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

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

METHODS TO IDENTIFY WHAT IS IMPORTANT TO PATIENTS

APPENDICES

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How to design and implement qualitative studies? Section A provides some best practices on how to design and implement qualitative studies to identify what is important to patients on burden of disease/treatment and benefits and risks.

A. Best Practices for Designing and Implementing Qualitative Studies

Several important steps are necessary to develop and implement a high-quality qualitative study to gather patient input which can be applied to different qualitative methods. Note some but not all of these overlap steps and study materials expected in clinical trials.

General steps to follow to design a qualitative study to evaluate burden of disease or treatment and benefits and risks of patients' disease management include the following:

- Define the research purpose and objective(s) (**Section IIB of Guidance 2 Discussion Document**)
- Determine the target population (**Guidance 1**)
- Determine the study design and research setting (**Guidance 1**)
- Determine the source of qualitative data (**Section IIIA.1 of Guidance 2 Discussion Document**)
- Design of study materials (e.g., study protocol, interview/discussion guides, coding dictionary) (**Section A.1 of Appendix 1**)
- Collect data (**Section A.2 of Appendix 1**)
- Analyze data and report results (**Section A.3 of Appendix 1**)

1. Study Materials

What are the relevant study materials needed for qualitative studies? **Table 1** lists some of the key study materials for designing and implementing qualitative studies.

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Study Material	Components	Key Considerations
Study Protocol	• Details on how the research will be conducted • Evidence to support the conduct of the study (e.g., unmet need) • Description of all research-related activities and study activities that patients will undergo • Opportunity for participants to provide consent/assent	• Outline clear research objectives and questions • Specify details on target population, including demographics, clinical characteristics (e.g., phenotype, genotype, disease severity), and other pertinent characteristics (e.g., geographic representation) • Specify how data will be prepared for analysis (e.g., transcription, audio-/video-recorded, internet data, metadata, archives) • Include information regarding projected clinical site enrollment characteristics (e.g., geographic location; referral/academic centers versus community centers) to help further characterize the study sample • See **Guidance 1** for details regarding considerations for study sampling and representativeness • Identify the number and duration of discussion sessions you plan to conduct; this should be dependent on: o Number objectives and research questions o Level of heterogeneity (e.g., age, sex, in the target population) o Number of subgroups (e.g., disease severity levels, phenotypes, informants [just patients or patients and their caregivers])
Interview/Discussion Guide	• Interviewer/facilitator instructions • Study instruction • Warm-up questions • Core topic-related questions • Wrap-up questions • Discussion conclusion	Green & Thorogood, 2009; MSF, 2002: • Avoid posing the exact research question to participants during the interview • Use terms participants can understand and avoid technical terms where possible (e.g., choose to use the term “difficulty breathing” rather than “dyspnea”). • Avoid asking leading questions that guide participants to respond with a preferred answer. • Avoid asking questions that imply you are casting judgment on a participant’s beliefs or choices. • Use open-ended questions rather than

Study Material	Components	Key Considerations
		closed-ended questions, where appropriate, in order to elicit spontaneous information from participants. • Frame questions within the context of a participant's experiences; avoid questions about abstract or theoretical concepts. • Supplement interview data with other types of questions if data elicited is not useful (Boes 2014): o Diary questions (patients asked to describe a typical day) o Critical incidents (patient reports worst/best experience) o Free listing (patients list all symptoms, impacts, treatments, etc.) o Ranking (patients rank importance of symptom, treatment benefit, etc.)
Training Materials	• Detailed coverage of the protocol contents • Consent/assent forms • Mock discussion session (staff can evaluate flow of discussion)	• Train staff using standardized training materials (e.g., training documents, PowerPoint slides)
Glossary	• Definitions of terminology	• Clearly define key terminology within the qualitative text and ensure consistent terminology is used throughout study document(s).
Coding Dictionary (if applicable)	• Codes (category or concept descriptions) • Coding structure • Memos (ideas or thoughts how code derived)	• Outline clear instructions for categorization, including code definitions, instructions, and considerations • Derive initial codes from prior knowledge (e.g., natural history, conceptual model, disease model, discussion guide structure) • Avoid creating too many codes or nuanced categories as it may make it difficult for coders to capture and interpret concepts during the data analysis phase.
Data Analysis Plan	• Analytic methods, including coding software • Identification of coders/analysts (including	• Determine sample size needed for the study • Identify and specify appropriate analytic methods for data type • Consider what approach would be most

Study Material	Components	Key Considerations
	credentials) • Plans for resolving discrepancies among coders and other quality assurance measures (e.g., intra-rater reliability; Kappa statistic) • Description of coding stages (e.g., initial coding, interim checks – including plans for coding dictionary refinement) • Plans for data visualization • Table/figure shells	appropriate to present data (tables, figures, etc.)

2. Data Collection

As mentioned in **Section IIIA of the Guidance 2 Discussion Document**, data for qualitative studies can be collected in various ways:

- Interviews (**Section IIIA.1(i) of the Guidance 2 Discussion Document**)
- Focus groups (**Section IIIA.1(ii) of the Guidance 2 Discussion Document**)
- Consensus panels (**Section IIIA.1(iii) of the Guidance 2 Discussion Document**)
- Observations (**Section IIIA.1(iv) of the Guidance 2 Discussion Document**)
- Social media (**Appendix 7)**

3. Data Analysis and Reporting

Qualitative data can be voluminous, so it is important to have a standardized method to deal with the volume of data in a practical and consistent way, including interpretation.

