2)* and the *Electronic Common Technical Document (eCTD)*
- 21 eCFR, Volumes 1 – 8[2]
- Guidance for Industry on Providing Regulatory Submissions In Electronic Format—Standardized Study Data (December 2014)
- Guidance for Industry on Providing Regulatory Submissions in Electronic Format—Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act (745A(a) Implementation Guidance) (December 2014)
- Guidance for Industry on Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2017)
- Guidance for Industry on Electronic Source Data in Clinical Investigations (September 2013)
- The FDA Data Standards Catalog.

Current and more detailed information on study data standards resources, please see: https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm.

While compliance with these existing standards may not be required for studies[3] other than those conducted to support a regulatory medical product application (e.g., an IND, NDA, or BLA) or medical product labeling language, we encourage researchers to, at a minimum, bear these standards in mind since patient experience data are ultimately intended for use in clinical studies that *would* be subject to these standards.

[1] https://www.fda.gov/RegulatoryInformation/Guidances/default.htm
[2] https://www.ecfr.gov/cgi-bin/text-idx?tpl=/ecfrbrowse/Title21/21tab_02.tpl
[3] Such as stand-alone psychometric validation studies submitted to the COA Drug Development Tool (DDT) Qualification Program

Appendix 3. Qualitative Interview Question Framing: Best Practices



Source: Adapted from Green and Thorogood (2009) and MSF (2002)

If during the interview process you find that you are not generating data that is useful or informative, consider the following methods to help supplement the interview data (Boes 2014):

- **Diary questions.** Ask participants to describe a day in their life, or their last shift in the clinic, as a way to introduce the interview.

- **Critical incidents.** Ask participants about worst/best experiences to understand what is important about a topic.

- **Free listing.** Ask participants to list all of their symptoms or all of the possible treatments they have used to treat their symptoms as a written exercise during the interview.

- **Ranking.** Ask participants to rank items or concepts generated during the interview by listing them freely in order of importance as a written exercise during the interview.

Appendix 4. Delphi Panel Techniques and Characteristics

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 non-consensus Delphi
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: Adapted from Keeney, McKenna, & Hasson (2010)

Appendix 5. Considerations for Data Management

Resources to consider when developing a data management plan.

- Stanford University Libraries' guide to DMPs (https://library.stanford.edu/research/data-management-services/data-management-plans) (Stanford University Libraries n.d.(b));
- The Society for Clinical Data Management's (SCDM) standard for Good Clinical Data Management Practices (http://scdm.org/publications/gcdmp/) (SCDM 2013); and
- Data management considerations laid forth in the National Science Foundation (NSF) Grant Proposal Guide Chapter II.C.2.j (https://www.nsf.gov/pubs/policydocs/pappguide/nsf15001/gpg_2.jsp#dmp) (NSF 2014).

Some components of good data management plans and practices include (Stanford University Libraries n.d.(a); NSF 2014; SCDM 2013):

- Having a complete draft of the DMP "prior to enrollment of the first study subject" and ensuring that "an approved, signed version of the DMP is completed prior to starting on the work it describes" (SCDM 2013);
- Ensuring "compliance with applicable regulations and oversight agencies" (SCDM 2013);
- Identifying and defining the "personnel and roles involved with decision making, data collection, data handling, and data quality control" (SCDM 2013);
- Ensuring "data management processes are described and defined from study initiation until database closeout" (SCDM 2013);
- Developing the DMP "in collaboration with all stakeholders to ensure that all responsible parties understand and will follow the processes and guidelines put forth in the DMP from study initiation to database closeout" (SCDM 2013);
- Developing and maintaining a DMP template that "ensures consistency and standardization across all projects" (SCDM 2013);
- Ensuring the DMP for each study is "kept current, including proper versioning, and that all responsible parties are aware of and agree to the current content" (SCDM 2013);
- Pre-specifying the types of data to be collected over the course of the study (NSF 2014);
- Using standard, predetermined structure(s) for collecting patient experience data (e.g., interview scripts, questionnaire layouts, electronic devices, telephone prompts, etc.);
- Specifying "standards to be used for data and metadata format and content" (NSF 2014);
- Using "descriptive and informative file names" (Stanford University Libraries n.d.(a));

