Lessons learned along the path to qualification of an IBS outcome measure*

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Patient-Reported Outcome (PRO) Consortium
Critical Path Institute

IMMPACT-XX

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*** We haven't reached the destination yet**

Critical Path Institute (C-Path)

- Established in 2005 by the University of Arizona and FDA's Center for Drug Evaluation and Research (CDER) as a public-private partnership
- An independent, non-profit organization
- Funded, in part, by grant number U18 FD005320 from FDA
- Dedicated to implementing FDA's *Critical Path Initiative* by providing a neutral, pre-competitive venue for collaboration aimed at accelerating development of safe and effective medical products

Patient-Reported Outcome (PRO) Consortium

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Formed in late 2008 by C-Path in cooperation with FDA's CDER and the pharmaceutical industry

- **Membership**
  - 26 members (pharmaceutical firms)
- **Other Participants**
  - Representatives of governmental agencies (FDA, NIH)
  - Clinical consultants, patients, academic researchers, and contract research organizations partnering in the development of PRO measures and other clinical outcome assessment (COA) tools

PRO Consortium Mission

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To establish and maintain a collaborative framework with appropriate stakeholders for the qualification of patient-reported outcome (PRO) instruments and other clinical outcome assessment (COA) tools that will be publicly available for use in clinical trials where COA-based endpoints are used to support product labeling claims

PRO Consortium Goals

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- Enable pre-competitive collaboration that includes FDA input and expertise
- Develop and obtain FDA qualification of PRO measures and other COA tools for use in assessing primary or secondary clinical trial endpoints
- Avoid development of multiple endpoint measures for the same purpose
- Share costs of developing new endpoint measures
- Facilitate FDA's review of medical products by standardizing COA-based endpoint measures that will be publicly available

CDER's "DDT Guidance"

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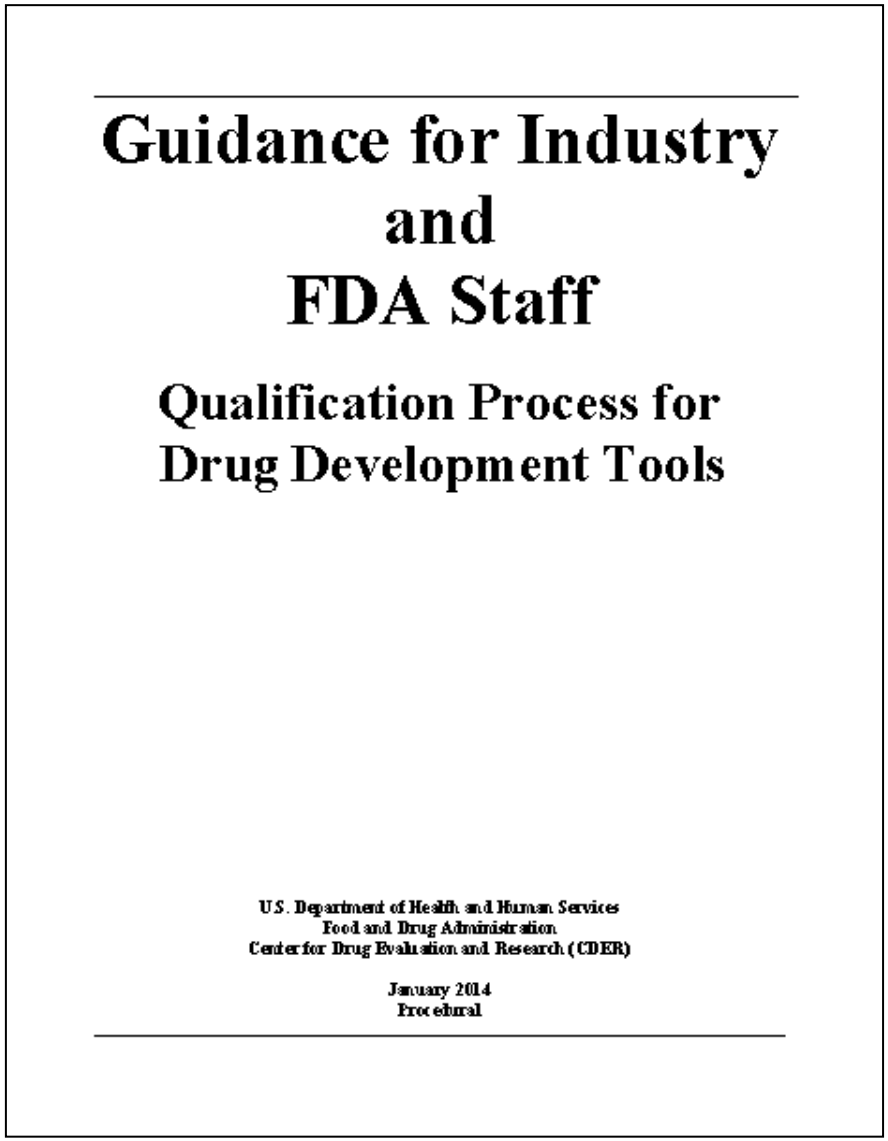

