PGI29

Selecting Chronic Constipation (CC) Clinical Trial Endpoints: Incorporating the Patient's Voice

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Introduction

- Per the 2009 FDA guidance on patient-reported outcomes (PROs), the development and selection of PRO clinical trial endpoints must be based upon input from patients[1]
- Assessment of treatment response in chronic constipation (CC) clinical trials has historically focused on bowel symptoms
- Qualitative evidence from patients is necessary to identify all symptoms important to the CC patient population so that they can be assessed in clinical trials

Objectives

- Identify a comprehensive set of symptoms and optimal terminology to assess those symptoms in CC clinical trials
- Achieve concept saturation and provide support for the content validity of the corresponding set of endpoints in accordance with the FDA's PRO guidance

Methods

- Two iterative sets of interviews were conducted with CC patients in Raleigh, North Carolina (Round 1) and Las Vegas, Nevada (Round 2)
- Participants were referred by local gastroenterologists and met modified Rome II criteria for CC
- In accordance with the FDA PRO guidance, recruited patients were similar (clinically and demographically) to participants in ongoing and planned CC clinical trials (Table 1)

Table 1. Demographic Characteristics of Interview Participants

Demographic Information	N = 28
Gender, n	
Female	24
Male	4
Age, mean years (range)	44.9 (19 – 74)
Race, n	
White	19
African American/Black	9
Education, n	
High school	5
Some college or 2-year degree	11
College graduate	12

- A semi-structured interview guide, composed primarily of open-ended questions, was used to ensure consistency within each round of interviews
- Participants were asked to identify and describe their CC symptoms and the relationships among them:
  - *"What types of symptoms do you experience?"*
  - *"When you say [symptom], what exactly does that mean to you?"*
  - *"How do these symptoms relate to each other?"*
- Additional rating and ranking methods were used to narrow the full list of CC symptoms and impacts to those of greatest importance to the patients. For example:
  - Participants in both sets of interviews were probed to identify their most bothersome CC symptoms
  - Round 1 participants rated the importance of selected bowel and abdominal symptoms
  - Round 2 participants identified the 5 symptoms they would most like improved

Results

Spontaneous Symptom Reports

- Participants reported 62 potentially distinct concepts:
  - 12 bowel symptoms and 21 abdominal symptoms (Table 2)
  - 25 additional physical symptoms and 4 mental or emotional issues (Table 3)
- Although participants generally described a similar constellation of bowel and abdominal symptoms, there was variability in their choice of descriptors
- A list of bowel and abdominal symptoms spontaneously reported by multiple participants is provided in Table 2

Table 2. Spontaneously Reported CC Symptoms*

	Round 1 (n = 15)	Round 2 (n = 13)	Total (%) (N = 28)
Bowel Symptoms, n			
Infrequent BMs	15	13	28 (100.0)
Hard (or lumpy) stool	14	8	22 (78.6)
Straining	8	12	20 (71.4)
Stools too small (or too large)	7	11	18 (64.3)
Unsuccessful attempts to have a BM	8	10	18 (64.3)
Incomplete BMs	6	7	13 (46.4)
Long duration of bathroom visit	4	4	8 (28.6)
Digital manipulation	2	2	4 (14.3)
Abdominal Symptoms, n			
Bloating	12	10	22 (78.6)
Abdominal pain	12	10	22 (78.6)
Abdominal discomfort (uncomfortable)	6	9	15 (53.6)
Stomach pain/aches, "belly ache"	6	8	14 (50.0)
Abdominal cramping	5	8	13 (46.4)
Feeling of fullness/feeling "stuffed"	5	8	13 (46.4)
Feeling backed up, "loaded", or impacted	9	3	12 (42.9)
Gas	5	6	11 (39.3)
Trapped gas, backed up gas, gas pockets	3	8	11 (39.3)
Passing gas	0	7	7 (25.0)
Gas pain	1	5	6 (21.4)
Pain in sides or on one side	0	3	3 (10.7)
Upset stomach, acid in stomach, stomach sours	0	2	2 (7.1)
Strong odor of gas	0	2	2 (7.1)
Burping/belching	1	1	2 (7.1)

* Includes only symptoms reported by at least 2 participants

- Additional symptoms were generally regarded by patients as the consequence of severe bowel or abdominal symptoms
  - Patients reported rectal pain, hemorrhoids, and rectal bleeding secondary to straining and hard stools
  - Severe constipation (commonly defined by patients as having gone many days without a bowel movement [BM]) was associated with additional gastrointestinal (GI) problems such as nausea and early satiety, as well as non-GI issues such as headaches, fatigue, and irritability
- A list of other symptoms and impacts spontaneously reported by multiple participants is provided in Table 3

