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Measuring symptoms in the irritable bowel syndrome: development of a framework for clinical trials

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SUMMARY

Background
There is uncertainty about how to measure patient-reported outcomes (PROs) in IBS. The Food and Drug Administration (FDA) emphasizes that PROs must be couched in a conceptual framework, yet existing IBS PROs were not based on such a framework.

Aim
To perform qualitative analyses to inform a new conceptual framework for IBS symptoms.

Methods
Following FDA guidance, we searched the literature for extant IBS questionnaires. We then performed interviews in IBS patients to learn about the illness experience in their own words. We cultivated vocabulary to inform a conceptual framework depicted with domains, sub-domains, and item categories, per FDA guidance.

Results
We identified 13 questionnaires with items encompassing 18 symptoms. We recruited 123 IBS patients for cognitive interviews. Major themes included: pain and discomfort are different – asking about discomfort is nonspecific and should be avoided in future PROs; bowel urgency is multifaceted – PROs should measure bowel immediacy, controllability, and predictability; and PROs should divide bloating into how it feels vs. how it looks. Symptom experience may be determined by 35-item categories within five domains: (i) pain; (ii) gas/bloat; (iii) diarrhoea; (iv) constipation; and (v) extraintestinal symptoms.

Conclusions
We applied FDA guidance to develop a framework that can serve as the foundation for developing a PRO for IBS clinical trials.

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INTRODUCTION

Irritable Bowel Syndrome (IBS) is a multi-symptom condition defined by abdominal pain, abdominal discomfort, and abnormalities in stool frequency and form.[1] IBS remains a symptom-based condition that cannot yet be reliably diagnosed or monitored with biomarkers alone; patient report is essential to determine the diagnosis, gauge overall disease severity, develop rational treatment plans and assess outcomes.

Yet, there remains uncertainty about how best to measure patient-reported outcomes (PROs) in IBS. This challenge is at the centre stage for clinicians, investigators, and regulatory agencies such as the United States Food and Drug Administration (FDA). The Rome Foundation conducted an Endpoints and Outcomes Conference in 2009 to help chart a course for optimizing PRO development in IBS and other functional gastrointestinal disorders. The conference proceedings, recently summarized by Chang and Drossman,[2] highlight the importance of developing a PRO that is reliable and valid. An optimal PRO must also be easily administered, able to discriminate between illness severity states, predictable in behaviour when tracked with other indicators of illness severity and readily interpretable.[3] Without a valid and reliable PRO, it is not possible to test adequately the efficacy of existing and novel compounds.

In its PRO guidance document, the FDA emphasizes that an acceptable PRO must be couched in an explicit and evidence-based conceptual framework.[4] A PRO lacking an underlying framework is not acceptable for use in supporting label claims. Even if a PRO demonstrates reliability and validity in psychometric testing, it remains incomplete if there is no framework supporting its structure. Although there are many PROs in IBS,[5] few were developed based on an explicit conceptual framework,[6] and none was derived from a framework built with all the tools outlined in the explicit FDA guidance. In a recent position statement published by the FDA Study Endpoints and Label Development (SEALD) team and the Division of Gastroenterology Products,[6] Trentacosti and colleagues emphasize that existing IBS PROs are sub-optimal, and further indicate that several PRO topics remain unresolved: (i) what patients mean by bowel 'urgency'; (ii) whether there is a difference between abdominal 'pain' and 'discomfort' – an important distinction as the current Rome III IBS diagnostic criteria combine these terms;[1] and (iii) what recall period is acceptable for a questionnaire to capture accurately the frequent dynamic symptom experience of IBS.

In light of the disconnect between FDA guidance and the level of evidence supporting existing PROs, we must delineate a clear conceptual framework for IBS symptoms; this is an essential first step towards creating and validating a PRO for IBS clinical trials. This study provides the basis for a new conceptual framework. We present mixed-methods data from 123 patients with IBS that serve as foundation for this framework, including data regarding the patient perception of bowel urgency, the difference between pain vs. discomfort, and beliefs about what recall period is appropriate across a range of cardinal symptoms. We believe that these results can serve as the foundation for future PRO development.