Qualitative data should be prepared prior to analysis. Preparation can include the following methods:

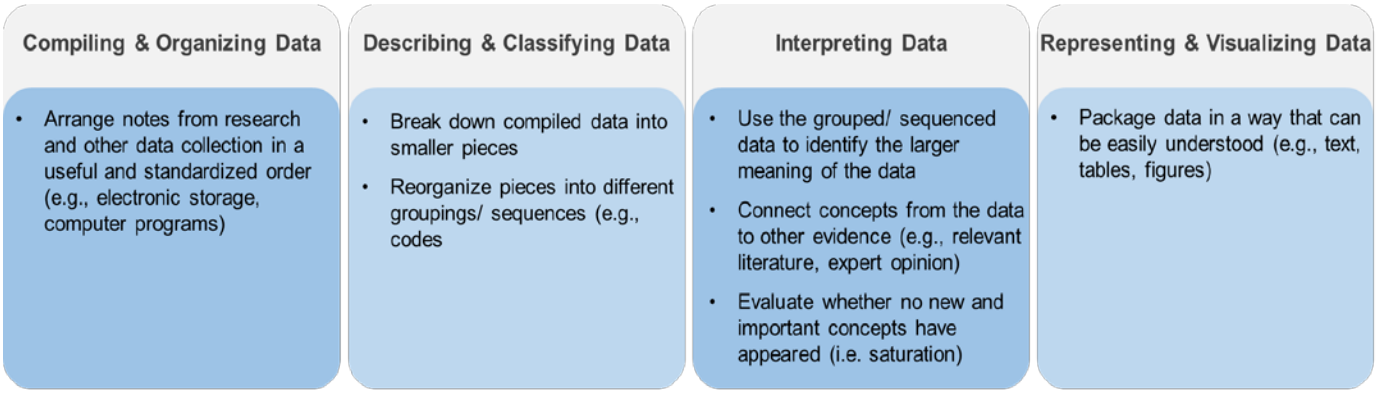
- Transcription
- Video-/Online-recordings
- Internet (e.g., social media, chat room dialogues)
- Metadata (e.g., date of interview, name of interviewer, demographic details of respondent, source of field notes, initial ideas of analysis)

FDA recommends stakeholders consider the following general steps when analyzing qualitative data:

- Compiling and organizing data
- Describing and classifying data
- Interpreting the data
- Representing and visualizing the data

Figure 1 provides some considerations on analyzing qualitative data.

Figure 1. General Steps for Data Analysis in Qualitative Studies



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) and displayed in a saturation table.

> **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.

There are different approaches to describe and classify qualitative data, some that may involve coding and some that may not. You should determine what approach is best for the objectives of the study. FDA is open to either approach with appropriate rationale and justification.

Key considerations if a coding approach is selected for analysis, includes but are not limited to the following (Gibbs, 2007):

- Select the appropriate coding approach for the data of interest
- Determine the appropriate level of detail of what is to be coded (e.g., line-by-line coding or select segments of text)
- Decide on what data is relevant enough to be coded
- Move methodically to a slightly higher conceptual level initially when coding data
- Carefully consider the grammatical form of the coded words (actions versus processes versus nouns)
- Ensure codes are applied consistently to all data

Key considerations if a coding approach is not selected for analysis, includes but are not limited to the following (Gibbs, 2007):

- Arrange notes (notes about original data) in a thematical manner
- Ensure your notes precisely cite the original data (or precisely locate the places in the database)
- Implement a procedural check (take notes and crosswalk them backwards into the original database)

It is important to note that if you choose to not code qualitative data from your study, you will need to maintain a methodic analytic procedure to avoid non-systematic and inconsistent judgments.

Example:

Coding line-by-line

	01 INTERVIEWER **02** *How do you feel when you take your* **03** *medicine?* **04 PATIENT**
Fatigue	**05** *I feel extremely tired after taking my medicine. I*
Time-sensitive medication	**06** *am not sure if it is related to the time of day that I*
Interference with daily activities	**07** *take it or not. Regardless, I cannot complete chores*
Limits physical functioning	**08** *around the house or take long walks.*
Rash	**09** *I also have noticed a rash along my upper arm,*
Itchy	**10** *which has caused a lot of itching.*

Example:

Coding by Themes (with select segments of text)

Pain Requesting regimen evaluation Hospitalization Medical access Family support	**01 PATIENT** **02** *Because I was in extreme pain, my doctor wanted to* **03** *re-evaluate some of my meds. The doctor told me I* **04** *would have to stay in the hospital for monitoring. I* **05** *was afraid that this was would not be covered under* **06** *my insurance. I ended up calling my family to see if* **07** *they could visit me.*

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 2**.

Table 2. 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 (e.g., 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)

After analyses are completed, data should be organized and summarized in a report in a clear manner. The report should have the following components at the minimum:

- Study title (including study number, if applicable)
- Abstract/Executive Summary
- Background/Research objectives
- Methods
- Results
- Discussion/Conclusion
- Appendices with supportive documentation (e.g., transcripts or any other documentation used to collect data)

APPENDIX 2. Considerations for Special Populations and Cultural Differences for Qualitative Studies

How to talk to special patient populations (pediatrics, cognitively impaired, rare diseases) and different cultures? Sections A and B provide considerations on how to talk to certain populations in qualitative studies.

