

*Case Study:*  
***Irritable Bowel Syndrome***  
***Working Group***  
*A Journey Through Time*

*Ninth Annual*  
***Patient-Reported Outcome Consortium Workshop***

**April 25 - 26, 2018 • Silver Spring, MD**



# Disclaimer



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# Session Objectives



- Present methods and results of IBS Working Group on the development of the *Diary for Irritable Bowel Syndrome Symptoms– Constipation predominant, Diarrhea predominant, Mixed (DIBSS -C, -D, -M)*
  - Development included three subtypes, in this presentation the focus will be on IBS-D
- Review and discuss key challenges, lessons learned and considerations across instrument development projects

# Session Outline



- Introduction
- Development of the *DIBSS-C/D/M*
  - Stage 1: Qualitative Research
  - Stage 2: Quantitative Pilot Study
  - [Ongoing] Stage 3: Endpoint Selection and Full Qualification Packages
- Technology and Implementation Lessons Learned
- Lessons Learned Throughout the Journey
- Panel Discussion and Q&A

# Session Participants



## Moderator

- *Jennifer Hanlon, MPH* – Associate Director, Study Endpoints, Ironwood Pharmaceuticals

## Presenters

- *Claire Ervin, MPH* – Senior Director, Patient-Centered Outcomes Assessment, RTI Health Solutions
- *Lori McLeod, PhD* – Vice President, Patient-Centered Outcomes Assessment, RTI Health Solutions
- *Adam Butler* – Sr. Vice President, Strategic Development and Corporate Marketing, Bracket
- *Robyn Carson, MPH* – Executive Director, Patient-Centered Outcomes Research, Global Evidence & Value Development, Allergan Inc.

## Panelists

- *Stephen Coons, PhD* – Executive Director, Patient-Reported Outcome Consortium, Critical Path Institute
- *Sheri Fehnel, PhD* – Vice President, Patient-Centered Outcomes Assessment, RTI Health Solutions
- *Sarrit Kovacs, PhD* – Reviewer, Clinical Outcome Assessments (COA) Staff, Food and Drug Administration

# Introduction

Jennifer Hanlon, Associate Director Study Endpoints, Ironwood Pharmaceuticals

# DIBSS Current Development Team



Company/Organization	Representatives
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; Brian Talon, PharmD
Nonmember Participants	Affiliation
Nancy Norton, BS	International Foundation for Functional Gastrointestinal Disorders (IFFGD)
Expert Panel Members	Affiliation
Lin Chang, MD <sup>1</sup> ; William D. Chey, MD <sup>2</sup> ; Douglas A. Drossman, MD <sup>3</sup> ; Jeffrey M. Lackner, PsyD <sup>4</sup> ; Brian E. Lacy, MD, PhD <sup>5</sup>	<sup>1</sup> University of California, Los Angeles; <sup>2</sup> University of Michigan; <sup>3</sup> University of North Carolina, Chapel Hill; <sup>4</sup> University at Buffalo, SUNY; <sup>5</sup> Mayo Clinic, Jacksonville
Critical Path Institute	Research Team
PRO Consortium Representatives	Stephen Joel Coons, PhD; Sonya Eremenco, MA; Theresa Griffey, MBA; Christian Noll, MBA; Theresa Hall
Contract Research Organization	Research Team
RTI Health Solutions	Sheri Fehnel, PhD; Claire Ervin, MPH; Lori McLeod, PhD; Diana Goss
ePRO System Provider	Representative
Bracket Global	Adam Butler

# IBS Working Group Rationale and Goal



- Rationale for the Working Group
  - FDA and PRO Consortium identified irritable bowel syndrome (IBS) as a priority area
  - FDA IBS Guidance provided provisional endpoints but cited that no appropriate PRO instruments had been identified for IBS endpoint development
- Goal of the PRO Consortium's IBS Working Group
  - To achieve FDA Qualification status for COA measures to assess symptoms of IBS that are fit for purpose to support efficacy endpoints in clinical trials



# FDA IBS Guidance Take-aways



- FDA no longer recommends a single general item to support efficacy
  - “A single general item cannot adequately capture whether benefit is achieved in all, or only some of the important signs and symptoms.” (p3 IBS guidance)
- FDA cites that there are no well-defined and reliable PRO instruments available that measure clinically important signs and symptoms associated with IBS subtypes (C and D) to support clinical trial labeling claims
  - IBS-M and IBS-unsubtyped are not included in the guidance
- Provisional endpoints for IBS-C and IBS-D: primary endpoint that measures the effect of treatment on two major IBS signs and symptoms: abnormal defecation and abdominal pain
- The FDA is actively collaborating with the PRO Consortium Working Group members on the development and qualification of PRO measures for the signs and symptoms of IBS-C and IBS-D per their guidance
- Once qualified, endpoints derived from the IBS-C and IBS-D subtype measures will replace the provisional endpoints defined in the FDA guidance to measure treatment benefit

# Measurement Gap



- No COAs were identified that were developed in accordance with the FDA PRO Guidance
- IBS Working Group members decided to develop 3 de novo COAs
  - For each of the 3 predominant subtypes of IBS: constipation predominant, diarrhea predominant, and mixed symptoms IBS
  - Specific issues identified by the FDA could be addressed during the development process
- IBS Working Group is actively working towards filling this measurement gap

# **Development of the *Diary of Irritable Bowel Syndrome Symptoms – Constipation, Diarrhea and Mixed (DIBSS-C/D/M)***

*Claire Ervin, MPH*

Senior Director, Patient-Centered Outcomes Assessment, RTI Health Solutions

# Overview of *DIBSS-C/D/M* Development Stages



## **Stage 1: Qualitative Research**

- Literature Review
- Instrument Development
  - Concept elicitation interviews
  - Expert panel meeting
  - Item pool development
  - Cognitive debriefing interviews
  - Translatability assessment
  - Electronic implementation assessment
  - Interim Qualitative Research Briefing Document
- Final Qualitative Research Briefing Document and Discussion with FDA
  - Review of development process and results
  - Review of quantitative analysis plan

## **Stage 2: Quantitative Pilot Study**

- Observational pilot study
- Quantitative evaluation

## **Stage 3: Endpoint Selection and Full Qualification Packages (*DIBSS-C/D/M*)**

- Upcoming Activities:
  - Expert panel meeting
  - Endpoint selection
  - Qualification packages
  - User manuals

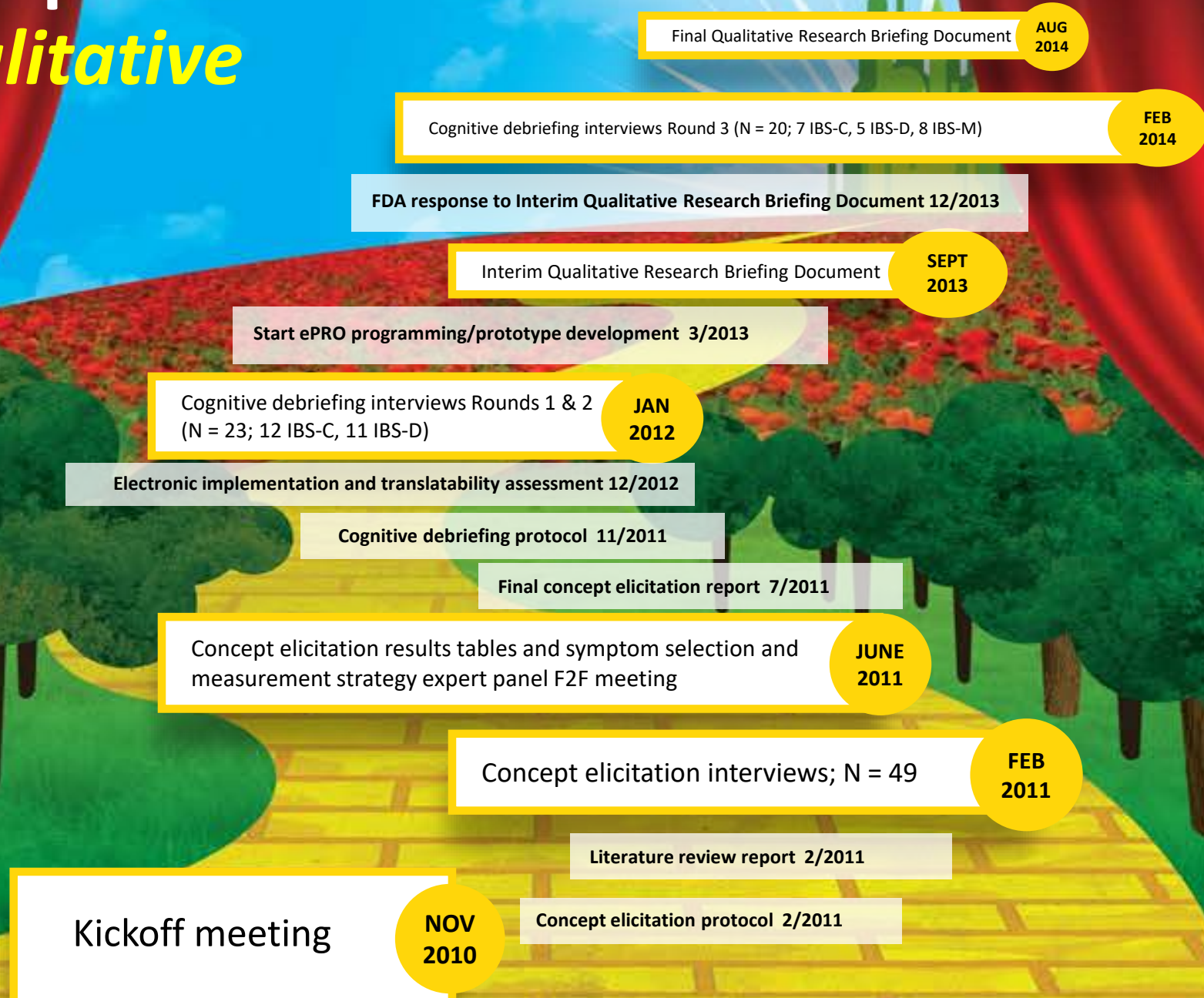
# Timeline of Development Steps

*Essentially, when we started down this yellow brick road, I looked something like this...*