- Choosing "file formats that will ensure long-term access" to the data (Stanford University Libraries n.d.(a));

- Having a systematic method for tracking different versions of datasets and documents (e.g., data and metadata) (Stanford University Libraries n.d.(a));

- Creating metadata for each analysis performed (Stanford University Libraries n.d.(a));

- Having processes in place to ensure compliance with regulatory requirements regarding the protection and ownership of source data (SCDM 2013);

- Having policies in place for accessing and sharing data, including:

    - Provisions for appropriate protection of privacy, confidentiality, security, intellectual property, or other rights or requirements (NSF 2014);

    - "Policies and provisions for re-use, re-distribution, and the production of derivatives" (NSF 2014);

- Handling sensitive, confidential, and personally identifiable information and data in an appropriate manner, including ensuring an appropriate level of network and infrastructure security (Stanford University Libraries n.d.(a)) (SCDM 2013); and

- Planning how data, samples, and other research products will be archived, and how access to these materials will be preserved for future access (NSF 2014).

Other considerations and recommendations include:

- Data validation rules and electronic edit checks should be programmed to enhance data quality at the point of data entry. Prior to database lock, appropriate quality control measures should be taken to ensure that records with inconsistent values of variables (e.g., age or gender) are identified, examined, and addressed.

- For observational studies, ensure proper logistics are in place to collect and manage data generated by follow-up queries, if needed. Variables should be cross-checked to verify subgroup assignment, subject disposition, reason for exclusion (where applicable), and type of error(s) detected in the record, if any.

- Researcher(s) should design data management features to enhance data quality, minimize missing or erroneous data, and minimize data cleaning. In addition, use of customized error messages and automated data validations may facilitate survey completion.

- If a research subject is excluded from an analysis, the reason for excluding the experience data collected from said subject should be thoroughly documented (and included in your submission to FDA).

Appendix 6. Methods for Collecting Patient Experience Data

1. Methodological Overview

As noted in **Section 1.3** of the discussion document, three main research approaches are commonly used to help guide the collection of patient experience data: qualitative research, quantitative research and mixed methods research (Johnson and Christensen 2017). A brief overview of each method is shown in **Table 1**.

Table 1. Comparison of the Qualitative, Quantitative, and Mixed Method Approaches

	Research Approaches		
	Qualitative Research	**Quantitative Research**	**Mixed Methods Research**
Scientific Approach	Exploratory or "bottom-up"—The researcher *generates* or *constructs* knowledge, hypotheses, and grounded theory from data collected during fieldwork	• Confirmatory or "top-down"—the researcher *tests* hypotheses and theory with data	• Confirmatory and exploratory
Common Research Objectives	• Description, understanding, and exploration	• Numerical description, causal explanation, and prediction	• Multiple objectives; provide complex and fuller explanation and understanding; understand multiple perspectives
Common Study Characteristics	• Attempt to understand participant views, perspectives and meanings of concepts; study groups and individuals in natural or controlled settings	• Study behavior under controlled conditions; isolate the causal effect of single variables	• Study multiple contexts, perspectives, or conditions; study multiple factors as they operate together
Data Collection	• Qualitative data such as in-depth interviews, participant observations, field notes, and open-ended questions	• Quantitative data generated through precise measurement using structured data-collection instruments	• Both qualitative and quantitative data

Data Characteristics	• Words, images, categorizations	• Quantifiable variables	• Mixture of quantifiable variables, words, categorizations, and images
Data Analysis	• Use descriptive analysis to identify patterns, themes, and holistic features of qualitative data	• Identify statistical relationships among variables	• Quantitative and qualitative analysis used separately and in combination

Source: Johnson and Christensen 2017

2. Qualitative Research Methods

Some of the aims of qualitative research are shown in **Table 2**.