METHODS

Study overview

To develop a valid and reliable PRO for IBS, it is first necessary to develop and justify an explicit conceptual framework. According to the FDA PRO guidance, an adequate conceptual framework defines the concepts measured by the PRO.[4] The framework must be rendered as a diagram that portrays the hypothesized relationships between item categories, sub-domains, domains and concepts that a future PRO will ultimately intend to measure. For example, a concept in IBS is the 'IBS physical symptom experience' (see Measurement concept, below). This concept may comprise symptom domains, such as pain, diarrhoea, constipation, or extraintestinal symptoms, among others. These symptom domains, in turn, may have sub-domains; for example, 'urgency' might be a sub-domain of diarrhoea. And sub-domains may comprise more granular item categories; for example, 'controllability' or 'predictability' might be item categories of urgency. Item categories are ultimately converted to scripted items that will appear in a future PRO; for example, the item category of 'urgency controllability' might yield a specific item like: 'How well did you control your bowel urgency today?', where options might range from 'without any difficulty' to 'unable to control'.

In light of these distinctions, it is clear that a properly developed framework provides structure for investigators to create a PRO; without the conceptual framework, the PRO developmental process can become random or disorganized. Although the framework may be later updated or changed based on empirical testing, the initial framework should nonetheless be constructed based on the best available information.

As outlined by both the FDA[4] and the NIH Patient Reported Outcome Measurement Information System

(PROMIS) Consortium,[7, 8] multiple steps are necessary to inform the construction of a conceptual framework. First, investigators should conduct a literature review to identify extant questionnaires and scripted items that may relate to the concept of interest. Second, the resulting items should be reviewed and by experts with clinical knowledge of the disease in question; these experts then identify additional item categories that are not represented by the existing items from published questionnaires. Third, the expanded list of candidate item categories should be sorted into an initial structure based on qualitative review by experts. Fourth, investigators must obtain open-ended, qualitative information from patients with the target condition. These patients should have a range of symptom expressions and be demographically diverse. The evaluations must seek information about the patient experience of their illness in their own words, including a description of the cardinal symptoms, the dimensions of those symptoms (e.g. frequency, severity, bothersomeness, predictability, duration, etc.), and the recall period that best captures those symptoms. The patient elicitations must follow a structured script designed to elicit open-ended feedback. Fifth, investigators must review and categorize the patient feedback to cultivate patient vocabulary and inform the conceptual framework. The sections below outline how we addressed and achieved each of these FDA and PROMIS-recommended steps in developing our IBS symptom conceptual framework.

Measurement concept

The measurement concept of interest for our framework is the IBS physical symptom experience. We focused on physical symptoms because these are generally the primary outcome in IBS clinical trials.[2, 5, 9] This is in contrast to other important symptoms and concepts, including IBS emotional symptoms, IBS cognitions, IBS health-related quality of life, and IBS work productivity. The term 'Symptom experience' emphasizes that patients experience their underlying disease in many different ways, and those experiences may, or may not, mirror the physiological severity of the disease.[10, 11] An IBS PRO is designed to measure the patients' symptom experience, first and foremost; this may ultimately correlate with objective markers of disease, but that can only be determined in time. Therefore, we sought information regarding the intestinal and extraintestinal physical symptom experience in IBS, as manifested by individual physical symptoms and their dimensions. This is in contrast to the downstream psychosocial or functional impact of these symptoms, as captured by questionnaires such as the IBS-QOL,[12] Visceral Sensitivity Index[13] and IBS Work Productivity Activity Index,[14] among other questionnaires commonly used in IBS clinical research.[15]

Literature search strategy and expert review

We searched PubMed using a structured strategy developed in concert with an expert biomedical librarian. The strategy employed validated search strings for PRO instruments, as developed by PROMIS investigators at the University of Pittsburgh.[16] Appendix S1 provides the details of our search strategy. This yielded previously developed PROs in IBS, from which we extracted a list of intestinal and extraintestinal symptoms. We then compiled these symptoms and presented them to a panel of six IBS experts (L.C., W.C., L.H., A.L., S.L., B.S.) who evaluated the comprehensiveness of the list, added additional symptoms that were missing and helped to develop bins to group symptoms based on the degree to which they measured a similar concept. The main purpose of binning, as outlined by PROMIS, is to identify item categories and to create a taxonomy linking each item category to the conceptual framework.[17] The next step was to reduce the number of item categories in different bins, also known as winnowing. We deleted (winnowed) item categories from within a bin in accordance with the two PROMIS criteria for elimination: (i) lack of face validity; or (ii) redundancy.[17] The purpose of winnowing was to eliminate inferior item categories rather than to select the best item categories. We applied the PROMIS criteria for redundancy, including semantic redundancy (i.e. item categories are identical or nearly identical) and availability of a superior alternative (i.e. another item category from the same bin is superior). We also applied the PROMIS criteria for rejecting items due to face validity concerns, including inconsistency with the domain definition, vagueness, and confusing or misleading vocabulary. We also winnowed items that were only rarely endorsed (i.e. by only 1 or 2 patients), or that did not appear related to IBS in particular.