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# DIBSS Development Timeline: Stage 1 Qualitative



# **Stage 1**

# **Qualitative Development Steps**

# Literature Review



- Reviewed 81 studies involving the identification, description, and/or rating of IBS symptoms by patients
  - Qualitative studies, patient surveys, and observational studies
- Symptoms most commonly identified or assessed were those relevant to all three IBS subtypes
  - Abnormal stool frequency and abnormal stool form/consistency
  - Abdominal pain and/or discomfort; abdominal bloating
- Additional symptoms were IBS subtype specific
  - IBS-C: Straining; Incomplete evacuation
  - IBS-D: Urgency



# Concept Elicitation Interview Objectives



- Primary objective
  - Identify, based on patient input, a comprehensive set of IBS symptoms and the relationships among these symptoms by IBS subtype
- Secondary objectives
  - Document how patients perceive and describe varying levels of symptom severity and impact
  - Identify the specific improvements needed for patients to perceive a treatment benefit
  - Reach “concept saturation” with respect to the symptoms experienced by individuals with each IBS subtype before the completion of the participant interviews

# Concept Elicitation Interview Participants



- A total of 49 adults with IBS
  - 14 with IBS-C; 17 with IBS-D; 18 with IBS-M
- Participants recruited and screened through gastroenterology clinics in 3 locations
  - Raleigh, NC; San Antonio, TX; and San Diego, CA
- Inclusion/exclusion criteria
  - Adult patients (18 years and older; males and non-pregnant females)
  - Diagnosis of IBS of 3 main subtypes (i.e., IBS-C, IBS-D, and IBS-M)
  - Patients without known or suspected organic disorder (e.g., Crohn's disease) that would better explain symptoms
  - Patients not concomitantly using medications known to affect gastrointestinal (GI) motility, constipation, or other IBS symptoms
  - Additional demographic and clinical criteria to ensure interview participants mirrored IBS clinical trial populations

# Concept Elicitation Interview Methods



- A standardized, semistructured interview guide was developed to ensure consistency of data collection across participants
- Each interview included 3 components:
  - **Spontaneous Concept Elicitation:** Open-ended questions were designed to identify all relevant IBS symptoms, how participants experience and speak about these symptoms, the relationships among these symptoms, and the most bothersome symptoms among all those identified spontaneously
  - **Probed Concept Elicitation:** If not mentioned spontaneously, other symptoms considered clinically relevant on the basis of expert input and the literature were queried to assess their potential relevance and importance
  - **Most important concepts:** Participants were asked to describe how bothered they were by their IBS symptoms, the extent to which symptoms interfered with their lives, and the 5 symptoms they would most want an IBS medication to improve

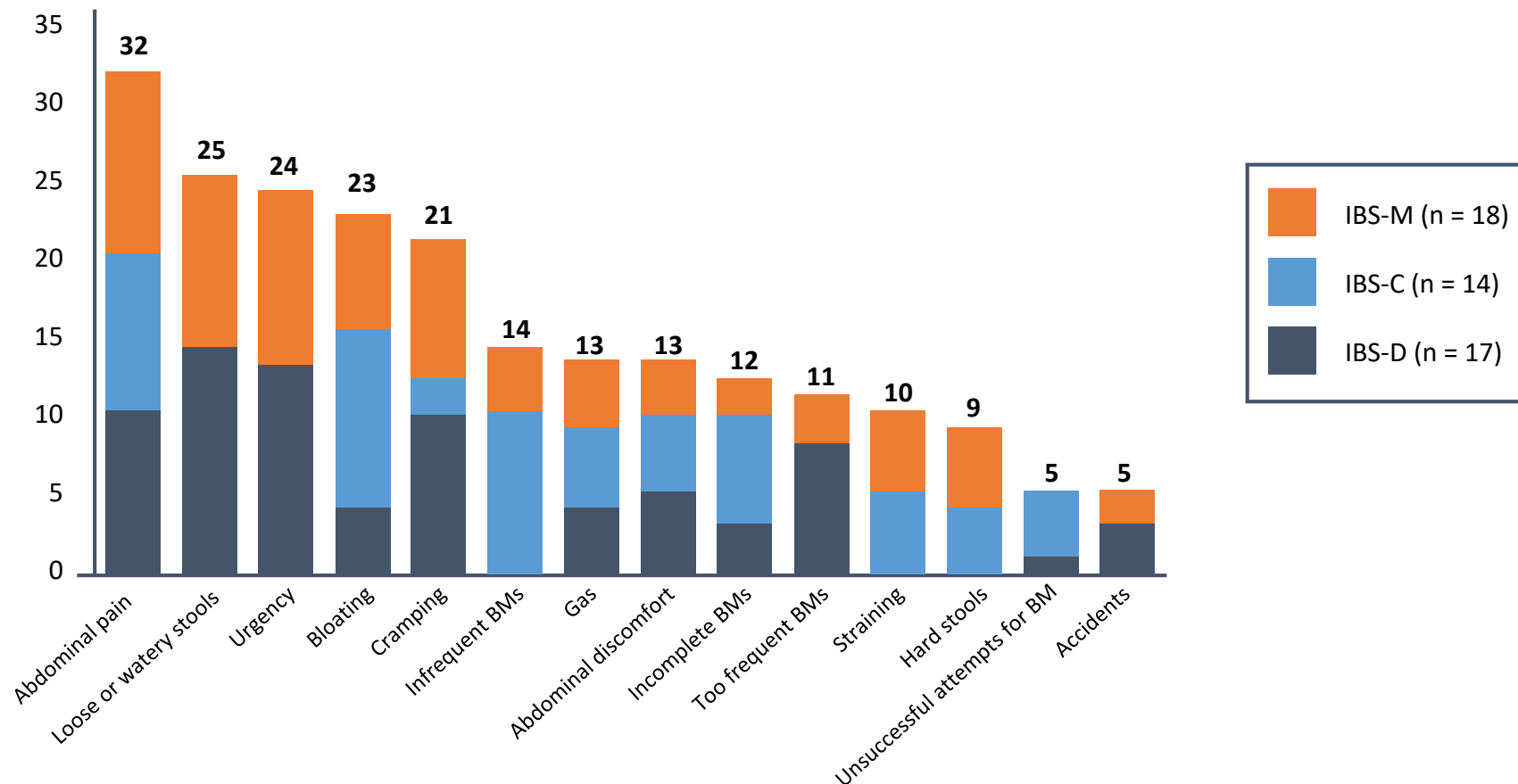
# Concept Elicitation Interview Results



- IBS-C (n = 14): Spontaneously reported by at least 7 participants (50%)
  - Constipation, infrequent BMs, “can’t go,” small stools, straining, hard stools, and incomplete bowel movements (BMs)
  - Bloating; abdominal pain; gas; abdominal discomfort; feeling of fullness; and gurgling, rumbling, or churning
- IBS-D (n = 17): Spontaneously reported by at least 8 participants (~ 50%)
  - Diarrhea, loose or watery stools, urgency, too frequent BMs, and recurrent BMs
  - Abdominal pain, cramping, gas, abdominal discomfort, and bloating
- IBS-M (n = 18): Spontaneously reported by at least 9 participants (50%)
  - Diarrhea, recurrent BMs, loose or watery stools, too frequent BMs, and urgency
  - Constipation, infrequent BMs, unsuccessful attempts for BM, “can’t go,” hard stools, and straining
  - Incomplete BMs and long time in bathroom
  - Abdominal pain, cramping, bloating, and abdominal pressure

# Concept Elicitation Interview Results

## Participant Reports of the 5 Most Important Symptoms to Treat (N = 49)



BM = bowel movement; IBS-C = irritable bowel syndrome with constipation; IBS-D = irritable bowel syndrome with diarrhea; IBS-M = mixed irritable bowel syndrome.

Note: Frequency represents the frequency with which each symptom or impact was included by concept elicitation participants in their list of the 5 most important IBS symptoms to treat. Figure includes only those symptoms or impacts reported by at least 5 participants across IBS subtypes.

# Expert Panel Meeting



- Reviewed results of concept elicitation interviews with experts, including expert panelists and members of the IBS WG in detail
- Key decisions/agreements:
  - Focus on symptoms of IBS; not impacts of IBS (e.g., rectal bleeding, rectal pain, accidents)
  - Item pool for IBS-M would be a combination of the items developed for use in IBS-C and IBS-D
  - Concepts chosen or recommended for item development:
    - Common to IBS-C and IBS-D item pools: stool frequency, stool consistency, incomplete BMs, abdominal pain, abdominal discomfort, and bloating
    - Specific to IBS-C item pool: straining
    - Specific to IBS-D item pool: urgency, recurrent BMs, and cramping
  - Concepts discussed but ultimately excluded from item pool (primarily due to close relationship with other symptoms): frequency of unsuccessful attempts for BMs; “gurgling, rumbling, or churning;” stool size; feeling of fullness; and gas

# Item Pools: Bowel Symptoms



- Stool frequency within past 24 hours (1 item)\*
- Stool form/consistency per BM (2 items)
  - Bristol Stool Form Scale (7-point scale)
  - New item focused only on consistency (5-point scale)
- Complete evacuation per BM (1 item)
  - Dichotomous (yes/no)
- Frequency of recurrent BMs within past 24 hours (1 item; IBS-D and IBS-M only)\*
  - Maximum number of BMs within a 1-hour period
- Urgency per BM (1 item; IBS-D and IBS-M only)
  - Dichotomous (yes/no)
- Straining per BM (2 items; IBS-C and IBS-M only)
  - Both 4-point and 5-point verbal rating scales

\* Included only to facilitate testing, recognizing frequency would be assessed based on number of events recorded in the ePRO version of the diary.