Table 2. Qualitative Research Aims

Qualitative Research Aims[4]	Examples of potential research questions	Illustrative examples of qualitative data generation by question type
To Understand 'What'	• What symptoms do heart failure patients experience?	• Patient #101: "I have trouble going up long flights of stairs."
	• What signs do caregivers observe that tell them their loved one is having asthma symptoms?	• Caregiver #201: "I know my daughter is having a hard time with her asthma when she is wheezing."
	• Based on your experience with COPD patients, what would you consider to be signs of severe COPD?	• Clinician #301: "When a patient presents with typical symptoms and has had more than one COPD flare per year or if they have been hospitalized due to your COPD, I would consider them severe."
To Explore 'Why'	• Why are asthma symptoms bothersome to you?	• Patient #101: "My asthma prevents me from being able to exercise without an inhaler."
	• Why do you prefer the auto-injector to intravenous (IV) injection?	• Patient #201: "The auto-injector is more convenient because I can administer it at home and it takes less time.

[4]Note: any qualitative study could address one or more of these aims

		My IV injections require a clinic visit and take hours."
To Examine 'How'	• How have arthritis symptoms impacted a patient's mobility?	• Patient #101: "My knees are stiff because of my arthritis. I find it hard to go up and down stairs."
	• How has a patient's dementia impacted the relationship dynamics in their family?	• Caregiver #201: "My mom now requires 24 hour care. I'm often stressed about this and it's putting a strain on my marriage."
	• How have symptoms improved with treatment?	• Patient #101: "Since receiving my lupus treatments, I've not been in the hospital as much as before."

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130 **Table 3. Common Sources of Qualitative Data**

Sources of qualitative data	Description
One-on-one interviews	• Most common source of qualitative data in outcomes research. • A one-on-one interview is a conversation between a research participant and interviewer, 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.
Focus groups	• Focus group interviews are carefully planned discussions conducted among a small group of participants, led by a trained moderator. • Discussions are designed to elicit information regarding participants' experiences, feelings, and perspectives on a certain topic.
Observations	• Observations of individuals or groups often can be done to supplement interviews (individual or group) by documenting cues from the environment and behaviors such as facial expressions, gestures, tone of voice, and other non-verbal indicators. • Observations are helpful in situations for individuals who have barriers to communicating their thoughts orally or in writing.

Consensus panels (Delphi)	• The Delphi Panel technique is a multi-stages survey process with the intent to achieve consensus among experts on an important topic or issue. • Delphi panels can provide valuable data to help describe a phenomenon.
Social media	• Social media and online patient communities can provide a forum and dialogue on patient experience (Hamm, Chisholm, et al. 2013). • Data can provide supplemental information that can complement both qualitative and quantitative data.

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132 **Table 4. Types of One-on-One 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 lead 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.

In addition to interview methods, you should also consider the mode of interview administration (i.e., in-person, telephone, video). The advantages and disadvantages of each interview mode are listed in **Table 5**.

Table 5. 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
Telephone Interviews	• 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 • Participants may be more comfortable providing more personal information when they are not face-to-face with the interviewer	• Unable to assess non-verbal cues (e.g., eye contact, body language, and level of distraction) to help inform an interviewer's interpretation of participant responses • May be difficult to establish rapport with interviewer • Some participants have limited access to telephones; this should be taken into account when determining if telephone interviews are appropriate • Participants often dislike the intrusion of a call to their home or personal telephone line; telephone interviews need to be kept relatively short or people might feel imposed upon • 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 Interviews	• 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 conferencing equipment (e.g., web cams); studies should supply participants with necessary video conferencing equipment when personal devices are unavailable • Participants might not feel comfortable with video interviews • When video 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

2.1. Focus Group Interviews

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.

Special considerations for focus groups include the following (Krueger & Casey, 1988):

- **Number of Focus Groups to Conduct.** 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 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 the number of subgroups you plan to elicit information from (e.g., different age groups, disease severity groups). After conducting these focus groups, you should evaluate the data and determine whether additional sessions are necessary to cover topics sufficiently (i.e., saturation).

- **Sample Size:** Additional considerations for sample size in focus groups 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. Note that a group generally becomes fragmented (i.e., multiple, simultaneous conversations occur) when it exceeds 12 participants, decreasing the likelihood of engagement and responses from each individual.

