SAMPLE SIZE, GROUNDED THEORY, AND SATURATION IN COA DEVELOPMENT

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Guidance for Industry: Sample size

- Does not make any specific sample size recommendations
- Stresses the importance of:
  - Saturation
  - Interview quality
  - Patient diversity

Saturation in PROs

- What is it?
- Why is it necessary to achieve it?
- When do you start thinking about it?
- How do researchers know when they achieve it?
- How do we present findings to indicate that saturation has been achieved

When To Start Thinking About Saturation

- When you formulate your research question
- When you select your sample?
  - Homogeneous? Heterogeneous?
- When you develop your discussion guide?
- When you iteratively develop a coding scheme (what do the codes mean?; when are codes reflecting distinct concepts?)
- When you conduct data analysis and if necessary, further data collection
  - Need to also search for disconfirming evidence and assure maximum variation – negative case
Developing a PRO instrument: Data collection and analysis

Do we have a deep understanding of the concepts?

Phenomenological Theoretical Framework

- Accessing a concept through the eyes of a person experiencing the concept
  - Not constrained by preconceived theories
  - Not taken from an instrument
  - Open-ended questions
    - "What is it like for you to have diabetes?"
Grounded Theory Methods

- Set of data collection and analysis methods whereby the meaning of a concept is discovered in the words and actions of participants from the ground up – not from application of a priori theory or concepts
- Application to COA: Help investigators develop a conceptual framework that can be used to design a questionnaire and/or quantitatively test a PRO instrument (reliability, psychometric properties, responsive)
- Inductive rather than deductive reasoning
- Simultaneous and iterative data collection and analysis
- Reliability through multiple coders and harmonization
- Achievement of saturation

What is Saturation?

- Limited research
- Originates in Grounded Theory
  - Methodological and analytical approach to qualitative research
  - Theory evolves during actual research, and it does this through continuous interplay between analysis and data collection
  - Iterative process of sampling, data collection, and analysis
- When have you reached saturation?
  - Concepts cannot be further specified with additional analysis or new data collection
  - No new codes
  - Saturation table

Looking for the Essence in Concepts: An Analogy

Through rigorous, detailed, documented, and transparent work Rosalind Franklin, a British biophysicist, identified the essence of the DNA molecule with an X-ray diffraction photograph 1953.

The DNA story involved describing the essence of the molecule, mixing methods to describe and test its structure, and multidisciplinary effort.

Developing a PRO: Study Design

Criteria for sample diversity
- Diversity of patients with different characteristics to cover breadth of context
- Variations in disease severity
- Epidemiology of disease (rare/common, subtypes based on genetic factors) and subtypes based on prior and/or future treatments (first line, second line chemotherapy, stem cell transplant (eligible, not eligible)
- Representative of the population of interest (age, ethnicity, gender

Types of Coding
- Open (examining, comparing conceptualizing, categorizing data)
- Axial (reassembling data into groupings based on relationships and patterns within and among the categories identified)
- Selective (identifying and describing the central phenomenon or core category)
Providing Evidence of Saturation

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Concept</th>
<th>1 vs. 2</th>
<th>1-2 vs. 3</th>
<th>1-3 vs. 4</th>
<th>Total</th>
<th>Saturation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloating</td>
<td>1 vs. 1</td>
<td>2 vs. 1</td>
<td>3 vs. 1</td>
<td></td>
<td>4</td>
<td>Merged, yes</td>
</tr>
<tr>
<td>Distension</td>
<td>0 vs. 1</td>
<td>1 vs. 0</td>
<td>1 vs. 1</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Other Discomfort</td>
<td>Tightness</td>
<td>0 vs. 1</td>
<td>1 vs. 1</td>
<td>2 vs. 1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heavy</td>
<td>0 vs. 1</td>
<td>1 vs. 1</td>
<td>2 vs. 1</td>
<td>3</td>
<td>Merged, yes</td>
</tr>
<tr>
<td></td>
<td>Fullness</td>
<td>1 vs. 1</td>
<td>2 vs. 1</td>
<td>3 vs. 1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Itching</td>
<td>1 vs. 0</td>
<td>1 vs. 0</td>
<td>1 vs. 0</td>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Abdominal pressure</td>
<td>1 vs. 1</td>
<td>2 vs. 0</td>
<td>2 vs. 1</td>
<td>3</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Merged concepts= As you develop a deeper understanding of the patient experience, codes/concepts that have the same meaning to patients may be merged


Hypothetical Saturation of IBS (first 2 focus groups)

Rectal pain
Abdominal pain
Fullness
Bloating
Flatulence
Cramping
Frequent bowel movements
Incomplete evacuation
Rectal bleeding
Hypothetical Saturation of IBS
(first 4 focus groups)

Rectal pain
Abdominal pain
Distension
Nausea
Incomplete evacuation
Fullness
Bloating
Flatulence
Cramping
Frequent bowel movements
Rectal bleeding

Hypothetical Saturation of IBS
(first 6 focus groups)

Rectal pain
Abdominal pain
Distension
Nausea
Incomplete evacuation
Fullness
Bloating
Flatulence
Cramping
Frequent bowel movements
Rectal bleeding
Mixing qualitative AND Quantitative methods analogous to DNA Structure and process

- Qualitative data can be tapped throughout life cycle of the development and use of the PRO
- During cognitive interviews one often goes back to the concept elicitation data for clarification and comparison purposes
- Development of scoring algorithms and responder definitions often require further insight from the qualitative data (e.g., developing composite scores of symptom clusters)
- Interaction with the FDA/EMA may either require re-analysis of qualitative data or collection of additional qualitative data
- Quantitative analysis will describe and test the structure of the data; if additional qualitative data is collected, will need to show responder definition is still supported
- Analysis of efficacy and effectiveness results may be further explicated with qualitative research