Guidance for Industry
and
FDA Staff

Qualification Process for
Drug Development Tools

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2014
Procedural

Describes CDER's drug development tool (DDT) qualification process. Includes biomarkers, animal models, and clinical outcome assessment (COA) tools

Draft: October 2010

Final: January 2014

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf

Drug Development Tool (DDT) Qualification Process

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Intent: To expedite development of publicly available DDTs that can be widely used in drug development

Definition: Qualification is based on an FDA review of evidence that supports the conclusion that within the stated context of use, the DDT can be relied upon to have a specific interpretation and application in drug development and regulatory review.

FDA's *Guidance for Industry and FDA Staff: Qualification Process for Drug Development Tools*

PRO Consortium
Current Working Groups (WG)

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Asthma WG – 10 firms
Cognition WG – 9 firms
Depression WG – 9 firms
Functional Dyspepsia WG – 2 firms
Irritable Bowel Syndrome (IBS) WG – 3 firms
Multiple Sclerosis (MS) WG – 5 firms
Myelofibrosis WG – 2 firms
Non-Small Cell Lung Cancer (NSCLC) WG – 10 firms
Pediatric Asthma WG – 3 firms
Rheumatoid Arthritis (RA) WG – 5 firms

Goal of Working Groups

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To produce and/or compile the necessary evidence to enable new or existing COAs to be qualified by the FDA

COAs include

- Patient-reported outcome (PRO) measures
- Observer-reported outcome (ObsRO) measures
- Clinician-reported outcome (ClinRO) measures
- Performance outcome (PerfO) measures

IBS Working Group

- March 2009 – IBS Working Group established
- Three pharmaceutical industry sponsors: Allergan, Ironwood, and Takeda
- RTI Health Solutions was selected as the WG's contract research partner
- **Goal:** To develop and obtain FDA qualification of three patient-reported measures of the signs and symptoms of IBS-C, IBS-D, and IBS-M for use in assessing primary endpoints in clinical trials to establish treatment benefit

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Development of the Diary for Irritable Bowel Syndrome Symptoms to Assess Treatment Benefit in Clinical Trials: Foundational Qualitative Research

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Qualitative Research

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Participants

Recruited through gastroenterology clinics in six US regions and met the following criteria:

- Male or non-pregnant female ≥ 18 years
- Meets Rome III criteria for IBS-C, D, or M
- English speaking, ambulatory, community-dwelling
- Reported an average abdominal pain intensity score of 3 or more on a 0 to 10 scale over the seven days before screening

Concept Elicitation Interviews (N=49)

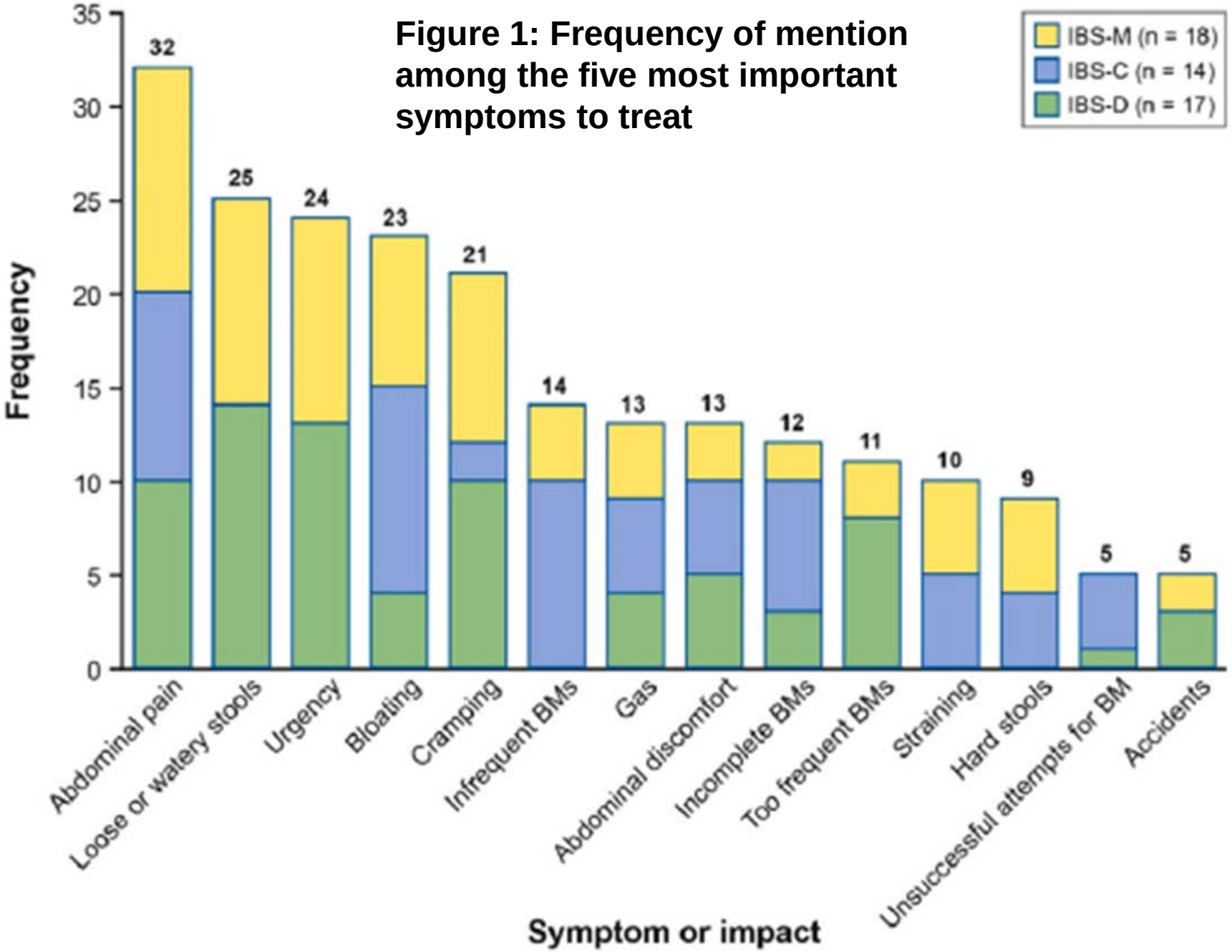
Designed to identify relevant signs and symptoms of IBS and determine