A. Considerations for Special Populations within qualitative studies

1. Pediatrics

There are many advantages to using children as content experts in qualitative research. However, there are many unique considerations for conducting qualitative research with pediatric patients.

Some factors to consider include, but are not limited to the following areas:

- Source of qualitative data (e.g., interviews vs. focus groups)
- Patient characteristics
- ***Informed consent*** vs. ***assent***
- Protocol development and study procedures
- Power dynamics and building rapport

Table 3 provides some considerations for each of these factors.

188 **Table 3. Factors to consider for pediatric qualitative studies**

Source of Qualitative Data

- **Interviews vs. Focus Groups**
  - Interviews may create a more comfortable environment where children can openly share their thoughts and experiences without fear of judgment; may yield richer data.
  - Dyad interviews may be an option to capture the entire patient and caregiver experience at once; however the following should be considered:
    - Instructions should be given to the respondents
    - Questions to the caregiver should be specific to direct observations

Patient Characteristics

- **Characteristics to consider when designing pediatric qualitative study:**
  - Cognitive and linguistic development differences
  - Willingness to self-report and motivation to comply with study assessments
  - The complexity of the measurement concept and the assessment methods used (e.g., recall period, averaging responses, etc.)

Informed Consent and Assent

- **Informed consent versus Assent**
  - Both informed consent and written assent should be obtained in pediatric studies.
  - Informed consent must be obtained from a parent or guardian for minor children in addition to child assent (agreement to participate in the study) prior to the start of the study

Protocol Development/Study Procedures

- **Study Materials**
  - Study materials should be age-appropriate and easy to comprehend; materials should be understood by the youngest of patients and at the lowest reading and comprehension level.
- **Interview structure**
  - Interviews should be conducted with the children alone when children can reliably report on their own experiences independent of their caregivers.
  - Plan in advance the extent of involvement of the caregiver(s) in the study and where in the study design phase their participation is needed; this should be specified in the protocol.
- **Power dynamics & Building Rapport**
  - Avoid controlling behaviors
  - Consider using same-gender interviewing
  - Adopt the participant's communication style
  - Avoid projecting

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Example:

Scenario: The caregiver is present during their interview with their child.

How can the interviewer elicit a genuine and meaningful response from the child?

If the caregiver is to remain present for the interview with the child, the following instructions should be given:

- Caregivers should sit away from and behind the child to reduce the risk of influencing their child's responses (e.g., with non-verbal communication) and to minimize referencing.
- Caregivers should allow their children to provide responses on their own and not interject or direct their opinions or evaluations (verbally or non-verbally) toward the child or interviewer.

Example:

Scenario: A child and caregiver will be interviewed together (dyad interview).

How can the interviewer elicit genuine and meaningful responses from both the child and caregiver?

The interviewer can consider splitting the interview into a joint response portion (with child and caregiver in the room together) and independent response portion (where one of the participants leaves the room while the other provides independent responses). This hybrid approach is particularly useful when you are generating information related to sensitive topics (e.g., abnormal behaviors, caregiver burden).

2. Cognitively Impaired

For cognitively impaired patients who cannot respond reliably for themselves, you should consider the following approaches:

- Generate qualitative data solely from caregivers or other reporters who are intimately involved in the patient's daily care (for those who have severe cognitive impairment);
- Supplement patient interviews with caregiver interviews (for those with mild to moderate impairment);
- Conduct dyad interviews (for those with mild to moderate impairment).

Patients with moderate to severe cognitive impairment may find it difficult to introspectively reflect on their own experiences. Therefore, alternative approaches should be adopted to maximize the likelihood of generating reliable data.

3. Rare diseases

There are unique set of challenges in conducting qualitative research with patients with rare diseases:

- Difficult recruitment
- Low response or completion rates
- Communicating on sensitive or difficult topics

Key factors to consider when recruiting for a qualitative study in a rare disease population include but are not limited to the following:

- Extend recruitment time
- Partner with patient advocacy groups or rare disease specialists
- Ask patients, caregivers, clinicians, and/or patient advocacy groups for referrals
- Utilize social media
- Recycling respondents from other studies

To improve response or completion rates for a rare disease population, you should consider the following:

- Leverage other modes of data collection (telephone or video conferencing, social media)
- Follow-up and/or check-in with respondents throughout the study
- Allow participation of the respondent's caregiver(s) and/or families

B. Considerations for Cultural Differences during Qualitative Studies

When conducting multinational, multicultural and/or multiregional qualitative studies, it is important to adopt culturally-sensitive research methods. While discussion guide questions should be framed based on *a priori* research questions and objectives, methods should be adapted, where feasible, to incorporate the following knowledge of cultural group(s) during the study design phase:

- Social norms (e.g., whether individuals of the opposite sex or a different race or ethnic group can interact with one another in public or alone in a room; whether it is acceptable for younger interviewers to engage with older participants)
- Specific vocabulary (e.g., adapt discussion guide to include culturally recognized and acceptable terminology and idioms)
- Non-verbal cues (e.g., determine the acceptability and interpretation of hand gestures and direct eye contact)

It is important that research methods are selected and refined based on cultural sensitivities to ensure the most optimal research outcomes among culturally diverse participants, while maintaining scientifically sound research practices.