Obtaining patient input

We conducted two types of patient elicitations: (i) intensive semi-structured individual cognitive interviews of a cohort of 15 diverse IBS patients, and (ii) online 'virtual cognitive interviews' of 108 IBS patients including both open-ended qualitative probes and close-ended data collection. The UCLA Institutional Review Board approved all patient elicitations.

Individual cognitive interviews. We recruited patients who had been diagnosed with Rome III positive IBS[1] by a gastroenterologist at one of the following locations: Atlanta Gastroenterology Associates, University of California at Los Angeles, and Washington University. We excluded patients if they had alarming signs or symptoms or evidence of a competing organic aetiology for IBS.[18] To enhance generalizability of our sample, we sought a range of patients across demographics, symptom severity profiles, and IBS sub-types.

To create a structure for the cognitive interviews, we conducted whiteboard exercises to delineate attributes of the interviews based on the findings from our systematic review. This resulted in a structured cognitive script designed for a 45-min interview. We designed the interviews to be flexible so that new information and ideas could be positioned within the evolving conceptual model.

Each interview began with an open-ended probe employing the 'think aloud' technique of cognitive interviewing.[19] For example, we instructed patients to 'please tell us what comes to the top of your mind when you think about your IBS symptoms'. Similarly, we explained that 'patients with IBS often experience many different symptoms and describe them in many different ways'. We followed this by instructing the patient to 'list for us, in your own words, each of the most important symptoms that come to mind'.

The interviewer then focused the respondent with a series of directed scripted probes.[19, 20] This technique allowed the interviewer to explore the basis of a response, and to apply the structure of the interview to the open-ended format. For example, if patients used the term 'urgency' to describe their bowel movements, we then asked: 'What does "urgency" mean to you?' We further sought information about the dimensions of individual symptoms. For example, if a patient reported abdominal pain as an important symptom, we then evaluated whether it was the intensity, frequency, duration, predictability, bothersomeness, or impact of the pain (or combination thereof) that led them to choose pain as an important symptom.

Refer to Appendix S2 for the full script, including introductory comments, think aloud instructions, and scripted probes. The interviews were audiotaped and transcribed for subsequent qualitative analysis. The research team then reviewed the dialogue and abstracted each report onto a semi-structured form that included open fields to comment on dominant trends. This qualitative process identified domains, sub-domains, and individual item categories regarding IBS physical symptoms and their dimensions.

Online 'virtual cognitive interviews'. Whereas individual cognitive interviews provide a rich portrait of the patient illness experience, they are limited because of their inherently small sample size. We expanded our patient outreach to a larger sample using 'virtual cognitive interviews' – a technique we have employed in previous PRO research.[21] This approach also helps to ensure that saturation is reached – i.e. enough patients are interviewed so that no new relevant or important information emerges, and that additional patient elicitations are unlikely to provide incremental understanding about the illness experience.[4] For these elicitations, we prospectively recruited patients from the IBS Patient Reported Observed Outcomes and Function (PROOF) cohort. An overview of the PROOF cohort can be found in previous publications.[22, 23] PROOF is an internet-based, longitudinal, observational registry of IBS patients identified within a network of eight geographically diverse U.S. centres, including both University-based and community-based practices.

Patients in PROOF received an email with a link to an online cognitive interview site. The site included the same think aloud and scripted probes as the individual cognitive interviews. Patients entered open-ended responses into essay boxes, as demonstrated in Figure 1. Following the open-ended section of the online interview, we asked patients to select their most bothersome symptom(s) among a list of symptoms established from our review of extant items. Patients selecting individual symptoms were then asked to explain, in their own words, what the symptom means to them. In response to FDA concerns,[6] we specifically asked about how patients define bowel urgency. We also focused on patient definitions of other incompletely understood symptoms, including constipation and bloating. As it remains unclear whether patients distinguish abdominal pain vs. discomfort, we also elicited patients' understanding of the difference. Finally, we asked patients to provide input regarding an optimal recall period for various cardinal IBS symptoms. Refer to https://www.surveymonkey.com/s/5Q2SRGF for the full online cognitive interview and related instructions.