# Item Pools: Abdominal Symptoms



- Symptoms assessed:
  - Abdominal pain
  - Abdominal discomfort
  - Abdominal bloating
  - Abdominal cramping (IBS-D and IBS-M only)
- Multiple items for each symptom
  - Any\*, average, and worst
  - 0 to 10 numeric rating scales (NRS) (2 variants); 5-point verbal rating scale (VRS)
- All referenced the past 24 hours

\* Included only for testing to see which concepts participants thought of naturally/spontaneously.



# Cognitive Debriefing Interviews and Interim Activities



- Three iterative sets of interviews were conducted to test and refine the *DIBSS*
  - Participants recruited and screened through gastroenterology clinics (Erie, PA; Chicago, IL; and Little Rock, AR)
  - Inclusion/exclusion criteria same as concept elicitation interviews
- Rounds 1 and 2 included only participants with IBS-C and IBS-D (n = 23)
  - 12 with IBS-C; 11 with IBS-D
  - Tested paper-based versions of the measures
- Additional activities undertaken between Rounds 2 and 3
  - Translatability assessment
  - Electronic implementation assessment
  - ePRO programming (Bracket)
  - Interim Qualitative Briefing Package submission and feedback from FDA (at FDA request)
- Round 3 included patients with all 3 subtypes (n = 20)
  - 7 with IBS-C; 5 with IBS-D; 8 with IBS-M
  - Tested ePRO formats of the measures

# Cognitive Debriefing Interview Results



- Recall periods:
  - **Event-driven** data collection would facilitate accurate reporting of BM-related symptoms, particularly for participants with frequent BMs
  - **24-hour** recall appropriate for abdominal symptoms
- Most bothersome BM-related symptoms:
  - IBS-C:
    - **#1 = Frequency**; #2 = Straining; #3 = Incomplete evacuation; #4 = Stool consistency
  - IBS-D and IBS-M:
    - **#1 = Urgency**; #2 = Stool frequency; #3 = Stool consistency
    - Concerns related to stool consistency were commonly tied to urgency, the symptom that had the greatest impact on participants' lives
  - Findings consistent with concept elicitation results
    - Suggest BM-related component of provisional IBS-D endpoint (stool consistency) may not be most appropriate



# Cognitive Debriefing Interview Results










- Item reduction:
  - Incomplete evacuation was included in all 3 item pools but subsequently removed from the IBS-D diary based on patient feedback
    - Less salient concept in relation to diarrhea (compared to constipation or mixed subtypes)
    - Recurrent BMs and incomplete BMs were highly related
    - Measurement error:
      - Some participants indicated BMs were incomplete because they knew they would have to go again in a short period of time (even if they felt like they had completely emptied their bowels)
  - No other symptom was removed or added based on the cognitive debriefing interviews

# Cognitive Debriefing Interview Results

## Measurement of stool consistency vs. stool form

- The *Bristol Stool Form Scale (BSFS)* is routinely used to measure stool form, which includes what the stool “looks like” rather than focusing on consistency (the concept patients said was important during concept elicitation)
  - *BSFS* tested form
  - Newly developed item tested consistency

**The Bristol Stool Form Scale**

Stool Form	Appearance	Type
Separate hard lumps like nuts (difficult to pass)		1
Sausage shaped but lumpy		2
Like a sausage but cracks on surface		3
Like a sausage or snake, smooth and soft		4
Soft blobs with clear-cut edges (passed easily)		5
Fluffy pieces with ragged edges, a mushy stool		6
Watery, no solid pieces (entirely liquid)		7

### Newly Developed Item

How would you describe the consistency of your stool?

Very hard
Hard
Neither too hard nor too soft
Loose but not watery
Very loose and watery

DIBSS-D v0.1  
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# Cognitive Debriefing Interview Results



- Measurement of stool consistency vs. stool form
  - Both the *BSFS* item and the newly developed item addressing stool consistency tested reasonably well, however:
    - *BSFS* options 1 and 2 were out of order to some participants with constipation (a 2 looked worse than a 1)
    - *BSFS* text and pictures did not always provide an accurate reflection for all stools passed
  - Both items were included in the quantitative pilot study to gather further information

# Cognitive Debriefing Interview Results



- Concept for abdominal symptom items:
  - Items addressing symptom severity on average and at its worst were answered similarly, particularly for bloating and discomfort, which tend to be fairly stable throughout the day
  - Final items all ask about symptoms at their worst to facilitate accurate recall
- Response scale for abdominal symptom items:
  - 0 to 10 numeric rating scale (NRS) favored for pain
  - More participants preferred the verbal rating scale for the remaining symptoms but easily answered using the 0 to 10 NRS
  - **0 to 10 NRS** was selected for all abdominal symptom items for consistency (to facilitate completion and scoring)

# Translatability Assessment



- Translatability Assessment:
  - Conducted in collaboration with PharmaQuest following the second set of cognitive debriefing interviews
  - Five languages were chosen to represent geographic regions in which clinical trials are commonly conducted by the project sponsors: French (Canada), German (Germany), Portuguese (Brazil), Spanish (US), and Ukrainian (Ukraine).
  - The only substantive modifications were made to the BSFS
    - For example, the word “blob” was replaced with the word “pieces” and “passed easily” was modified to “easy to pass” in option 5.
    - Translators also noted that the use of the word “sausage” would not be culturally appropriate in some regions. *[no change made]*
  - All modifications based on the translatability assessment were tested (with positive results) in the third round of cognitive debriefing interviews.

# Electronic Implementation Assessment



- Conducted by the C-Path ePRO Consortium's Instrument Migration Subcommittee in December 2010
  - Representatives from six ePRO vendors
- Objective was to assess the viability of implementing the *DIBSS* on all available electronic platforms.
- Recommendations included the following:
  - Event-based data capture across subtypes
  - Alarms to help ensure data entry/completion
  - The use of a hand-held device
  - Conservative use of **bold** and underlined text as the ability to do this is operating system dependent
  - Additional translatability work for counties (e.g., Russia) where text length becomes an issue in ePRO implementation on hand-held devices.

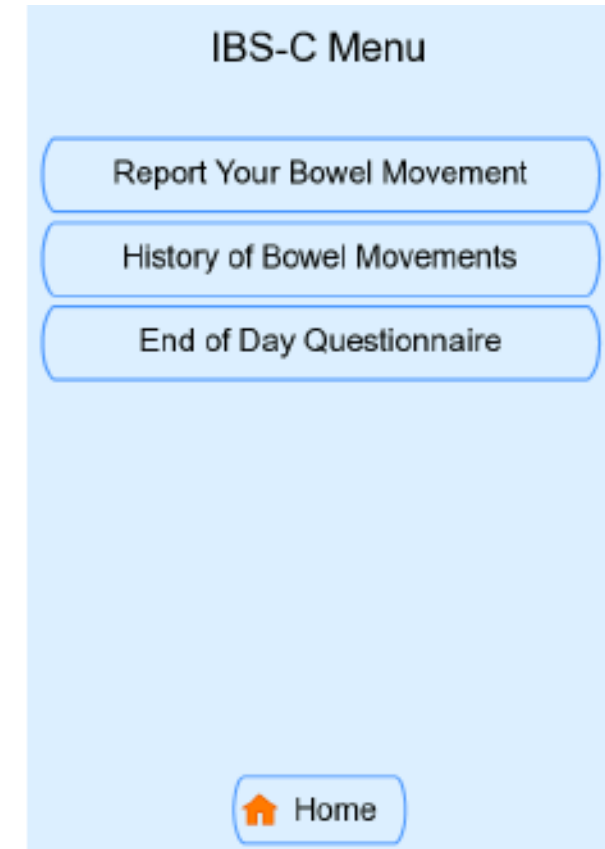


# Cognitive Debriefing Interview Results



- Usability Assessment

- The *DIBSS-C/D/M* were tested on an electronic handheld device in the third set of debriefing interviews (programmed by Bracket)
- Participant feedback was overwhelmingly positive
  - All 20 participants, regardless of age or education, said the ePRO device was easy to use.
  - Many volunteered that answering a diary using this (or a similar) electronic format would be much better (easier, more convenient) than a paper or interactive voice response (IVR) assessment.
  - All said they would be willing to participate in a clinical trial using a handheld device.
- Only very minor formatting modifications were made based on participants' feedback