If research methods are not cultural sensitive, you may risk the following:

- Uneasiness from participants to participate
- Delays in communication during interview or discussion
- Data generated may not serve a specific cultural group's issues and interests in improving their lives

APPENDIX 3. Considerations for Different Types of Qualitative Studies

How to design and implement qualitative studies for different types of settings (observational, screening/exit interviews)? Sections A and B provide considerations on how to design and implement qualitative studies for the following settings:

- Observational qualitative studies
- Screening/Exit interview studies

A. Considerations for Designing and Implementing Observational Qualitative Studies

Within the context of qualitative research conducted to support regulatory decision-making, observational study methods including video recording (rather than live participant observation in a laboratory or natural setting) can be useful as video recorded data are often thought to add additional credibility and precision to the data collection process (Patterson et al 2003). Specific advantages of video recording over in-person, participant observation include:

- Generation of data that cannot be readily captured by participant observation alone (e.g., contextual cues and environmental factors that may be missed when a coder is focusing too closely on the participant)
- More naturalistic behaviors and reduced likelihood of participants allowing knowledge of observation to influence their behaviors (e.g., behaving in ways they believe would be acceptable to the researcher)
- Video documentation and archiving that allow for coding and data analysis in a systematic way among multiple coders (e.g., establishing inter-rater reliability)
- Detection of observer effects and increased validity in data interpretation

Some factors to consider when designing and implementing observational qualitative studies include, but are not limited to (Patterson et al. 2003):

- **Cost.** You should consider the number of participants, amount of video equipment, software requirements, among other factors, when planning your study to appropriately estimate your study budget.

- **Observational field work.** If you use video recording as your primary data collection method, you should design your study with a preliminary period of direct participant observation in the field (e.g., one in-person observational session). This can help provide guidance on the most appropriate time and place to videotape activities of interest as well as inform video camera placement, and the number of cameras that need to be used in order to capture a sufficient number of angles in the study setting.

- **Protocol modifications.** After the preliminary observation is complete, you can take the time to modify the original research question or revise the study protocol to better capture specific behaviors or activities that you intend to observe. For example, preliminary data

captured through participant observation could direct you on which interactions would generate the richest amount of data (e.g., interactions with a specific caregiver) and the optimal location for recording these interactions (e.g., the living room and kitchen in their home).

- **Data management and transcription.** A ***data management plan*** should be developed ahead of time before data collection. Ensure the clear labeling, cataloging, and safe storage (e.g., cloud/server storage) of data. Recordings should be transcribed and transcripts should be archived and analyzed using qualitative computer software programs that allow visual and sound clips or frames to be integrated into the transcripts; these visual images and sound files will help with providing context to the transcription data.

B. Considerations for Designing and Implementing Screening/Exit interview studies

Screening/exit interviews are unique in that they are implemented within the context of a clinical trial. Screening/exit interviews can be helpful in affording sponsors the opportunity to gather patient feedback regarding various topics, such as the following:

- Reported symptom changes (benefits, tolerability and other unintended effects) experienced by patients throughout a trial
- Participant treatment expectations
- Anticipated and unintended symptoms and AEs
- Viability of proposed dosing regimen
- Patients' experience with clinical trial participation (e.g., whether they could tell if they were on treatment, thoughts regarding study procedures, experience with modes of data administration [user experience with eCOA implementation])
- Informal benefit-risk trade-off assessments, from the patient/caregiver perspective(s)

The following are examples of advantages associated with conducting screening/exit interviews:

- They share all of the benefits related to one-on-one interviews
- They can inform initial development or refining a clinical outcome assessment (COA) through cognitive interviews as part of a mixed method approach
- They can add greater depth to data in rare diseases (or possibly other diseases with not much patient input) where standalone qualitative studies are less feasible.
- They can be used to obtain patient input on meaningful outcomes or meaningful change by eliciting patient definitions of symptom improvement, stability or worsening

Limitations of screening/exit interviews include:

- Extra burden on site staff (staff would need to be sufficiently trained)
- Extra burden for patients/caregivers, on top of standard clinical trial protocol
- Issues might arise regarding interview scheduling, administration time and confidentiality (e.g., certain sites/countries cannot pass on participant contact details to 3rd party vendors who might be conducting the interviews)

If screening/exit interviews are implemented, FDA recommends that interview protocols and interviewer guides be developed thoughtfully, keeping in mind the context of an individual study design. Likewise, interviews should be conducted before (screening interviews) or after (exit interviews) patients complete the main portion of the study to avoid any potential compromise to trial integrity.

1. *Screening interview studies*

Screening interviews can provide an opportunity to gather the following information about the following from patients:

- Symptoms and impacts that are relevant and important to treat
- Important symptoms that they expect to improve with treatment
- Their thoughts on what they believe constitutes a meaningful improvement in their symptoms
- What they consider to be a meaningful improvement in terms of PGIS category changes (e.g., 1-category change, 2-category change, etc.), as well as in PGIC categories (e.g., reporting “a little better,” “a lot better”)

Screening interviews can be particularly helpful for gathering additional information that can be used to develop clinical outcome assessments (COAs).

2. *Exit interview studies*

Exit interviews can also be helpful in affording drug developers the opportunity to ask patients the following regarding COAs:

- Whether any important symptoms should be added or removed from the instrument
- Their thoughts on what they believe constitutes a meaningful improvement from baseline in their symptoms in terms of each item or response option
- What they consider to be a meaningful improvement on patient global rating scales. For example, in terms of Patient Global Impression of Severity category changes (e.g., 1-category change, 2-category change, etc.) and/or Patient Global Impression of Change categories (e.g., reporting "a little better," "a lot better")
- Whether they believe they experienced a meaningful improvement from baseline Specifically, they can be used to capture information related to disease/treatment burden; and benefits and risks in patients' disease management

You may refer to the following literature references and relevant FDA review document where an exit interview strategy was successfully implemented in helping determine meaningful change.