Figure 1 outlines factors to consider when determining the appropriate sample size for a focus group study (within and across focus groups):

Figure 1. Factors to Determine Appropriate Sample Size for Focus Groups

2.2. Observations

Observational research methods, while not common, can also be used to generate meaningful patient experience data. For example, these methods could be useful in instances where patients experience episodic behavior that cannot be observed in a controlled environment. In these cases, researchers can observe patients in real-time to generate data related to symptomatology or daily life functioning. Some methods that might be of interest include but are not limited to the following (Kawulich 2005):

- Participant as observer. The researcher is a member of the group being studied, and the group is aware of the research activity. An example of this could be when a patient advocate, who is also a patient themselves, observes naturalistic behaviors of fellow

patients in a community setting. The patient advocate fully discloses their role as a researcher for transparency and records observational data in real-time, during daily activities.

- Observer as participant. The researcher is not a member of the group being studied and identifies his/her researcher role to the group. The main role of the researcher in this role is to collect data.

- Complete observer. The researcher is neither seen nor noticed by the group under study and the group is unaware of being observed. This level of observation could take place at a research facility (via two-way mirrors) or through live streamed video.

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 **Section 4** of the discussion document for additional details regarding considerations for observational data collection.

2.3. Delphi panels

There are many different Delphi methods that can generate consensus data. Different Delphi panel techniques and characteristics are presented in **Appendix 4**.

2.4. Selecting qualitative methods

Table 6. Advantages and Disadvantages of Different Qualitative Data Collection Methods

Qualitative Research Method	Advantages	Disadvantages
One-on-One Interviews	• Can gain in-depth understanding of how a respondent interprets a question interpretation • Flexible – can tailor interviews to generate more or less detailed information based on research needs • Interviews can generate can generate rich, nuanced data about an individual's experience and perspectives robust data for analysis	• Timing (e.g., length of interviews; number of patients interviewed) • Data interpretation can be influenced by subjective interpretation • Studies can be expensive
	• Can gain in-depth understanding of respondents' question interpretation • Saturation can be obtained sooner than with focus	• Group setting may inhibit some individuals from providing sensitive information;

Focus Groups	groups than with one-one-one interviews. While individual data might not be available from each participant, general representative responses can be generated through group discussion. • Able to interview multiple people at one time; more cost-effective • Responses from one person provide stimulus for other people	• While individual data might not be available from each participant • Data analysis can be influenced by subjective interpretation • Data capture/analysis can be challenging as • Requires a highly skilled moderator to elicit useful data • Less flexibility in scheduling can present recruitment challenges • Single individuals might dominate the conversation and multiple perspectives may not be shared • Results can be dependent on the skills of the moderator
Observations	• Low burden for participants as the observation is non-invasive and does not require active participation • Advantages of naturalistic settings/real-world context	• May be time-consumingData interpretation can be influenced by subjective interpretation • 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
Systematic Consensus Methods	• Acceptable method for reaching consensus among experts on important issues and topics • Anonymous process 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
Social Media	• Low burden for people providing data • Relatively inexpensive and easy to implement • Can often generate a larger sample size than other methods	• Underlying selection process is difficult if not impossible to quantify • Respondent identification not verifiable • Personal Health Information (PHI) not verifiable (unless research is targeted to groups where research participants have provided/authorized their PHI to be released for research purposes) • Self-selection bias (social media participants); Representativeness is highly questionable without strong assumptions

Source: Adapted from (Keeney, Mckenna, & Hasson, 2011)

2.5. Analyzing qualitative data

How do you analyze data from studies using qualitative methods? FDA recommends stakeholders consider the following general steps when analyzing qualitative data (**Figure 11** in the discussion document):

2.6. Compiling and Organizing Data

How do you compile and organize qualitative data? FDA recommends stakeholders compile and organize qualitative data in a standardized way, preferably by electronic storage (i.e., organizing qualitative data, including notes, into computer files). If there are audio-recordings of qualitative interviews, then this should be transcribed verbatim and anonymized by removing information such as names and places. Additionally, a glossary should be created to help define key terminology within the qualitative text and ensure consistent terminology is used throughout study document(s). A database may also be considered to capture patient demographics including medical information.