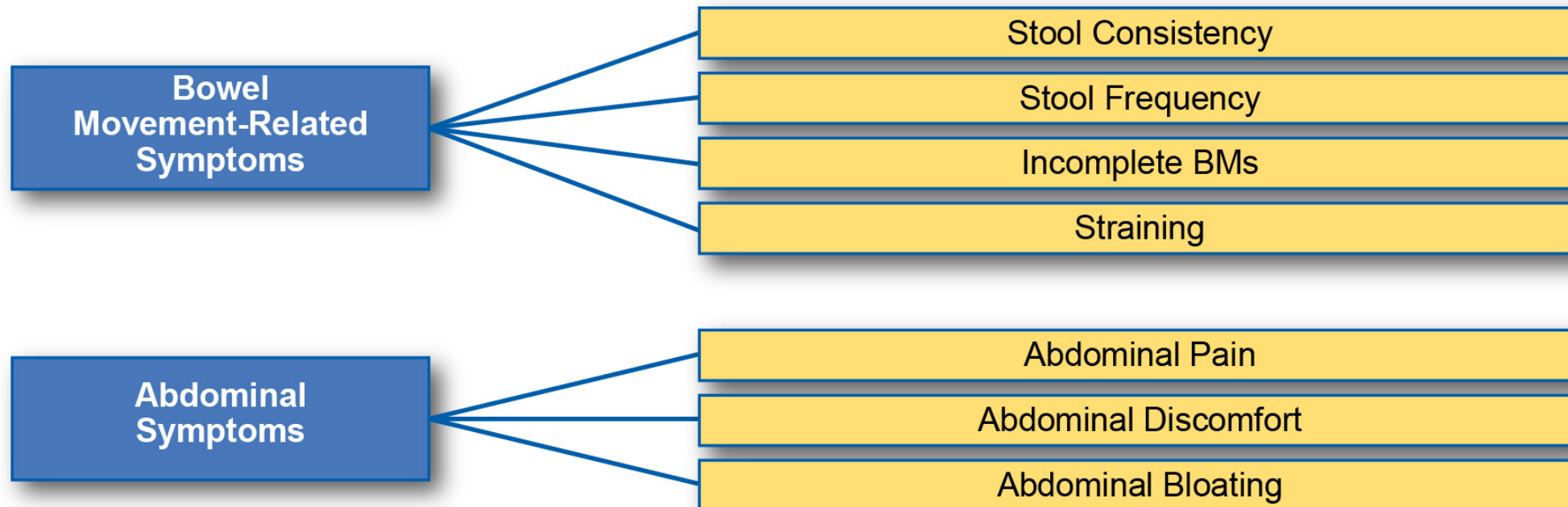


# Reviews by the FDA

- Just after the C-Path PRO Consortium meeting in April 2012, the FDA requested a document detailing all progress to date
  - This request was made between the second and third sets of cognitive debriefing interviews
    - Round 3 participants had already been recruited
  - The briefing document was prepared and submitted to FDA for review and comment (Sept 26, 2013)
  - Following receipt of feedback (Dec 6, 2013), a teleconference was held to discuss the Qualification Review Team's (QRT's) recommendations
  - The third and final set of cognitive debriefing interviews was then conducted
- The final Qualitative Research Briefing Document was submitted in its entirety following the third set of cognitive debriefing interviews (August 1, 2014)



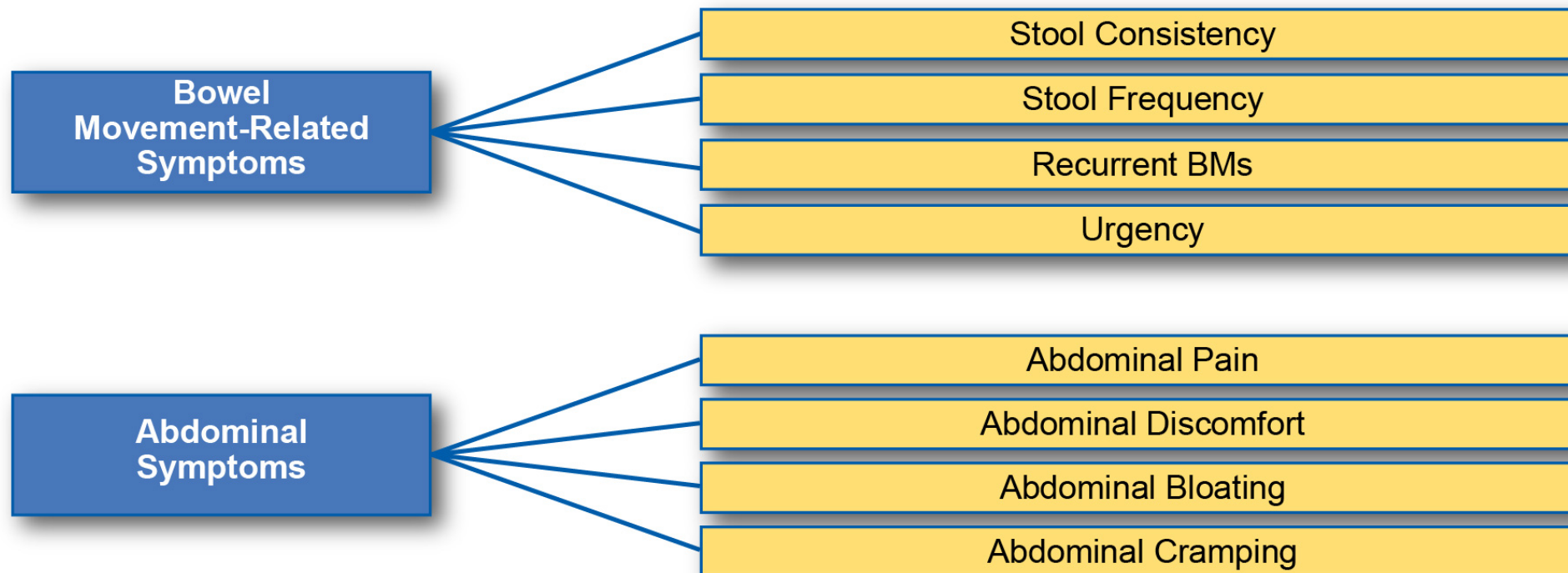
# Conceptual Framework: IBS-C



BM = bowel movement; IBS-C = irritable bowel syndrome with constipation.

Note: Stool frequency based on the number of events recorded in the diary. Two items included to address stool consistency.

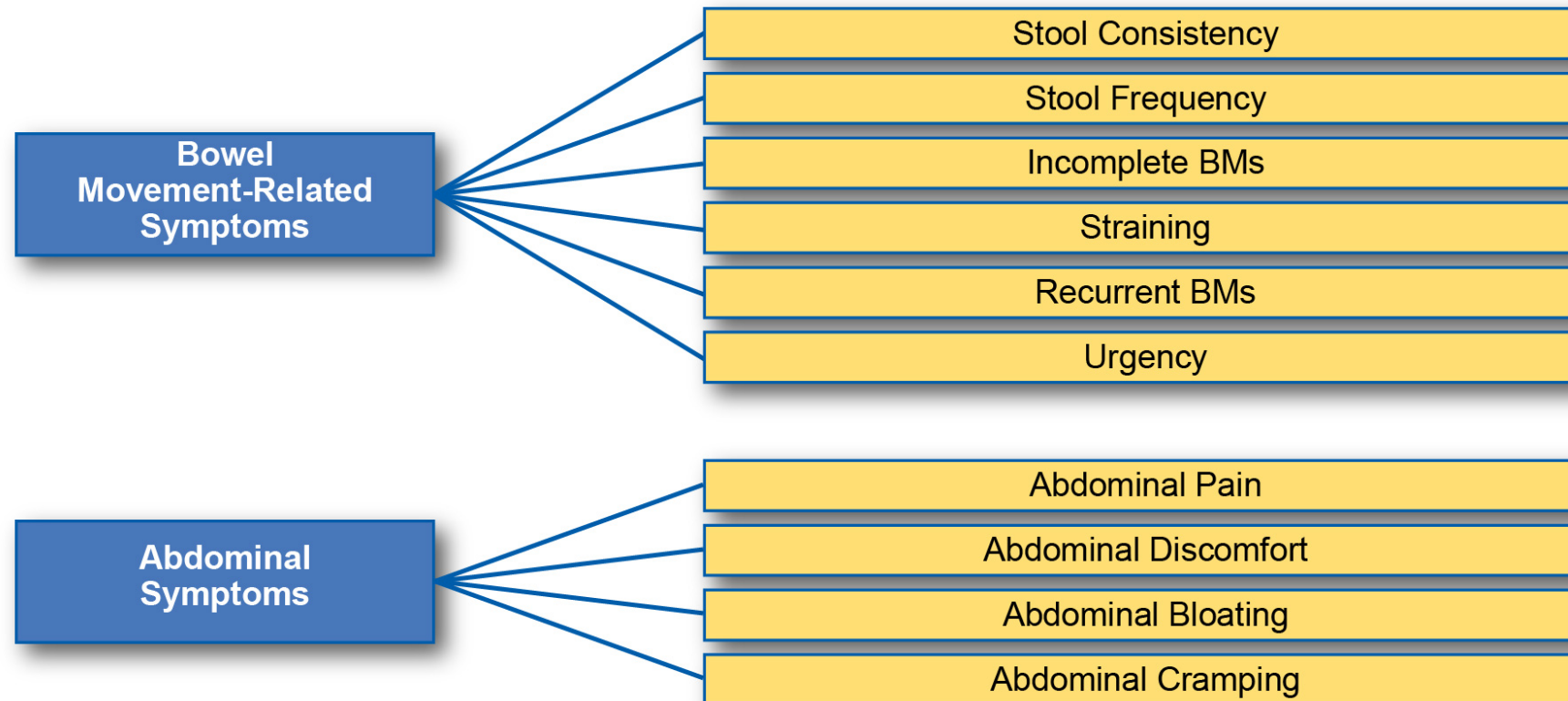
# Conceptual Framework: IBS-D



BM = bowel movement; IBS-D = irritable bowel syndrome with diarrhea.

Note: Stool frequency and recurrent BMs computed based on the number and timing of events recorded in the diary. Two items included to address stool consistency.

# Conceptual Framework: IBS-M



BM = bowel movement; IBS-M = mixed irritable bowel syndrome.