- Lowell A, Horsch D, Ervin C, et al. Assessing Treatment Benefit of Telotristat Etiprate in Patients with Carcinoid Syndrome: Patient Exit Interviews. Poster presented at the 2015 North American Neuroendocrine Tumor Society (NANETS) Annual Meeting; October 16-17, 2015, Austin, TX.
- Gelhorn H, Kulke M, O'Dorisio T, et al. Patient-reported Symptom Experiences in Patients With Carcinoid Syndrome After Participation in a Study of Telotristat Etiprate: A Qualitative Interview Approach. Clin Ther. 2016; 38 (4): 759-68.
- FDA COA Consult Review for telotristate ethyl (Xarmelo) approval https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208794Orig1s000OtherR.pdf

APPENDIX 4. Operationalization of Quantitative Studies to Elicit Burden of Disease/Treatment and Benefits and Risks (Harms)

How to design and implement qualitative studies using surveys? Section A provides some best practices on how to design and implement quantitative studies using surveys/questionnaires to identify what is important to patients on burden of disease/treatment and benefits and risks.

A. Best practices for Designing and Implementing Studies using Surveys/Questionnaires

There are various standards and practical procedures for the use of surveys/questionnaires and/or other technologies. This document will focus on standards for best practice to improve the quality of the data generated from these instruments.

There are different methodologies involved with research using surveys/questionnaires:

- Sampling (refer to **Guidance 1** for more details)
- Designing questions (items) (**Section IVA.1(i) of Guidance 2 Discussion Document**)
- Data collection (**Section A.2 of Appendix 5**)

For studies that involves surveys/questionnaires, you should consider the following general steps once you have defined the research objective:

- Develop study materials (**Section A.1 of Appendix 5**)
- Review the relevant sources and begin planning the survey/questionnaire (if not already available (**Section IVA.1(i) of Guidance 2 Discussion Document**)
- Create basic design (format) or structure of survey/questionnaire and develop structured questions
- Pre-test and revise survey/questionnaire
- Collect data
- Analyze data and report results

FDA recommends stakeholders engage with subject matter experts (e.g., survey methodologists, statisticians, psychometricians) when designing and implementing studies using surveys/questionnaires to evaluate the burden of disease and treatment and benefits and risks of disease management.

1. Study Materials

What are the relevant study materials needed for survey studies? Relevant study materials for survey studies include but is not limited to the following:

- Study protocol
- Instruments (survey)
- Data analysis plan

Study Protocol

A study protocol for a study involving a survey/questionnaire does not differ that much for developing a protocol for a qualitative study. Refer to **Section A.1 of Appendix 1** for important components of a study protocol and key considerations.

A unique consideration for developing a study protocol for a study involving a survey/questionnaire includes estimating the number of surveys or tools to field (i.e., how big should a sample be). This generally involves calculating a response rate (i.e., the number of people who complete the survey or utilize other technologies divided by the number of people sampled). You should incorporate a strategy within the study protocol to document reasons for non-response (e.g., patients who are unable to be interviewed, fill out a survey, or use specific technologies). Refer to **Guidance 1** for additional details on sampling.

Instrument(s)

Within the study protocol, you should provide a description of the instrument and an exact copy of the instrument to be administered in the study, if feasible. For specific considerations on the use of surveys/questionnaires, see **Section IVA.1(i) of Guidance 2 Discussion Document**.

Analysis plan

Within the study protocol, you should provide a brief description of methods that will be used to evaluate the study data. In addition, there should be a separate detailed analysis plan.

2. Data Collection

Data from surveys/questionnaires can be collected in various ways:

- Interviews
- Paper-based
- Telephone-based
- Electronic-based (e.g., computers, tablets, smartphones)

Table 4 lists some of the advantages and disadvantages of the different data collection methods for surveys/questionnaires.

Table 4. Advantages and Disadvantages of Data Collection Methods for Surveys/Questionnaires

Source	Advantages	Disadvantages
Interviewer-administered	• Interviewer can identify if respondent is having difficulty understanding the question(s) • Interviewer can rephrase the question in terms the respondent may better understand • Flexibility in	• Costly (time and money) • Interviewers must be trained • Susceptible to interviewer bias • Susceptible to transcription errors • See **Table 6 of Guidance 2 Discussion Document**

Source	Advantages	Disadvantages
	presentation of questions (interviewer can probe) • Interviewer can navigate through skip patterns in the survey • Interviewer can minimize missing data • See **Table 6 of Guidance 2 Discussion Document** for advantages of different interview modes	for disadvantages of different interview modes
Paper-based	• Transparency; respondent can see the full instrument • Accommodates respondents who are technology challenged (e.g., no access to computer/internet, poor technology literacy) • Less costly	• May take more time for respondent to execute • Design limitations (e.g., amount of space on paper may restrict certain question types) • Susceptible to transcription errors
Electronic-based (e.g., computer, tablet, smartphone, interactive voice response system)	• Allows for quicker data collection, providing real-time analysis • Customizable and flexible options for survey design • Allows access to a large sample of respondents from different geographical areas • Minimize missing data • No need for data transcription	• May be costly • Limited readability for some respondents (e.g., respondents with visual impairment) • May not accommodate all respondents (e.g., respondents with poor technology literacy) • Susceptible to electronic malfunctions • May require training to respondents • Potential risks and challenges related to data security and privacy