- the way they are experienced and spoken about
- the relationships between them
- the most bothersome
- the ways in which they interfere with daily life
- the five that each participant would want a medication to improve

Participants

- IBS-D: n=17; IBS-C: n=14; IBS-M: n=18

Figure 1: Frequency of mention among the five most important symptoms to treat



Concept Elicitation Interviews: Selected Findings

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Abdominal Pain

- Across the three subtypes, abdominal pain was reported spontaneously by 43 of the 49 participants
- Thirty-two of the 49 participants included abdominal pain among the five symptoms most important to treat ("top-five" list), which is more than any other IBS symptom
- Eleven participants identified abdominal pain as their single most bothersome symptom

Signs and symptoms selection criteria

- Directly attributable to IBS
- Experienced and deemed important to treat by most participants (within relevant subtype)
- Have the potential to respond to treatment within the context of a clinical trial (e.g., 12-week duration)

Note: It was decided that the signs and symptoms included for IBS-M should be a combination of those used for IBS-D and IBS-C

Signs and symptoms selected

Based on the concept elicitation interviews, a review of existing qualitative literature, and clinical expert input, the following signs and symptoms were selected for the draft PRO measures:

<u>Abdominal symptoms</u>

pain, discomfort, cramping, and bloating

<u>Bowel movement-related signs and symptoms</u>

stool frequency, stool consistency, incomplete bowel movements, urgency, recurrent bowel movements, and straining

Signs and symptoms chosen for each subtype

IBS-D, IBS-C, and IBS-M – stool frequency, stool consistency, incomplete bowel movements, abdominal pain, abdominal discomfort, and bloating

IBS-D and IBS-M only – urgency, recurrent bowel movements, and cramping

IBS-C and IBS-M only – straining

Note: It is recognized that not all of the signs and symptoms above will be used to derive clinical trial endpoints

Item generation

Multiple alternative items were generated for each sign or symptom

The items were then used to assemble draft PRO measures for further qualitative testing through cognitive interviews

The three measures were named the *Diary of Irritable Bowel Syndrome Symptoms* (*DIBSS*)—*D*, *DIBSS—C* , and *DIBSS—M*

Format and mode of data collection

Each of the three versions of the *DIBSS* was implemented on a handheld electronic data capture device (i.e., smartphone) for self-administration during the second and third rounds of cognitive interviews

The format for entry of bowel movement-related signs and symptoms responses is event (i.e., bowel movement) driven

The format for responding to the abdominal symptoms is 24-recall at the end of each day

Cognitive Interviews (N=43)

Three rounds of cognitive interviews were conducted to confirm the most important signs and symptoms were addressed and to optimize item wording and response scales

Participants were asked to read out loud and describe their thought processes as they considered and responded to each draft item. Differences between symptoms were explored.

Participants

- IBS-D: n=16; IBS-C: n=19; IBS-M: n=8

Cognitive Interviews: Selected Findings

Although often described as very related, the majority of participants reported a distinction between each of the abdominal symptoms (i.e., pain, bloating, cramping, and discomfort).