Note: Stool frequency and recurrent BMs computed based on the number and timing of events recorded in the diary. Two items included to address stool consistency.

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

Sheri E. Fehnel, PhD<sup>1,\*</sup>, Claire M. Ervin, MPH<sup>1</sup>, Robyn T. Carson, MPH<sup>2</sup>, Gianna Rigoni, PharmD, MS<sup>3</sup>, Jeffrey M. Lackner, PsyD<sup>4</sup>, Stephen Joel Coons, PhD<sup>5</sup>, on behalf of the Critical Path Institute Patient-Reported Outcome Consortium's Irritable Bowel Syndrome Working Group

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**ABSTRACT**

**Background:** Irritable bowel syndrome (IBS) is a chronic gastrointestinal disorder characterized by abdominal pain and alterations in bowel habits. Three subtypes are defined on the basis of stool patterns: diarrhea-predominant IBS, constipation-predominant IBS, and alternating or mixed IBS. **Objectives:** To develop patient-reported outcome measures for qualification by the Food and Drug Administration to support product approvals and labeling in IBS, the article focuses on the qualitative research that provided the foundation for the new measures. **Methods:** Forty-nine concept elicitation and 42 cognitive debriefing interviews were conducted with subjects meeting Rome III criteria; additional criteria were imposed to yield a sample representative of the target patient population. **Results:** Although incomplete bowel movements, abnormal stool frequency and consistency, and abdominal pain, discomfort, and bloating were reported most frequently across concept elicitation interviews, the relative importance of specific symptoms varied by subtype. Among their five symptoms most important to treat, diarrhea-predominant and alternating or mixed IBS subjects frequently identified urgency, loose/watery stools, abdominal pain, and cramping, whereas constipation-predominant IBS subjects commonly included infrequent and incomplete bowel movements, bloating, and abdominal pain. The cognitive debriefing interviews facilitated refinement of each item set, supported minor modifications following translatability assessment, and suggested improvements to the electronic interface. Furthermore, subjects reported that every item was relevant and no concepts of importance were missing. **Conclusions:** Results support the content validity of the IBS patient-reported outcome measures. A pilot study was recently initiated to inform item reduction, develop scoring algorithms, and provide preliminary psychometric information. Comprehensive psychometric evaluation and responder definition development will follow. **Keywords:** content validity, irritable bowel syndrome, patient-reported outcome measures, symptoms.

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### Introduction

In 2008, the Critical Path Institute, a private, nonprofit organization, established the Patient-Reported Outcome (PRO) Consortium in conjunction with the US Food and Drug Administration (FDA) and the pharmaceutical industry [1]. Concurrently, FDA's Center for Drug Evaluation and Research was advancing a program to provide a pathway for qualifying drug development tools for use in multiple programs to support product approval and labeling claims [2]. To achieve qualification, the center encouraged the creation of collaborative groups (e.g., consortia) to increase efficiency and share resources because of the substantial effort involved. The PRO Consortium is a public-private partnership involving the FDA, the pharmaceutical industry, consulting organizations, academia, and patient advocacy groups that facilitates collaborative, precompetitive development of PRO measures intended for qualification by the FDA.

One of the PRO Consortium's first areas of focus was the assessment of treatment benefit in irritable bowel syndrome (IBS). IBS is a chronic, oftentimes disabling gastrointestinal (GI) disorder characterized by abdominal pain associated with alterations in bowel habits (diarrhea and/or constipation). Although not required for diagnosis, additional bothersome symptoms such as urgency, straining, bloating, incomplete evacuation, and abdominal discomfort are commonly experienced. With a prevalence of 10% to 15%, IBS is one of the most common GI disorders seen by primary care physicians and gastroenterologists [3]. Three subtypes of IBS have been defined on the basis of stool

Conflicts of interest: S. E. Fehnel and C. M. Ervin are employees of RTI Health Solutions. R. T. Carson is an employee of Allergan plc and owns stock and stock options in Allergan plc. G. Rigoni was an employee of Takeda at the time of this study.  
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# Stage 2

# Quantitative Pilot Study: Data Collection

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# Timeline of Development Steps

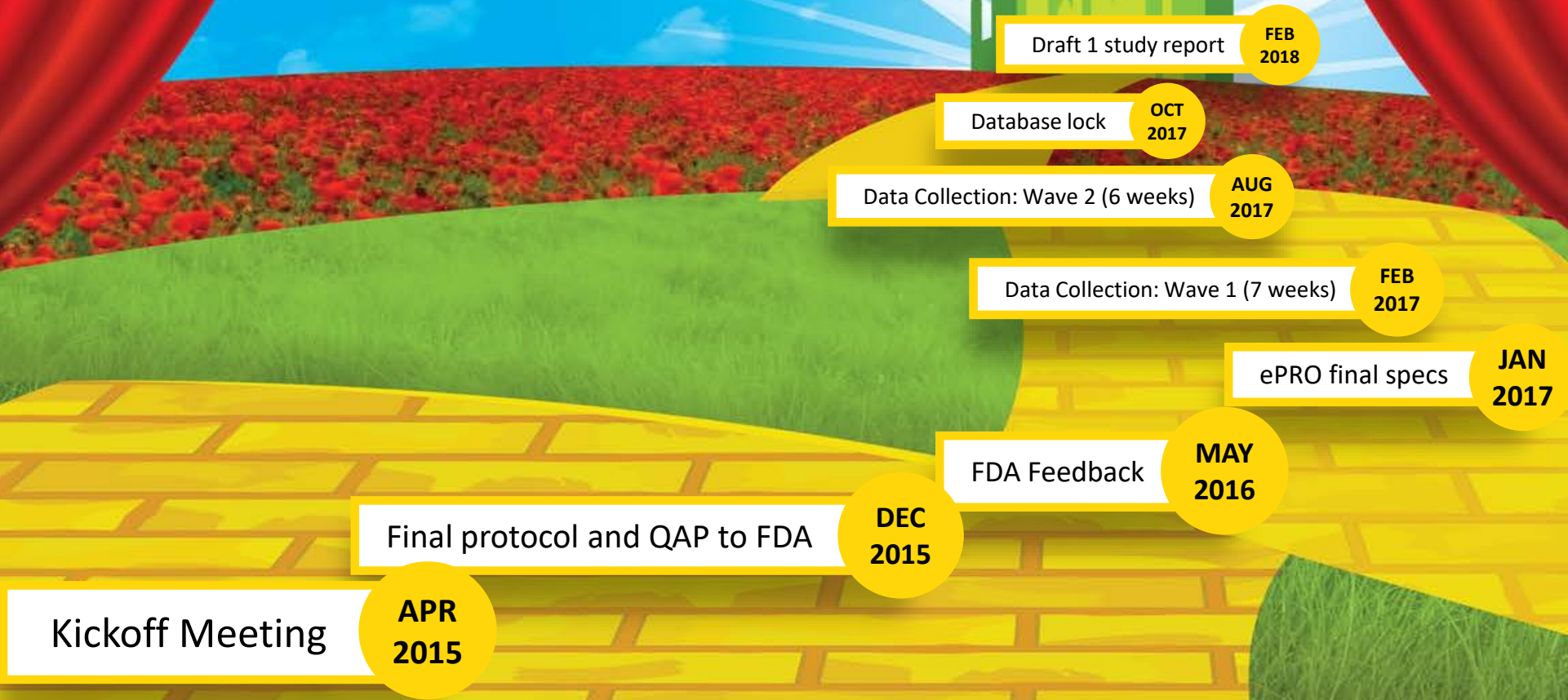
*Now, I've gotten a good hair cut,  
I'm walking and talking and setting  
completely unrealistic goals for  
college...*

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# DIBSS Development Timeline: *Stage 2 Quantitative Pilot Study*



# Quantitative Pilot Study Objectives



- To facilitate cross-sectional quantitative evaluations of each version of the *DIBSS*
  - Inform finalization of the 3 diaries (*DIBSS-C/D/M*)
    - Select better measure of stool consistency
    - Determine whether any item reduction needed/appropriate
  - Gather evidence to support measurement properties
    - Test-retest reliability, internal consistency of the abdominal symptom composite, construct validity, discriminating ability
  - Inform selection of optimal endpoints
  - Assess the utility and feasibility of event-based data collection for future studies using the new IBS symptom diaries

# Quantitative Pilot Study Design



- 10-site observational study
- Inclusion/exclusion criteria consistent with qualitative work (slide 15)
- Targeted 315 patients with IBS (approximately 105 of each subtype)
  - Target: minimum of 35 males
  - Target: minimum of 65 non-white subjects
  - Target: no more than 25% reporting less than a 3 for average abdominal pain in the 7 days prior to enrollment (on a 0 to 10 NRS)
- PRO data collected via handheld electronic diary developed and deployed by Bracket
- 17 days of data collection (3 days of training + 2 weeks of data for evaluation)

# Study Assessment Schedule



Patient-reported Assessments	Screening	Visit 1	Days 1-3 Training	Days 4-9	Day 10	Day 11-16	Day 17
Screening items	•						
Demographic and medical history items (including average abdominal pain rating)		•					
<i>DIBSS-C/D/M</i>			•	•	•	•	•
Daily medication use item(s)			•	•	•	•	•
Global status items					•		•
<i>GSRS-IBS</i>					•		•
<i>IBS-SSS</i>							•

*DIBSS-C/D/M = Diary of Irritable Bowel Syndrome Symptoms – Constipation/Diarrhea/Mixed*  
*GSRS-IBS = Gastrointestinal Symptom Rating Scale - IBS; IBS-SSS = IBS Symptom Severity Scale*

# Entering a Bowel Movement

Home

Date and Time of Last Data Transmission

Main Menu

Tools

Logout

Main Menu

Report Your Bowel Movement

History of Bowel Movements

IBS End of Day Questionnaire

GSRs/PGIS-IBS

IBS-SSS

Training

Home

?