Language cultivation and construction of *a priori* scales

We compiled the results into a written report and analysed the data to cultivate and categorize language used by patients to describe their symptom experience, and to identify domains and items of relevance to patients. We cross-matched this list with the item categories from the literature search and expert input, and added new item

Panel A

Panel B

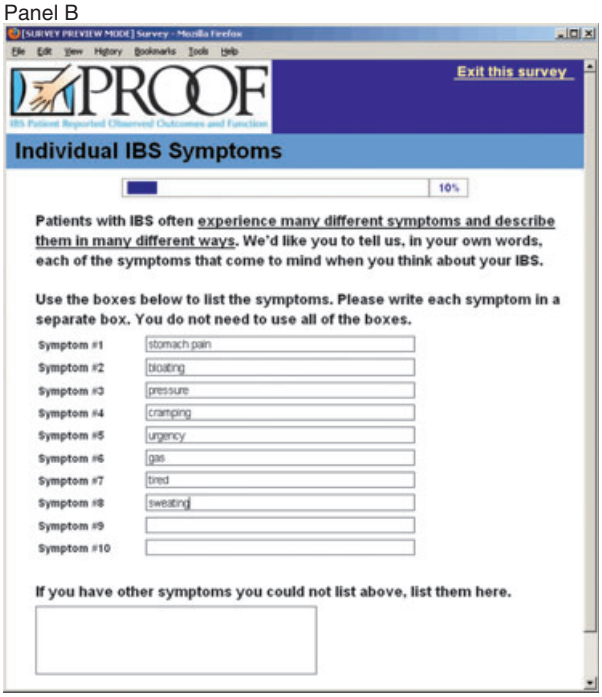

Figure 1 | Sample screenshots from online cognitive interview. Panel A demonstrates the introductory page in which patients were instructed to provide top-of-mind thoughts about IBS symptoms. Panel B demonstrates the instructions for cultivating patient-reported vocabulary about top-of-mind symptoms. Subsequent screens elicited open-ended symptom descriptions.

categories to the growing list of candidate items for the evolving framework. We then created a matrix that categorized symptoms within conceptual categories, and further categorized them by symptom dimensions identified by patients as important, including the frequency (i.e. how often?), intensity (i.e. how bad?), bothersomeness, predictability, and impact (i.e. how much does it interfere with daily activities?) of each symptom. Selection of relevant dimensions was guided by an evaluation of qualitative feedback from cognitive interviews. Finally, based on *a priori* hypotheses, the literature review, expert panel input, and patient input, we developed a conceptual framework using the format required by the FDA PRO guidance.[4]

RESULTS

Literature search strategy and expert review

Our search strategy identified more than 50 previously developed PROs designed for IBS or other functional GI disorders. Of these, we identified 13 that contain items pertaining to IBS-related physical symptoms.[24–33] We developed an initial list of symptoms based on a review of these PROs. Table 1 presents the list of PROs containing IBS symptoms along with 18 symptoms abstracted from the instruments.

Patient cognitive interviews

We recruited 123 patients for cognitive interviews – 15 for intensive one-on-one interviews, and 108 for online elicitations. Table 2 provides characteristics of the samples. The population spanned various demographic characteristics, including race, education and income. Eighteen percent of the cohort had IBS-C, 29% IBS-D and 53% IBS-M using Rome III sub-classification criteria.[1] Using IBS-SSS criteria for symptom severity,[25] 17%, 46% and 37% of patients in the online group had mild, moderate and severe IBS symptoms respectively. The full open-ended feedback from the online elicitations is available at the following site: http://vfg.ResearchCORE.org. The 108 online interviews yielded 49 symptoms, and the 15 one-on-one interviews elicited 24 symptoms (Appendix S3). The sections below summarize major themes that emerged from the interviews.