Surveys/questionnaires can be administered in different modes/methods, which includes administration by:

- Other individuals (e.g., clinicians, healthcare professionals, caregivers)
- Self
- Interviews (e.g., face to face, telephone)

There is also an option to use more than one method to administer surveys/questionnaires (i.e., mixed-mode). Mixed mode surveys/questionnaires may provide more flexibility to respondents

and enhance response rate. However, a disadvantage to the use of mixed-modes could be potential mode effects (i.e., differences in the way that a respondent may answer questions through one mode of survey data collection compared with another), which could impact data quality. You should plan accordingly within your study design if mixed mode surveys/questionnaires are used.

Example: A survey is conducted on-line (web) and followed by a shorter telephone interview to adult patients with attention deficit hyperactivity disorder to assess the impacts of their condition on their daily life.

What are some advantages of using a mixed-mode survey?

- Increase the likelihood of reaching respondents
- Provide respondents with more than one way to answer
- Minimizes respondent burden, which can persuade non-respondents to participate

When selecting the most appropriate mode/method to administer a survey/questionnaire and collect its data, you should consider the following factors:

- Time
- Resources and cost
- Research topic, including question content (e.g., sensitivity of questions)
- Target population characteristics
- Sample frame
- Sample size
- Response rates
- Survey/questionnaire formatting
- Complexity of survey/questionnaire (e.g., content difficulty, number of items, skip patterns)
- ***Literacy*** level of respondent, including native tongue and ***health literacy***
- Length of data collection
- Strengths and limitations of the mode/method

Similarly, with qualitative studies, the study setting can also vary in which a survey/questionnaire is administered. The survey/questionnaire can be administered outside of a clinical trial (observational study, such as a registry study) or within a clinical trial (e.g., trial endpoint, screening or exit period of the study). **Appendix 3** provides some key considerations for each respective setting.

If surveys/questionnaires are intended to be a study endpoint(s) in a clinical trial, FDA recommends that stakeholders adopt good measurement principles. Refer to the FDA PRO Guidance (FDA, 2009) on factors to consider when administering questionnaires in clinical trials.

3. Data Analysis and Reporting

Once data have been collected by a survey/questionnaire, you will need to prepare the data for analysis. There are different phases for coding or data reduction, which includes the following:

- Deciding on the way the data will be organized in a file (i.e., compiling data into a single place)
- Creating the rules by which survey/questionnaire responses will be assigned values that can be analyzed
- Converting survey/questionnaire responses into standard categories (i.e., coding)
- Putting the data into readable form (i.e., common format) for statistical program(s)
- Cleaning data. including conducting a "final check" on the data file for accuracy, completeness, and consistency prior to analysis

The analysis process consists of several parts including:

- Data quality evaluation
- Data discovery (e.g., observance of oddities and trends in data)
- Interpretation
- Presentation

The analytic approach you take will generally depend on the following:

- research objectives
- study design (e.g., clinical trials, observational studies)
- types of data generated in your research study (e.g., nominal, ordinal, interval, ratio)

Refer to **Guidance 1** for more details on possible data types, descriptive approaches to summary statistics, distributional assumptions/methods for inference, and approaches to presentation of results.

Issues that should be addressed to analyze survey/questionnaire data include:

- Adjusting for sample non-response and sample frame deficiencies (i.e., adjusting the sample data to look more like the target population)
- Handling item non-response (i.e., how to deal with missing responses or incomplete responses)
- Adjusting for different probabilities of selection of respondents
- Calculating sampling errors

After analyses are completed, data should be organized and summarized in a report. Refer to **Section A.3 of Appendix 1** for components of a study report.

APPENDIX 5. Considerations for Special Populations and Cultural Differences for Quantitative Studies

How to survey special patient populations and different cultures? Sections A and B provide considerations on how to survey certain populations in survey studies.

A. Considerations for Special Populations within Studies using Surveys/Questionnaires

When planning studies in special populations, an even greater emphasis should be placed on the following factors:

- Mode of administration
- Data collection method
- Survey/questionnaire length
- Length of data collection
- Employing special aids or tools (e.g., show cards, high contrast colors)
- Literacy level of respondents, including native tongue
- Environment
- External concerns (IRB, consent)

The mode of administration and data collection method is important to ensure that it meets the needs of your target population. Interviewer-administered surveys/questionnaires may be optimal in special populations, particularly in pediatrics, cognitively impaired, or those with physical limitations, as the interviewer can pick up on cues that might result in additional assistance (e.g., clarifications, probes).

You should plan to offer alternative modes of data collection if engaging special populations (e.g., social media networks may be an option for patients with rare disease). Additionally, a risk protocol should potentially be developed to avoid any unexpected amendments needed for your study.

FDA recommends stakeholders collaborate with patient advocacy groups when planning to study in populations that may be difficult to reach.

B. Considerations for Cultural Differences during Survey studies

You can expect to face a variety of languages and cultural contexts when collecting data in the context of a multinational, multiregional, and/or multicultural survey study. These cultural differences could impact data collection efforts (e.g., languages that do not have a standard written form; different respondent literacy rates within cultures; inaccessible populations; impacts on harmonization of fielding times across countries due to geographic topography, weather and seasonal impediments, national and religious holidays, or political upheavals), which subsequently impacts data quality. It will be important to have some local knowledge to

understand cultural traditions and customs, potential limitations, and the feasibility of the research (Survey Research Center, 2016).