After tapping on the white box below, please confirm or change the date of your bowel movement.

Select Date

+	+	+
Apr	07	2016
-	-	-

OK Cancel

DIBSS-D v0.1  
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Cancel Next

?

After tapping on the white box below, please confirm or change the time of your bowel movement.

Select Time

+	+	
8	41	AM
-	-	

OK Cancel

DIBSS-D v0.1  
© 2014 Critical Path Institute

Back Cancel Next

Help

Please count each toilet visit during which you passed any amount of stool as a bowel movement.

- Even if little time had passed since you last left the toilet, if you returned and passed stool again, please count this as a separate bowel movement.
- If you passed stool before making it to the toilet (had an accident), please count this as a bowel movement.

DIBSS-D v0.1  
© 2014 Critical Path Institute

OK

# Entering an IBS End of Day Questionnaire

Home

Date and Time of Last Data Transmission

Main Menu

Tools

Logout

Main Menu

Report Your Bowel Movement

History of Bowel Movements

IBS End of Day Questionnaire

GSRs/PGIS-IBS

IBS-SSS

Training

Home

You reported the following bowel movements since your last scheduled EOD Questionnaire:

12JAN2016-11:00AM

Do you have any other bowel movements to report?

Yes

No

Cancel Next

**'Yes' leads into Report Your Bowel Movement directly**

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

0 1 2 3 4 5 6 7 8 9 10

▲ ▲

No abdominal bloating Worst possible abdominal bloating

DIBSS-M v0.1  
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Back Cancel Next

# Pilot Study Sample: Waves of Data Collection



## Two Data Collection Waves Due to Daylight Saving Time Programming Error

### Wave 1 (n = 326)

February 1, 2017 – March 28, 2017

- 81 participants impacted by DST error

### Wave 2 (n = 81)

July 31, 2017 – September 7, 2017

- Of the 81 **Wave 1** participants:
  - 44 repeated the study (*data from Wave 1 excluded in analysis*)
  - 37 new participants

### 363 patients enrolled across both waves

- IBS-C = 108
- IBS-D = 133
- IBS-M = 122

# Pilot Study Sample (N = 363)



- IBS-C: 108; IBS-D: 133; IBS-M: 122
- Majority female (289, 80%); white (304, 84%); not Hispanic (281, 77%); had at least some college education (282, 78%); had not participated in an IBS clinical trial (249, 69%)
- Age ranged from 18 to 85 years; mean (SD): 44.0 (14.9)
- Over-the-counter and prescription use in the past 3 months was reported by 35% and 9%, respectively
- Majority (96%) reported a pain level of at least 3 (0 = no pain and 10 = the worst abdominal pain imaginable; mean (SD): 5.8 (1.8)) for average level of abdominal pain over the past 7 days (prior to enrollment)
- All recruitment targets met or exceeded with the exception of race
  - Targeted 65 (recruited 59) non-white participants



# Stage 2 Quantitative Evaluation: Results



*Lori McLeod, PhD*

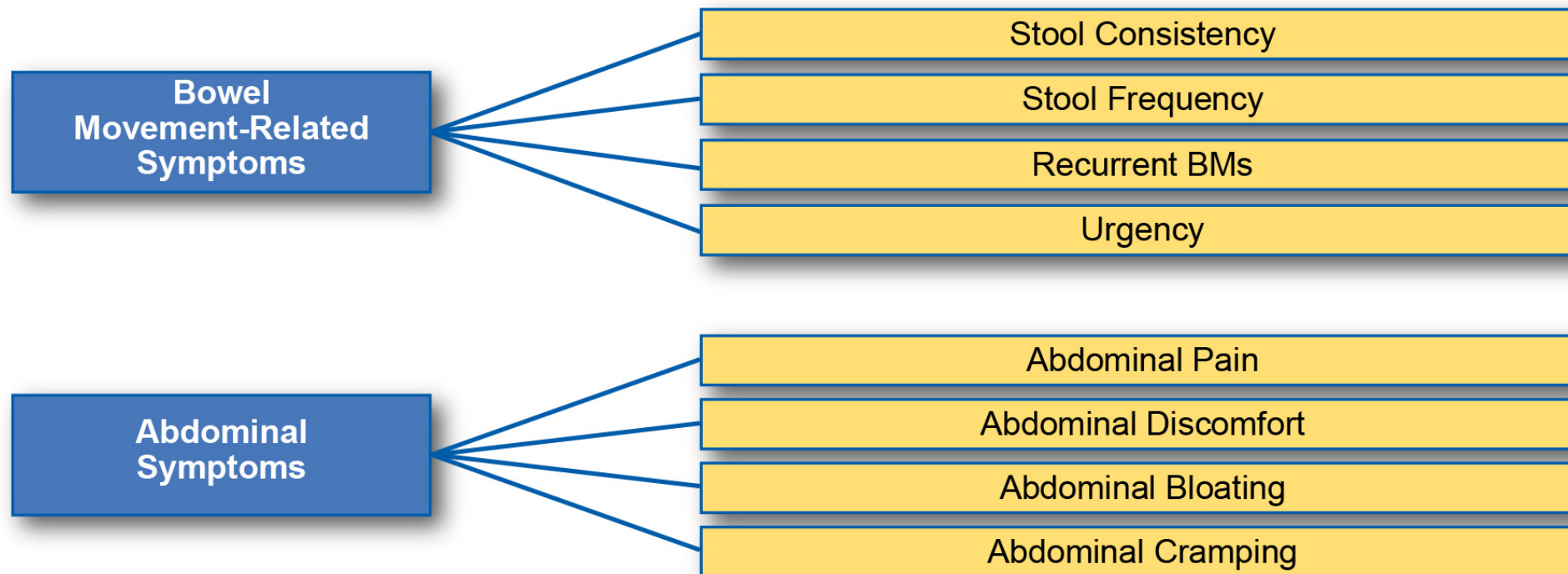
Vice President, Patient-Centered Outcomes Assessment, RTI Health Solutions

# Overview of the Evaluation Methods



Evaluation	Purpose	Brief Description of Method
Descriptive	Evaluate the impact of missing data at the participant and/or item level to inform scoring rules	Percentage of item-level missingness Frequency of missing data
	Assess the use and appropriateness of the response scales, identify possible floor/ceiling effects	Standard descriptive statistics Density plots
Reliability		
Internal consistency	Assess the degree to which the abdominal symptom scores are associated with each other to support an overall score	Cronbach's coefficient alpha
Test-retest	Ensure that outcome scores are consistent across time when the condition has not changed	Intraclass correlation coefficients
Validity		
Construct	Assess whether the <i>DIBSS</i> measures what it is supposed to measure	Correlation between <i>DIBSS</i> outcome scores and supporting measures
Known groups	Evaluate if the <i>DIBSS</i> is able to distinguish between groups that are known to differ	ANOVA by groups

# Conceptual Framework: IBS-D



BM = bowel movement; IBS-D = irritable bowel syndrome with diarrhea.

Note: Stool frequency and recurrent BMs computed based on the number and timing of events recorded in the diary. Two items included to address stool consistency.

# Results: Missing responses IBS-D Abdominal Symptoms (N = 133)



- Daily
  - Large amount of missing responses for all three abdominal symptoms
    - 14 (10.5%) at Day 10 to 29 (21.8%) at Day 11 were missing all three items
  - Rare (less than 2%) for participants to miss any single item if at least one abdominal symptom item was answered
- Weekly
  - Responses on at least 4 of 7 days were required (within each week) to compute a weekly score
  - Minimal missing data for the weekly scores
    - 2 (1.5%) at Week 1 and 4 (3%) at Week 2

# Results: Missing Responses IBS-D BM-Related Symptoms (N = 133)

- 69 (51.8%) participants provided complete BM-related data throughout the entire data collection period. Every day, these participants:
  - Completed the end-of-day diary and confirmed they had no additional BMs to report
  - Responded to all BM-related symptom items for each reported BM
- 115 (86.5%) provided complete BM-related data for at least 12 of the 14 days in the data collection period.
- 124 (93.2%) provided complete BM-related data for at least 10 of the 14 days in the data collection period.
- Only 3 participants (2.3%) ever (across the entire data collection period) failed to answer all of the BM-related symptom items if at least one BM was reported for the day.



# Results: *DIBSS-D* Floor and Ceiling

## *DIBSS-D* Descriptive Statistics for Weekly BM-Related Outcomes (N = 133)

Score	n	Mean (SD)	Median	Min-Max	Floor/Ceiling (%)	Missing (%)
<b>Week 1</b>						
Frequency of BMs	133	13.44 (7.22)	13.0	0.0-39.0	-/-	0 (0.0)
Frequency of BMs without urgency	133	7.29 (5.32)	6.0	0.0-26.0	-/-	0 (0.0)
Frequency of recurrent BMs	133	1.10 (1.88)	0.0	0.0-11.0	-/-	0 (0.0)
Stool consistency 1	132	3.67 (0.66)	3.7	1.6-5.0	-/-	1 (0.8)
Stool consistency 2 (based on <i>BSFS</i> )	132	4.90 (1.15)	5.0	1.0-7.0	-/-	1 (0.8)
Number of days with urgency	133	3.41 (2.15)	3.0	0.0-7.0	8.3/13.5	0 (0.0)
<b>Week 2</b>						
Frequency of BMs	133	13.02 (7.66)	12.0	0.0-41.0	-/-	0 (0.0)
Frequency of BMs without urgency	133	7.10 (5.21)	6.0	0.0-26.0	-/-	0 (0.0)
Frequency of recurrent BMs	133	1.02 (2.04)	0.0	0.0-14.0	-/-	0 (0.0)
Stool consistency 1	131	3.65 (0.66)	3.8	1.7-5.0	-/-	2 (1.5)
Stool consistency 2 (based on <i>BSFS</i> )	131	4.92 (1.08)	5.2	1.9-7.0	-/-	2 (1.5)
Number of days with urgency	133	3.09 (2.13)	3.0	0.0-7.0	8.3/12.8	0 (0.0)

BM = bowel movement; *BSFS* = Bristol Stool Form Scale; *DIBSS-D* = Diary of Irritable Bowel Syndrome Symptoms – Diarrhea; SD = standard deviation.