Symptom endorsement. Figure 2 presents the symptoms most commonly endorsed by patients in open-ended questioning. When asked to 'list each of the most important symptoms that come to mind' patients across all sub-types most commonly cited abdominal pain, bloating and its variants, and flatulence/passing gas. Regarding defecatory symptoms, IBS-C patients frequently reported constipation (66%) in top-of-mind responses for the

Table 1 | Symptom coverage in previously developed patient reported outcome (PRO) IBS legacy instruments. The table presents coverage for PROs that specifically measure IBS intestinal or extraintestinal physical signs and symptoms. Questionnaires that focus on IBS-related cognitions, emotions, or psychosocial impact (e.g. IBS-QOL,[12] VSI,[13] stigma questionnaire, coping questionnaire,[46] etc.) were not included in our review of extant items to remain focused on our clinical trial concept of interest: IBS physical symptom experience

		Legacy instruments												
Symptom grouping	Symptom	GSRS-IBS[24]	IBS-SS[25]	FBDSI[26]	IBS-IS[28]	BSQ[29]	Bristol stool scale[30]	Gastro-Q[31]	FDDQL[32]	Birmingham IBS symptom questionnaire[33]	IBS questionnaire[27]	PAC-SYM[43]	PAC-QOL[44]	BFI[45]
Pain	Abdominal pain	X	X	X		X		X		X	X	X	X	
Gas/bloat symptoms	Bloating	X	X			X		X	X			X	X	
	Distension		X			X		X						
	Rumbling							X	X					
	Gas/Flatus	X						X	X					
Defecatory Symptoms	Diarrhoea/Loose BM	X				X		X		X	X			
	Constipation/ Hard BMs	X				X		X		X	X	X	X	X
	Stool frequency		X								X			
	Stool form		X				X				X	X		
	Urgency	X	X			X		X		X				
	Incontinence							X		X				
	Mucus in stool		X			X		X		X				
	Incomplete evacuation	X	X			X		X				X		X
	Straining	X	X			X		X		X		X		
	Rectal pain							X				X		
Extraintestinal symptoms	Loss of appetite	X				X							X	
	Chest pain							X						
	Fatigue/Tired				X									

Table 2 | Characteristics of patient participants in cognitive interviews

	One-on-one interviews (n = 15)	Online interviews (n = 108)
Age in years (mean ± s.d.)	45 ± 14	42 ± 14
Gender (% female)	67%	79%
Race		
White	53%	78%
Latino	0%	9%
Asian/Pacific Islander	7%	5%
Black	27%	6%
Other	13%	2%
Education		
% Graduated high school	34%	78%
% Graduated college	33%	65%
% Postgraduate education	33%	27%
Income		
% <$50 000 annual	29%	48%
% $50 000 to $100 000 annual	28%	30%
% >$100 000 annual	43%	22%
Employment status (% employed)	67%	66%
Marital status (% married)	67%	59%
IBS subtype		
IBS with constipation (IBS-C)	33%	18%
IBS with diarrhoea (IBS-D)	47%	29%
Mixed IBS (IBS-M)	13%	53%
Unsubtyped IBS (IBS-U)	7%	0%
IBS duration		
% 6 months to 1 year	7%	4%
% 1–2 years	8%	8%
% 2–5 years	20%	20%
% 5–10 years	27%	24%
% 10–20 years	40%	28%
% More than 20 years	0%	14%
IBS pain severity (10-point numeric rating scale)	3.7 ± 2.4	4.7 ± 2.6
Global IBS severity (0–20 rating scale)	7.8 ± 4.7	11.2 ± 5
IBS-SSS trichotomized severity		
% Mild (score of 75–175)	47%	19%
% Moderate (score of 175–300)	53%	44%
% Severe (>300)	0%	37%
Worker Productivity Activity Index (WPAI:IBS)		
% Work week absent from IBS (absenteeism)	3.0%	36%
% Work week impaired from IBS (presenteeism)	31.0%	34.4%

most important symptom, and less frequently reported the specific constipation symptoms of straining (17%), hard stools (11%), or incomplete evacuation (6%) as most important. IBS-D patients reported diarrhoea (60%) and urgency (33%) as most important symptoms, and endorsed frequent stools (18%), loose stools (11%),