Table 3. Additional Symptoms and Impacts of CC Reported Spontaneously*

	Round 1 (n = 15)	Round 2 (n = 13)	Total (%) (N = 28)
Rectal Symptoms, n			
Rectal pain	8	7	15 (53.6)
Hemorrhoids	7	5	12 (42.9)
Rectal bleeding	8	3	11 (39.3)
Rectal tearing	4	3	7 (25.0)
Rectal "burning"	0	3	3 (10.7)
Other Symptoms/Impacts, n			
Moodiness, irritability	3	6	9 (32.1)
Loss of appetite/early satiety	3	4	7 (25.0)
Back pain, backache	2	5	7 (25.0)
Headaches	1	5	6 (21.4)
Nausea	2	3	5 (17.9)
Heartburn, indigestion	1	4	5 (17.9)
Fatigue, tiredness, low energy; lethargy	3	2	5 (17.9)
Chest pain (due to gas, pressure, feeling of fullness into chest)	1	3	4 (14.3)
Feel "blah," feel "miserable," don't feel good	0	4	4 (14.3)
Skin issues (e.g. acne; skin not as supple)	2	1	3 (10.7)
Weight gain, feel heavier	1	1	2 (7.1)

* Includes only symptoms and impacts reported by at least 2 participants

Most Bothersome Symptoms

- Participants mentioned bowel symptoms and abdominal symptoms as their most bothersome symptom(s) of CC with similar frequency; rectal consequences of hard stools and straining were also commonly reported
- The symptoms most frequently identified as among the most bothersome included infrequent BMs, bloating, abdominal pain, and rectal pain. Sample responses include:
  - *"Not being able to go. Just, well, that gives the whole picture as simultaneously as I get so big, makes me feel nauseous, hot and achy in the joints. All the symptoms all come the longer I go without going."*
  - *"Just that I don't like feeling bloated. It's just really, really uncomfortable. Not really sure what to do about it, because it gets better if I do go to the bathroom [but] I don't always, you know, feel like I've gone enough."*
  - *"The pain in my lower abdomen and the pressure on my rectum."*
  - *"I would say the straining and not really being able to go, like being able to have one hard stool and then that was it…getting a hemorrhoid from it, that's really bothersome. So, I guess the straining and [rectal] pain."*

Rating Exercise – Round 1

- When asked to rate the 7 symptoms shown in Table 4, Round 1 participants generally rated both bowel and abdominal symptoms as very important

Table 4. Frequency of Importance Ratings* (Round 1; N = 15)

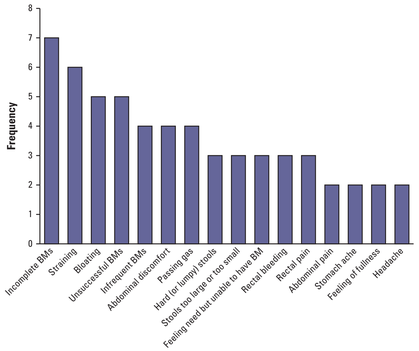
Symptom, n	0	1	2	3	Mean
BM completeness**	0	0	0	14	2.97
Abdominal discomfort	0	0	1	14	2.93
BM frequency	0	0	3	12	2.80
Straining	0	1	2	12	2.73
Bloating	0	0	4	11	2.73
Stool consistency	0	1	2	12	2.73
Abdominal pain	2	0	1	12	2.53

* Importance ratings: 0 = totally irrelevant; 1 = relevant but not important; 2 = moderately important; 3 = very important
** The 15th participant rated BM completeness as 2.5

Ranking Exercise – Round 2

- Figure 1 summarizes the "top 5" symptoms identified by Round 2 participants as those they wished to see improve with treatment
- Most of the 13 participants included both bowel and abdominal symptoms in their list

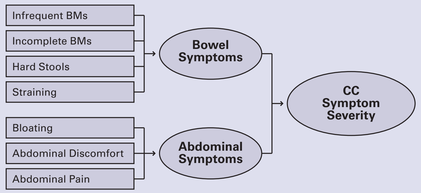
Figure 1. Frequency of Symptoms Included in Participants' "Top 5" List (Round 2; N = 13)



Summary and Conclusions

- This study reports symptoms spontaneously identified by CC patients through open-ended interviews using the methods outlined in the FDA PRO guidance
- Within and across the two separate rounds of interviews, participants consistently reported the importance of stool frequency, stool consistency, straining, incomplete evacuation, abdominal discomfort, bloating, and abdominal pain, demonstrating concept saturation with respect to these symptoms
- A proposed conceptual framework depicting the relationships among this core set of bowel and abdominal symptoms is shown in Figure 2

Figure 2. Conceptual Framework of Chronic Constipation Symptoms



Reference

1. US Department of Health and Human Services. Food and Drug Administration. December 2009. Guidance for industry patient-reported outcome measures: use in medical product development to support labeling claims. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf. Accessed December 10, 2009.

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