# Results: *DIBSS-D* Test-retest Reliability

## *DIBSS-D* Test-Retest Intraclass Correlation Coefficients (N = 52)

Outcome	Week 1 to Week 2 ICC (95% CI), n <sup>a</sup>
<b>Abdominal Symptoms</b>	
Abdominal symptom subscale	0.90 (0.83, 0.94), 52
Abdominal bloating	0.84 (0.74, 0.91), 52
Abdominal discomfort	0.89 (0.82, 0.94), 52
Abdominal pain	0.87 (0.78, 0.92), 52
Abdominal cramping	0.90 (0.84, 0.94), 52
<b>BM-Related Outcomes</b>	
Frequency of BMs	0.73 (0.57, 0.84), 52
Frequency of BMs without urgency	0.72 (0.57, 0.83), 52
Frequency of recurrent BMs	0.42 (0.17, 0.62), 52
Stool consistency 1	0.61 (0.40, 0.75), 52
Stool consistency 2 (based on the <i>BSFS</i> )	0.66 (0.47, 0.79), 52
Number of days with urgency	0.64 (0.44, 0.77), 52

**0.73 (0.57, 0.84), 52**

**0.72 (0.57, 0.83), 52**

**0.42 (0.17, 0.62), 52**

**0.61 (0.40, 0.75), 52**

**0.66 (0.47, 0.79), 52**

**0.64 (0.44, 0.77), 52**

BM = bowel movement; *BSFS* = *Bristol Stool Form Scale*; *DIBSS-D* = *Diary of Irritable Bowel Syndrome Symptoms – Diarrhea*; ICC = intraclass correlation coefficient.

<sup>a</sup> Indicates the number of participants with no change on the global status item.

# Results: *DIBSS-D* Construct Validity



	Inter-Outcome <sup>a</sup>										
	AS	AB	AD	AP	AC	BMs	BMs nu	RBM	SC	BSFS	UDays
<b>Abdominal Symptoms</b>											
Abdominal symptom subscale	0.86*	0.94*	0.98*	0.97*	0.96*	<b>0.10</b>	<b>-0.24*</b>	<b>-0.02</b>	<b>0.30*</b>	<b>0.32*</b>	<b>0.34*</b>
Abdominal bloating	0.95*	0.84*	0.92*	0.85*	0.86*	<b>0.07</b>	<b>-0.24*</b>	<b>-0.05</b>	<b>0.26*</b>	<b>0.29*</b>	<b>0.30*</b>
Abdominal discomfort	0.98*	0.94*	0.84*	0.94*	0.91*	<b>0.06</b>	<b>-0.27*</b>	<b>-0.03</b>	<b>0.29*</b>	<b>0.30*</b>	<b>0.32*</b>
Abdominal pain	0.97*	0.88*	0.94*	0.84*	0.95*	<b>0.13</b>	<b>-0.23*</b>	<b>0.00</b>	<b>0.27*</b>	<b>0.31*</b>	<b>0.35*</b>
Abdominal cramping	0.96*	0.86*	0.92*	0.94*	0.83*	<b>0.12</b>	<b>-0.20</b>	<b>-0.00</b>	<b>0.33*</b>	<b>0.34*</b>	<b>0.32*</b>
<b>BM-Related Outcomes</b>											
BMs	<b>0.21</b>	<b>0.20</b>	<b>0.19</b>	<b>0.24*</b>	<b>0.20</b>	0.77*	0.59*	0.64*	0.34*	0.34*	0.52*
BMs nu	<b>-0.16</b>	<b>-0.15</b>	<b>-0.16</b>	<b>-0.15</b>	<b>-0.16</b>	0.70*	0.73*	0.24*	-0.00	0.03	-0.22*
RBM	<b>-0.06</b>	<b>-0.09</b>	<b>-0.10</b>	<b>-0.01</b>	<b>-0.04</b>	0.59*	0.33*	0.56*	0.16	0.17	0.33*
SC	<b>0.27*</b>	<b>0.25*</b>	<b>0.22</b>	<b>0.29*</b>	<b>0.29*</b>	0.30*	-0.03	0.14	0.60*	0.93*	0.38*
BSFS	<b>0.27*</b>	<b>0.24*</b>	<b>0.22</b>	<b>0.31*</b>	<b>0.28*</b>	0.39*	0.08	0.21	0.90*	0.64*	0.37*
UDays	<b>0.42*</b>	<b>0.41*</b>	<b>0.39*</b>	<b>0.43*</b>	<b>0.41*</b>	0.55*	-0.06	0.31*	0.47*	0.49*	0.67*

\*  $P < 0.01$  for hypothesis:  $r = 0$ .

AS = abdominal symptom subscale; AB = Abdominal bloating; AC = Abdominal cramping; AD = Abdominal discomfort; AP = Abdominal pain; BM = bowel movement; BMs = Frequency of BMs; BMs nu = Frequency of BMs without urgency; BSFS = Stool consistency 2 (based on *Bristol Stool Form Scale*); *DIBSS-D* = *Diary of Irritable Bowel Syndrome Symptoms - Diarrhea*; IBS = irritable bowel syndrome; RBM = Frequency of recurrent BMs; SC = Stool consistency 1; UDays = Number of days with urgency.

<sup>a</sup> The correlation between Week 1 and Week 2 are in bold along the main diagonal.

Note: The Week 1 inter-outcome correlations are in the bottom left triangle below the main diagonal; the Week 2 inter-outcome correlations are in the top right triangle above the main diagonal.



# Key Learnings:

## *DIBSS-D* Psychometric Evaluation



- Psychometric evaluation results were strong
  - No concerns related to missing data at the weekly (outcome) level
  - No concerns related to floor/ceiling effects
  - Reliability evidence was positive
    - Abdominal symptom items were strongly related to each other (high Cronbach's alpha) and exhibited excellent test-retest reliability
    - BM-related symptoms were not as stable which is likely due to natural variability in BM frequency (e.g., the exact same number of BMs should not be expected week to week)
  - Construct validity results were positive
    - Correlations with external variables were in the expected direction and generally of the magnitude expected
    - Correlations among the abdominal and BM-related outcomes were not as strong as anticipated, confirming the need for both types of outcomes to be captured in the primary endpoint
  - Known-group validity results were positive especially for global status items addressing the most similar constructs
    - For example, the discriminating ability of the BM-related outcomes was strongest for the global rating of diarrhea

# Key Learnings: *DIBSS-D* Utility and Feasibility



- Real-time collection is feasible!
  - Type of missing data and time to event entry results indicate that participants can comply with a daily and event-based approach
    - Time stamps indicated that it was typical for participants to report BM events throughout the day
- Diary flow is critical!
  - Pattern of missing data suggests that the functionality or flow of the electronic diary was suboptimal
    - Rather than returning to a main menu after adding any missed bowel movements at the end of the day, future designs should flow directly into the end-of-day questions
    - Alarms to indicate the abdominal symptom items have not been completed (even if the end-of-day questionnaire has been accessed) may also be helpful

- Provisional endpoint for IBS-D requires reduction in abdominal pain and improvement in stool consistency based on responder definitions:
  - Abdominal pain: at least a 30% reduction in weekly mean score (on 0 to 10 worst pain NRS) compared with baseline
  - Stool consistency: at least a 50% reduction in the number of days with at least 1 Type 6 or 7 stool (based on the *BSFS*) as compared with baseline

# Key Learnings: IBS-D Potential Endpoints



- Abdominal Symptoms
  - Results support the computation of an abdominal symptom subscale as a component of the primary endpoint in future IBS-D studies
- BM-related Symptoms
  - Selection of this component of the primary endpoint is not as clear as the symptoms are highly related to one another
  - Stool consistency alone (as recommended in the IBS guidance) is likely to be insufficient
  - Urgency was commonly identified as the single most bothersome symptom by qualitative interview participants; stool consistency was least likely to be identified as the most bothersome symptom
  - Number of days with urgency was the only outcome measure that discriminated between participants based on global ratings of diarrhea, abdominal symptoms and overall IBS severity