Translation procedures play a critical role in multi-national, multi-regional, and/or multi-cultural survey studies. A successful survey translation should (Survey Research Center, 2016):

- Keep the content and meaning of the questions similar
- Keep the question format similar within the limits of the target language
- Retain measurement properties, including the range of response options offered
- Maintain the same stimulus.

Poorly translated surveys/questionnaires can prevent researchers from collecting comparable data to that of surveys/questionnaires in the source (original) language (Survey Research Center, 2016).

In addition to translation, adaptation (modification) of questions or the questionnaire (e.g., format, response scales, or visual presentation) may be needed to meet cultural needs and achieve the required measurement goals.

Example:

Scenario: A question in a survey has an agreement response scale that has a middle category of “neither agree nor disagree.”

Agreement scale response categories developed in English often have a middle or neutral category "neither agree nor disagree." In languages such as Hebrew and Swahili, this phrase cannot properly be translated by simply translating the words. The closest meaning available to translate "disagree" in Hebrew, for example, corresponds to "no agree." In addition, the words "neither" and "nor" are the same as the target language element corresponding to "no." As such, "neither agree nor disagree," if translated word for word, would translate to something like "no agree, no no agree" which makes little sense in Hebrew (Harkness, 2003); Survey Research Center, 2016).

Example:

Scenario: Adapting a question from United States (U.S.) English to United Kingdom (U.K.) English

A question developed in the U.S refers to being able to walk "several blocks." This question would need translation, as well as adaptation to adapt the phrase "several blocks" for U.K. and provide the distance for European locations in terms of yards or meters (Harkness, 2008).

To make a survey/questionnaire fit the needs of different nationalities, regions and cultures, consider the following (Survey Research Center, 2016):

- Identify and resolve elements to consider for adaptation in the source survey/questionnaire to enhance comparability across different questionnaire versions
- Review the translated survey/questionnaire for adaptation needs
- Document adaptations, including rationale
- Test adaptations in the target population

Some general considerations on data collection for multinational, multiregional and/or multicultural include the following but are not limited to (Survey Research Center, 2016):

- Assess feasibility of conducting research in each target country and culture
- Allow some flexibility in data collection protocols to reduce costs and errors
- Decide whether the data can be best collected by combining qualitative methods with the standardized survey; this may increase data quality and validity
- Select appropriate timing of data collection activities
- Establish and follow appropriate quality control measures

You may refer you to the following literature references for other considerations and best practices for the translation and cultural adaptation process.

- Survey Research Center. (2016). Guidelines for Best Practice in Cross-Cultural Surveys. Ann Arbor, MI: Survey Research Center, Institute for Social Research, University of Michigan. Retrieved July, 03, 2018, from http://www.ccsg.isr.umich.edu/

- Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, Erikson P; ISPOR Task Force for Translation and Cultural Adaptation. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. Value Health. 2005 Mar-Apr;8(2):94-104.

APPENDIX 6. Considerations for Different Types of Quantitative Studies

How to design and implement quantitative studies for different types of settings (observational, screening/exit surveys)? Sections A and B provide considerations on how to design and implement quantitative studies for the following settings:

- Observational qualitative surveys
- Screening/Exit interview surveys

A. Considerations for Designing and Implementing Observational survey studies

If surveys/questionnaires are intended to be used in observational studies, FDA encourages the following steps (Cooper et al., 2006):

- Select pool of participants or panelists (e.g., health panels) to be observed. Obtain the required permissions needed to gain access to the participants and/or panelists.
- Each participant in a sample is asked the same set of questions to the extent possible.
- Each participant in a sample is given the same type of technology to the extent possible.
- Create a system in which questions can be entered, as well as possible responses, into a database table.
- Generate tables to record the data entered through the questionnaire from the database table of questions and possible responses.
- Develop a simple, user-friendly paper-based or electronic-based questionnaire.
- Select feasible and user-friendly technology.
- Provide data validation during the entry process.
- Develop a coding manual that could be used as a reference document.
- For web-based surveys/questionnaires or other technologies, generate descriptive statistics that could be observed through the web during the entry phase of the questionnaire.
- Develop program files that allow opportunity to do more advanced statistics once the questionnaire is completed or use of technology is completed.
- Maintain a database to access the questionnaire table and data entered into the survey/questionnaire. This database should have built-in features or capacity to interface with software that has features such as forms, queries, and reports to further work with the data.

B. Considerations for Designing and Implementing Screening/Exit survey studies

Using surveys/questionnaires in screening and/or exit visits in a clinical trial may add greater depth to understanding the burden of disease and treatment, as well as provide more detail on the benefits and risks of patients' disease management. This is also an approach that could be useful

in special populations, such as rare diseases or possibly other diseases where additional patient input is needed.

Factors to consider when using surveys/questionnaires in this setting includes the following, but are not limited to:

- Logistics (contracting, site training)
- Designing the appropriate questions and/or selecting the appropriate technology to meet the research objective(s)
- Implementation (timing of assessment within the study visit, logistics for multinational studies, including translations and cultural adaptation)
- Reporting (integrated with clinical study report or separate report, accurate adverse event reporting)

For surveys/questionnaires that are interviewer-administered, see **Section IIIA.1(i) of Guidance 2 Discussion Document** for considerations for interviewing in this type of study setting.