Although not required, computer programs can help with this phase of analysis by providing a method to store and access the codes assigned by the researcher(s). There are many computer software programs available to choose from (e.g., ATLAS.ti, HyperRESEARCH, MAXQDA, NVivo, etc.). With different programs available, researcher(s) should select a qualitative software program that meets the needs of the study.

For observational survey studies, a database should also be used to compile data. The database for a paper or web-based observational study usually contains discrete records versus text units. In contrast to a glossary, a "data dictionary" should be created for quantitative analyses to describe the data objects or items in a data model for programmers and other members of the research team who need to refer to them.

2.6.1. Classifying and Interpreting Data

How do you classify qualitative data? Qualitative data is classified by coding. The process of coding involves (Creswell 2013):

- Combining the text into small categories of information
- Finding evidence for the code from databases
- Assigning a label to the code (i.e., build a concept)

There are different types of coding based on the qualitative approach used. FDA recommends using the grounded theory approach (Strauss and Corbin, 1990). Grounded theory uses detailed procedures for analysis and encompasses three types of coding described in **Table 7**.

Table 7. Coding Types

Types of coding	Description
Open coding	The process of breaking down, comparing, conceptualizing, and categorizing data to yield concepts which are later to be grouped and turned into categories.
Axial coding	A set of procedures where data are pieced together in different ways after open coding, by making connections between categories (sub-categories). This is done by linking codes to contexts, to consequences, to patterns of interactions, and to causes.
Selective coding	The process by which a core category is selected and then related to other categories; the core category can confirm other categories and explain those relationships.

After qualitative data are coded, themes of information should be identified. Themes are broad units of information that contain several codes combined to form a general concept (Creswell 2013).

Figure 2. Coding by Themes Example

• Friend support • Requesting regimen evaluation • Gaining medical access • Hospitalization • Getting "bad" doctor	**Patient:** *They (her friends) called the clinic to see if they could see me, if they would re-evaluate some of my meds and stuff, and they said, "Oh yeah." When I got there they said they were going to put me in, put me away whatever. And I ended up with a really bad doctor. Really bad. I even brought up charges against him, but I lost.*

Source: Adapted from Charmaz, 2011.

How do you interpret qualitative data? Interpretation of qualitative data involves conceptualizing the codes and themes to the larger meaning of the data (i.e., categories). The ideal interpretations will connect the concepts of interest derived from the data to other evidence (e.g., research questions, relevant literature, expert opinion, etc.).

In addition to confirming the adequacy of the sample size, this process highlights the emergence of new concepts to develop a comprehensive list of concepts, as well as the emergence of sub-concepts that will help to saturate broader concepts. Saturation should be evaluated in the entire sample.

Concepts emerging from the interviews should be analyzed and summarized in sets in the order the data are collected (i.e., as interviews are conducted).

> **Example:** Concepts reported in the first 25% interviews with patients is compared to the next 25% interviews conducted. Both sets of interviews (50%) is compared with the next 25% interviews and subsequently, all of these interviews (75%) is compared to the next 25% interviews and so on. The goal of the saturation process is to compare the amount of new information that is observed in the first interview set compared to the second interview set and so forth.

2.6.2. Representing and Visualizing the Data

How do you represent and visualize qualitative data? Qualitative data should be presented in a clear manner. Stakeholders should use their best judgment on how best to present the data. There are three modes to display qualitative data, which are described in **Table 8**.

Table 8. Modes for Displaying Qualitative Data

Type of display	Illustrative example
Word tables and lists	• Summary of findings, placed in a table or matrix of rows and columns • Chronology • Summarize characteristics (i.e., demographics) of participants studied or interviewed • List of de-identified individual participants in a study (usually using pseudonyms) and their study characteristics (other than demographics)
Graphics	• Hierarchical chart (e.g., tree diagram, conceptual framework) • Flowchart • Spatial layout of a study area
Pictures	• Photographs • Reproductions (e.g., participant's drawings or pictures)

Source: Adapted from Yin (2016)

3. Quantitative Research Methods

Table 9 summarizes some potential aims of quantitative research.