# Stage 3

# Endpoint Selection and Qualification

# Packages

*Lori McLeod, PhD*

Vice President, Patient-Centered Outcomes Assessment, RTI Health Solutions

# DIBSS Development Timeline:

## Stage 3

### Select Endpoints and Prepare Qualification Packages

**Qualification!**

Full Qualification Package for Exploratory Use: *DIBSS-M* Q3 2019

Full Qualification Package for Exploratory Use: *DIBSS-D* Q1 2019

Full Qualification Package: *DIBSS-C* Q4 2018

Endpoint Finalization Meeting Meeting (All hands) June/ July 2018

# Technology and Implementation Lessons Learned

Adam Butler, Sr. VP, Strategic Development, Bracket

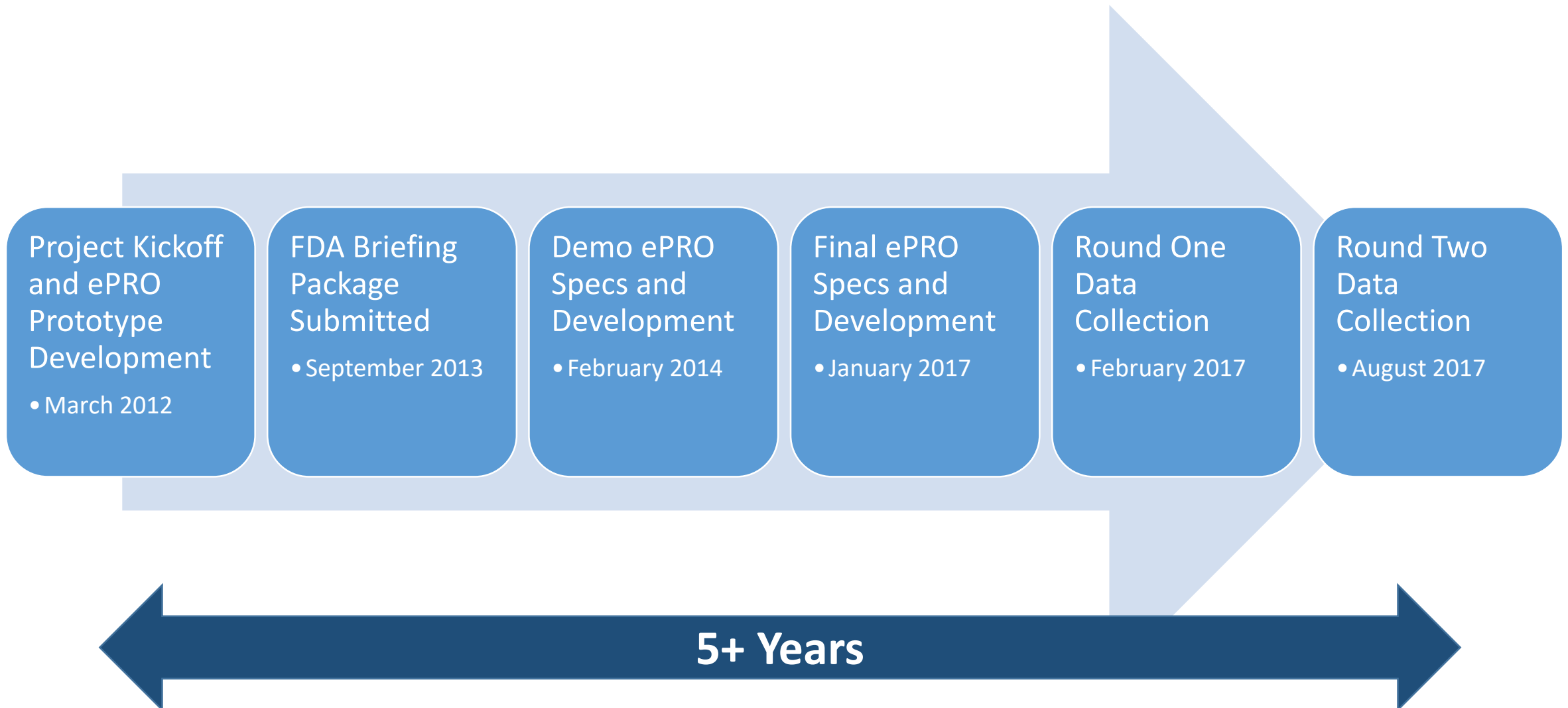
# Technology and Implementation



- Platform Stability and Changes
- Diary Design Challenges
- Project and Team Experience
- Programming Challenges



# Technology and Implementation



# Technology and Implementation



- Platform Stability and Changes
  - The original technology design components of the study began in 2013
  - Hardware, Operating System, and data transmission paradigms all changed during the long lifecycle of this project
  - Windows to Android
  - Cognitive debriefing interviews and Quantitative study happened in different hardware environments

# Technology and Implementation



- Diary Design Challenges
  - IBS-C, IBS-D, IBS-M required collection of both event-driven reports AND a 24-hour recall
  - Alerts design required careful planning to limit alert fatigue and ensure consistent daily reporting
  - Simultaneous development of IBS-C, IBS-D, IBS-M
  - Quantitative Pilot Study required development of GSRS, IBS-SSS
    - Slightly different data requirements and completion schedule

# Technology and Implementation



- Project and Team Experience
  - Lengthy design stage
- Institutional Memory and Project Management
  - Team Turnover
  - Project Evolution

# Technology and Implementation



- Programming Challenges
  - Alerts and Daily Recall structure required some customization
  - Devices were modified and restricted to prevent some device-based updates on clocks and calendars
  - Data collection covered a daylight saving change that wasn't properly configured
- Hardware Challenges
  - Ensure Chargers and Batteries are ready
  - Backup hardware!

# **IBS WG: Lessons Learned Throughout the Journey**

**Robyn T. Carson**

Head, Patient-Centered Outcomes Research, Allergan



**2008:**  
***The Journey Begins***

# Key Aspects to a Successful Journey



**Destination**  
"The End in Mind"



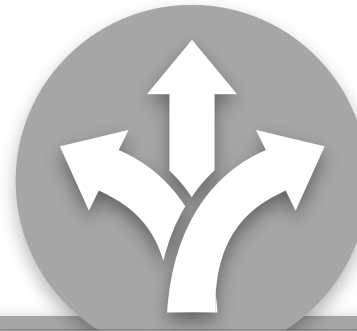
**Budget**



**Travel  
Companions**



**Transportation**



**Directions**



**Activities**



# Lessons Learned: Navigating to Our Destination



## *Challenges:*

**New structure & framework for measurement development with process development occurring in parallel**

**Scientific and regulatory landscape is evolving which impacts scope of work, budget and timelines**

## *Lessons Learned:*

- Manage WG member expectations regarding need for flexibility and evolution
- Consider time & materials consulting as part of scope of work to allow for flexibility
- Willingness to modify our path to accommodate updated guidelines (i.e., qualification process)
- C-Path facilitated communication with FDA ensured WG was aware of current expectations
- Sharing learnings across WGs for standards/best practices useful in documentation development
- Education of internal stakeholders regarding evolving landscape and value of consortium approach critical to ensure continued commitment

# Lessons Learned: Travel Companions



## *Challenges:*

**Assembling a team of committed stakeholders with various backgrounds, interests and skillsets**

**Originally, given the lack of precedence with the Consortium and varied Sponsor interests, WG composed of: FDA, C-Path, Sponsor Companies: Allergan, Ironwood and Takeda, Patient Advocate: IFFGD, RTI-HS, Expert clinicians (Gastroenterologists/Psychologists)**

**WG members knew how to navigate instrument development in their own environments (industry, academia); however, needed to find a common path**

## *Lessons Learned:*

- Critical to have engagement of Regulatory, Clinical colleagues from Sponsor organizations in addition to PRO/HEOR representatives
- Ultimately, the WG adopted more traditional model of engagement with expert thought leaders at key development milestones with resulted in greater operational efficiency
- Education for WG members on methodological expectations for instrument development for regulatory purposes may be useful at beginning of the project

# Lessons Learned: Activities - Qualitative Research



## *Challenges:*

Three instruments required identification & recruitment of three unique patient populations

Need to ensure inclusion & exclusion (I&E) criteria representative of future clinical trial populations given context of use

Interim document review requests from FDA led to challenges with site & patient recruitment and retention

## *Lessons Learned:*

- Input from clinicians (Sponsors and KOLs) critical to aligning on appropriate I&E criteria and how to operationalize in clinical research setting
- May need to oversample some demographic populations
- Collaboration with sponsors to identify experienced study sites in therapeutic area can greatly expedite the data collection process
- Communicate timelines/delays with sites and consider additional compensation for their additional efforts to maintain patient engagement during delays

# Lessons Learned: Activities - Observational Study



## *Challenges:*

**Critical to ensure design build considers scientific intent of instrument and meets objectives for data collection**

**Event-driven approach to data capture introduces complexity to design build and execution**

## *Lessons Learned:*

- Close collaboration is required between the eCOA provider and instrument development team to ensure successful implementation
- Include team members with expertise in both instrument development and eCOA system development (requirements, design, build, implementation)
- Evening diary should be programmed as a continuous flow with appropriate order of items to prevent missing data due to requiring re-entry into the diary to complete each component



**2018: *Approaching Our Destination!***

# Panel Discussion and Q&A



## Moderator

- *Jennifer Hanlon, MPH* – Associate Director, Study Endpoints, Ironwood Pharmaceuticals

## Presenters

- *Claire Ervin, MPH* – Senior Director, Patient-Centered Outcomes Assessment, RTI Health Solutions
- *Lori McLeod, PhD* – Vice President, Patient-Centered Outcomes Assessment, RTI Health Solutions
- *Adam Butler* – Sr. Vice President, Strategic Development and Corporate Marketing, Bracket
- *Robyn Carson, MPH* – Executive Director, Patient-Centered Outcomes Research, Global Evidence & Value Development, Allergan Inc.

## Panelists

- *Stephen Coons, PhD* – Executive Director, Patient-Reported Outcome Consortium, Critical Path Institute
- *Sheri Fehnel, PhD* – Vice President, Patient-Centered Outcomes Assessment, RTI Health Solutions
- *Sarrit Kovacs, PhD* – Reviewer, Clinical Outcome Assessments (COA) Staff, Food and Drug Administration

# Thank You to Additional Contributors!



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- Joseph Lavins, MD
- Jason Lundy, PhD
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- Victoria Soyfer, BS, Med
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