APPENDIX 7. Considerations for Use of Non-traditional Research Approaches to Elicit Information about the Burden of Disease/Treatment and Benefits and Risks (Harms)

How to design and implement qualitative studies using non-traditional research approaches (e.g., accelerometry, room surveillance, social networks)? Section A provides some best practices on how to design and implement quantitative studies using data from non-traditional sources.

A. Best practices for Designing and Implementing Studies using data from Non-traditional Sources

1. Technologies that collect health data

There are many technologies available that can be used to collect health data related to the patients' burden of disease and treatment, and benefits and risks of their disease management.

These technologies can include, but are not limited to information from:

- Mobile health technology (e.g., accelerometers, heartrate trackers)
- Mobile applications
- Other forms of health information technology

Similar to using surveys/questionnaires, it will be important for you to:

- Decide what to measure
- Select the appropriate tool to measure the intended outcome(s)

FDA recommends stakeholders engage with subject matter experts (i.e., technology experts) when designing and implementing studies using technologies to evaluate the burden of disease and treatment and benefits and risks of disease management.

i. Deciding what to measure

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 with a certain type of technology. See **Section IVA.1(i)(a) of Guidance 2 Discussion Document**.

ii. Selecting appropriate technology

Key considerations for selecting technology:

- Review the scientific literature related to the tool(s) (e.g., concept or content intended to measure; prior use in clinical trials)
- Identify the strengths and limitations of the tool(s)
- Check user reviews and ratings (usability, functionality, and efficacy)
- Pilot test the tool(s)

- Obtain feedback from users

Additional considerations for selection of technologies may include:

- Relevancy to target population
- Usability in special populations (e.g., pediatrics, elderly)
- Feasibility of data retrieval along with ease of linkages to analysis platforms (e.g., statistical software)

iii. Operationalization

The steps described for studies using surveys/questionnaires can also be taken to operationalize studies using technologies with some modification. See **Appendix 4.**

iv. Data Collection

Technology can be used to collect data in different ways. Different types of technologies may include but are not limited to:

- Wearable and biosensor devices (e.g., accelerometers, room sensors)
- Electronic-based (e.g., computers, tablets, smartphones)
- Mobile applications

The same factors that you would consider in selecting the appropriate mode/method to administer a survey/questionnaire (see **Section A.2 of Appendix 4**), would be applicable when considering which technology to use. In addition to these factors, you should consider the ease of use of the technology for the target population, as well as respondent burden (e.g., will the product impact or disrupt any of their daily activities?) and logistics (e.g., electricity to charge the technology).

Table 5 lists advantages and disadvantages of data collection methods using a few different types of technology.

Table 5. Advantages and Disadvantages of Data Collection Methods Using Example Technology

Source	Advantages	Disadvantages
Wearable and biosensor devices	• Efficient • Convenient tracking of data • Allows for quicker data collection, providing real-time analysis • Allows for more passive engagement and data collection	• Costly • Must be worn consistently • Susceptible to device malfunctions • Potential risks and challenges related to data security and privacy • Potential inaccuracies
Electronic-based	• See Table 4 of Appendix 4 for advantages of electronic-based data collection for surveys/questionnaires	• See Table 4 of Appendix 4 for disadvantages of electronic-based data collection for surveys/questionnaires
Mobile applications	• See advantages for social networks	• Costly • Potentially limited in terms of design and devices

FDA recommends that you engage in early discussions with the appropriate review division about the data collection technology for a study endpoint(s) in a clinical trial.

v. Data Analysis and Reporting

The steps described for studies using surveys/questionnaires can also be taken to analyze data using technologies, with some modification. See **Section A.3 of Appendix 4**.

2. Social Networks

Social networks may be a feasible option to elicit information on burden of disease and treatment, as well as treatment benefits and risks. The best practices described for designing and implementing studies using surveys/questionnaires and technology are applicable to social networks.

Data from social networks can be collected in different ways, which may include but is not limited to free text response for blogs and surveys/questionnaires.

Some general considerations on the use of social networks include the following but are not limited to:

- When possible, social media research should examine a variety of social media networks and communities. Different communities appeal to different segments of the population,

and a community's degree of user anonymity may affect what users are willing to discuss. Ideally, research will examine data from communities that require personal information (such as verified patient communities) and communities that allow users to remain anonymous or post under a username (such as many blogs and forums).

- Social media research can be used for hypothesis generation, as well as to complement literature review findings, inform the development of research tools (e.g., qualitative study discussion guides) or as a supplement to traditional research approaches (e.g., literature, one-on-one interviews, focus groups or expert opinion).

- Other research designs such as mixed-methods sequential research designs can further strengthen the depth of knowledge gained from social media research.

Table 6 lists some of the advantages and disadvantages of using social networks to elicit information from patients.

Table 6. Advantages and Disadvantages of Using Social Networks

Qualitative Research Method	Advantages	Disadvantages
Social Media	• Low burden for people providing data • Relatively inexpensive and easy to implement • Can often generate a larger sample size than other methods • Permits the analysis of data via the use of both qualitative and quantitative research methods • Allows for flexibility in data gathering/search terminology (iterative in nature)	• 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 may be difficult to determine • Findings across social platforms may be distinctly different (e.g., certain platforms may have strong advocacy/support community presence, while others may predominantly capture industry/academic perspectives surrounding certain issues)