Table 9. Quantitative Research Aims

Quantitative Research Aims	Examples of potential research questions	Examples of potential quantities of interest
To Describe	• How many (proportion of) patients experience stomach pain symptoms? • How frequently do epileptic patients experience seizures in a week? • How severe are patients' heartburn symptoms? • Please rank your 3 most bothersome symptoms.	Frequencies, proportions, means, medians, distributions
To Compare	• What is the difference in daily exacerbations among mild, moderate, and severe COPD patients? • To what extent do questionnaire responses differ among members of separate subgroups?	Differences in frequencies, proportions, means, medians
To Relate	• What is the correlation between patient-reported sleep disturbance and actigraphy ratings?	• Measures of association, trend, or interaction

Table 10. Data Types

Data Types	Models	Descriptive Statistics	Data Presentations
Continuous	• Normal distribution • Linear Regression • Analysis of Variance	• Sample mean/median/mode • Standard deviation (or variance) • Standard error of the mean • Confidence intervals • Range (minimum and maximum values)	• Tables • Graphs (e.g., scatter plots, density plots) • Stratification by demographic characteristics (age groups, gender, race/ethnicity)
Categorical/ Frequency	• Binomial/Multinomial/ Poisson distribution • Logistic regression for binary outcomes • Logit models for multinomial outcomes • Poisson regression for frequency outcomes	• Frequencies and proportions	• Tables • Graphs (e.g., histograms and cumulative histograms) • Stratification by demographic characteristics (age groups, gender, race/ethnicity)
Longitudinal	See Diggle, Heagerty, et al (2002)	• Sample means, frequencies, proportions at specific time points	• Tables • Graphs of trends over time • Stratification by demographic characteristics (age groups, gender, race/ethnicity)

Missing data should be reported in a table using frequencies and percentages. In the case of longitudinal missing data, counts and percentages should be reported for each assessment time point. Reasons for missingness should be captured whenever possible. In addition to capturing and reporting the extent and nature of missing data in your study, you should have a plan in place (specified in your study protocol) to minimize the occurrence of missing data to the greatest extent possible. As missingness has the potential to invalidate your study results, you should consider the use of analytical methods that addresses missing data (Little, Rubin,2002; Molenberghs, Kenward, 2007).

Regardless of which analytic approaches you pursue, you should check the statistical assumptions required by the methods. Using an analytic approach that is not appropriate for your research may lead to erroneous conclusions and/or result in imprecise or unreliable results.

3.1. Analysis Under Probability Sampling

As noted in **Section 2.4.1** of the discussion document**,** probability samples enable you to make statements about patient experiences that are generalizable to or representative of the target population. In addition to the previously mentioned analytical considerations, you must also incorporate these additional features of probability sampling, without which generalizations to the target population cannot be made:

- sampling probabilities,
- sample nonresponse.

Sampling probabilities can be thought of as the probabilities or chances of being selected into the study and they depend on the sampling method that you select (see **Table 2** in **Section 2.4.1** of the discussion document) and the sampling frame. The reciprocal of the sampling probabilities provides a quantity that is sometimes referred to as base weights. These weights can be thought of as the number of individuals that each individual in the sample represents in the population.

Example: Suppose there were 100000 individuals in the sampling frame and 2000 were sampled, then for simple random sampling with replacement, each individual has a probability of 0.02 of being selected. Each individual is then assigned a weight of 50 as determined by the reciprocal of 0.02. That is, each individual in the sample represents 50 individuals in the target population. For multistage designs, the sampling probabilities are obtained as the product of the sampling probabilities from each stage.

In general, however, not all individuals that you sampled will participate in your study. In some cases, the proportion of sampled individuals who do not respond to requests to participate can be substantial. This not only leads to sample size attrition that results in the loss of statistical information but more importantly the non-response raises concerns about the representativeness of the data contributed by those that agree to participate in your study. These concerns may not diminish even if the study

- is well-designed and well-executed,
- has access to a well-constructed sampling frame,
- employs established probability sampling methods.