For instance, abdominal pain was commonly described as a "sharp," "tight," or "shooting" sensation, whereas abdominal discomfort was often described an "irritation," "fullness" and/or "ache."

Cognitive Interviews: Selected Findings

Abdominal pain is a highly salient and important symptom to patients, regardless of IBS subtype.

- **But how do we measure it?**

Abdominal pain items tested during the cognitive interviews

OPTION 1:

How would you rate your abdominal pain at its worst in the last 24 hours?

- None
- Mild
- Moderate
- Severe
- Very severe

Abdominal pain items tested during the cognitive interviews

OPTIONS 2 and 3:

On average, how would you rate any abdominal pain you experienced in the last 24 hours?

- Response scale: 0 to 10 NRS, where 0 is “No abdominal pain” and 10 is “Worst abdominal pain I can imagine”

OR

- Response scale: 0 to 10 NRS, where 0 is “No abdominal pain” and 10 is “Worst possible abdominal pain”

Abdominal pain items tested during the cognitive interviews

OPTION 4:

How would you rate your abdominal pain at its worst in the last 24 hours?

- Response scale: 0 to 10 NRS, where 0 is “No abdominal pain” and 10 is “Worst possible abdominal pain”

“past” vs. “last” 24 hours

- The words ‘last’ and ‘past’ can be interpreted in different ways; the use of the word ‘past’ most commonly refers to the most recent 24 hours.

- Decision: “past 24 hours” chosen

“on average” vs. “worst”

- Participants described different methods of averaging their pain over the course of the day; however, participants consistently interpreted “worst” as their most severe pain during the past 24-hour period.
- Although participants were generally able to articulate the difference between a symptom at its “worst” and “on average,” they responded the same or very similarly to both items.
- Decision: “worst” chosen

Numeric vs. Verbal Rating Scale

- Across rounds, a slight preference for the NRS (as compared to the VRS) was reported for the assessment of pain.
- In addition, the NRS is also used more commonly for the measurement of pain and recommended by FDA in the IBS Guidance.

- Decision: NRS chosen

"worst abdominal pain I can imagine" vs. "worst possible abdominal pain"

- Although all participants were able to select a response using either version of the NRS, some participants stated that they could imagine pain more severe than they ever experienced and thus they would not use the upper end of the scale.

- Decision: "worst possible" chosen to increase the probability that respondents would use the entire response scale

Placement of “worst” in item stem

Two participants reported that moving the word “worst” could improve question clarity. Their recommendation was supported by the translators who recommended changing the sentence structure to facilitate future translation.

Decision: “How would you rate your worst abdominal pain…” was chosen rather than “How would you rate your abdominal pain at its worst….”

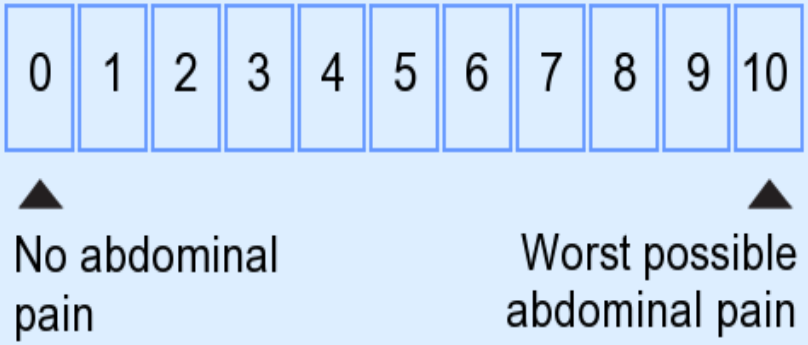
FINAL ITEM

How would you rate your worst abdominal pain in the past 24 hours?

- Response scale: 0 to 10 NRS, where 0 is “No abdominal pain” and 10 is “Worst possible abdominal pain”

Note: This is almost identical to the wording recommended in the FDA’s IBS Guidance which used an 11-point NRS to ask patients to rate their “worst abdominal pain over the past 24-hours”

How would you rate your worst abdominal pain in the past 24 hours?



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Limitations

Although the study participants are reasonably representative of the IBS clinical trial population in terms of age, sex, race, ethnicity, and education, 92 people recruited from six U.S. clinics are unlikely to fully represent this target population.

WG Members

- Allergan
  - Robyn T. Carson, MPH (Co-Chair)
  - Steven J. Shiff, MD
- Ironwood Pharmaceuticals, Inc.
  - Jennifer Hanlon, MPH (Co-Chair)
  - David Reasner, PhD
- Takeda Pharmaceuticals International
  - Maria Claudia Perez, MD
  - Amy Duhig, PhD (Consultant - Xcenda)

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Brennan M.R. Spiegel, MD, MSHS	University of California, Los Angeles
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