To the extent that it is possible to do so, base weights should be adjusted for non-response. Possible approaches to non-response adjustments that are discussed in the literature include:

- weighting class-adjustment (Copeland and Ganesh, 2015; Korn and Graubard, 1999; Valiant, Dever, et al., 2013).
- calibration adjustment (Särndal and Lundström, 2005).
- propensity score modeling (Valiant, Dever, et al., 2013).

The weights are then used in the estimation of the appropriate quantities of interest.

Example: Suppose the scores for three individuals from a questionnaire are $y_1 = 7$, $y_2 = 10$, and $y_3 = 14$ and their weights after adjusting for non-response are $w_1 = 3$, $w_2 = 3$, and $w_3 = 6$. Then the weighted average of the scores based on these three individuals are

$$\bar{y} = \frac{3\times7 + 3\times10 + 6\times14}{3 + 3 + 6} = 11.25\ .$$

It should be noted that non-response adjustment has the potential to recover representativeness only to the extent that the assumptions underlying the non-response approach are valid. The ideal

solution is to utilize sampling procedures that minimize non-response. Levy and Lemeshow (2008) suggest possible techniques that may improve the response rate.

Formulae for standard errors (SE) depend on the study design; stratification, clustering, and other design features should be taken into account. Levy and Lemeshow (2008) provide SE formulae for totals, means, and proportions under

- simple random sampling,
- stratified random sampling,
- cluster sampling.

For simple quantities such as totals, means, and proportions, the $(1-\alpha)\%$ confidence interval may be approximated by

$$\hat{\theta} \pm z_{1-\alpha/2}\mathrm{SE}(\hat{\theta})$$

where

- $\hat{\theta}$ is an estimate of a quantity of interest (e.g., means or proportions)
- $\mathrm{z}_{1-\alpha/2}$ is the $1-\alpha/2$ quantile from the standard normal distribution. For example, if $\alpha = 0.05$, then $z_{0.975} = 1.96$
- $SE(\hat{\theta})$ is the standard error of the estimate $\hat{\theta}$.

Korn and Graubard (1999) replace the standard normal quantile $z_{1-\alpha/2}$ with the quantile from the Student t distribution:

$$\hat{\theta} \pm t_{d,1-\alpha/2}\mathrm{SE}(\hat{\theta})$$

For complex quantities and complex sampling designs, formulae for $\mathrm{SE}(\hat{\theta})$ may not be available. In such cases, it can estimated by the method of linearization (Binder 1983) or the method of replication, the latter of which includes

- jackknife,
- bootstrap,
- balanced half sample replication.

Details of these replication approaches can be found in Korn and Graubard (1999).

In cases where the design does not make use of stratification, gains in precision may be obtained by performing a post-stratification analysis via

- weighting class adjustment or
- raking.

In addition to increasing precision, these approaches have the potential to adjust for frame undercoverage.

Post-stratification in the sense of weighting class adjustment was briefly discussed above in the context of using auxiliary information to lessen the impact of non-response on bias. The same approach can also be used to increase precision of estimates of population quantities. The idea is to further adjust weights of respondents in each cell so that the sum of the weights in each cell equals known population totals.

Raking is used when cells obtained from cross-classifying multiple factors lead to sparse or empty cells. Unlike weighting class adjustment where cell-specific weights sum to population totals, raking normalizes weights so that marginally, they sum to some pre-specified target population marginal totals.

These algorithms are discussed in Korn and Graubard (1999) and Copeland and Ganesh (2015).

3.2. Software for Analyzing Quantitative Patient Experience Data

Many statistical software are available for analyzing quantitative patient experience data. Some commonly used statistical software include R, SAS, SPSS, and SUDAAN. SUDAAN, SAS, STATA, and R are also commonly used to analyze survey data obtained from probability sampling as each permits the specification of relevant design features such as clustering, stratification, weights, and methods of variance estimation.

Regardless of which software you use, we recommend checking the current defaults and computational algorithms utilized as they vary both across software and across versions of the same software. Different estimation procedures and defaults may generate different results. In addition, be sure to note which software *version* was used as part of the study analysis documentation.