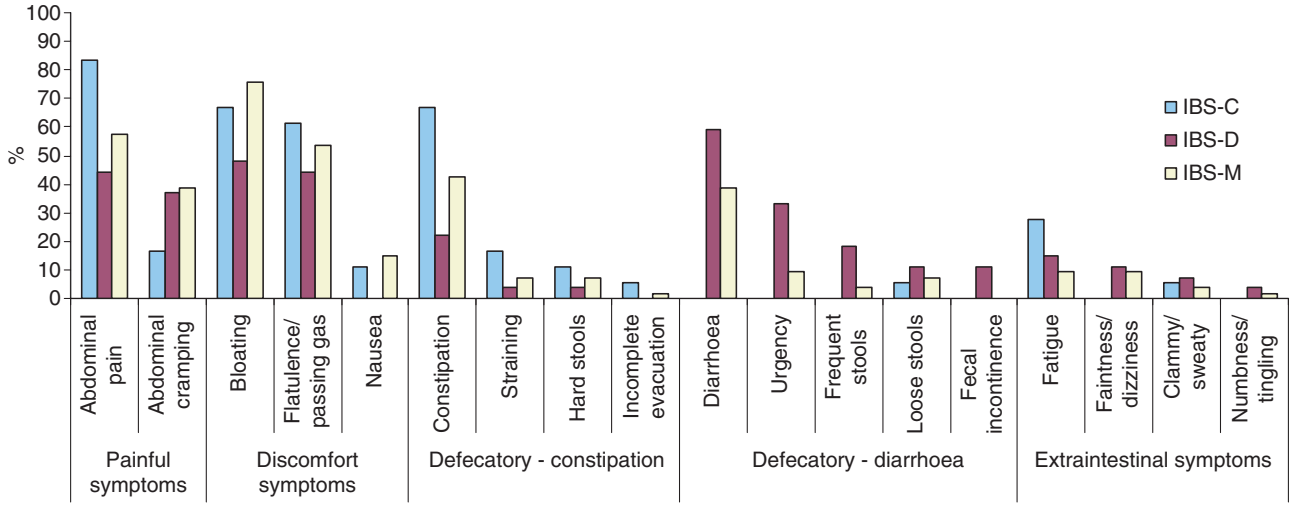

Figure 2 | Symptom endorsement of IBS patients in open-ended interviews. Patients were asked to 'list each of the symptoms that come to mind when you think about your IBS'. The figure depicts the most commonly endorsed symptoms from open-ended responses stratified by IBS sub-type and categorized by symptom type (pain, discomfort, defecatory, extraintestinal). It is important to note that these symptoms were top-of-mind, open-ended responses, not endorsement using a pre-populated checklist of cardinal symptoms. The two techniques are likely to yield different results.

and faecal incontinence or soilage (11%) less commonly. Fatigue was the most common IBS-related extraintestinal symptom reported in top-of-mind responses (28% in IBS-C, 15% in IBS-D and 9% in IBS-M).

Pain vs. discomfort. Eighty-eight percent of patients reported that pain and discomfort are different; 9% said that they were the same and the remainder were unsure. When asked to explain the difference, patients exhibited wide variations in their understanding. In qualitative responses, 14% described pain vs. discomfort as extremes on a shared sensory scale, 36% described them as different symptom categories, and 50% described them in terms of varying functional impact. Refer to Table 3 for sample responses. Other than abdominal pain itself, none of the other IBS intestinal symptoms evaluated was perceived to be predominantly painful, rather >40% of subjects reported each of the IBS symptoms as predominantly uncomfortable, except for straining (36%). Figure 3 presents the full set of data regarding patient perceptions of pain vs. discomfort.

Definition of urgency. There were 38 D-IBS patients in the cognitive interviews of whom 36 reported urgency (mean age = 43; 79% F). In qualitative responses, patients reported four hierarchically ordered characterizations of urgency: (i) simple description of symptom and/or sensory experience (e.g. 'feeling like my gut is going to explode'; 'feeling that faeces is about to explode out of my rectum'); (ii) emphasis on the immediacy of symptom (e.g. 'dropping everything and getting to the bathroom immediately'; 'suddenly have to go without warning'); (iii) emphasis that immediacy impacts controllability (e.g. 'feeling like I can't stop a bowel movement from coming before I reach the bathroom'; 'feeling of "I can't hold it"'); and (iv) emphasis that immediacy and controllability impact psychosocial functioning (e.g. 'fear of not getting there in time'; 'it means not travelling or going out of the house'). Additional quotes for each characterization level are provided in Table 4.

Definition of bloating. Patients generally classified bloating into two major categories: how bloating looks, and how bloating feels. Patients described the look of bloating as 'swollen', 'full of air', 'looking fat', 'looking pregnant', 'puffy', 'rounded out', and 'extended out'. Although some patients described the look of bloating as 'distended', many patients did not know what the word distended means, and suggested that the word sounded 'overly clinical' or 'medical, like something a doctor would say'. Patients described the feeling of bloating as 'a feeling of tightness', 'feeling full of air', 'feeling pressure', 'feeling gassy', 'feeling that I need to pass gas', 'fullness', 'heaviness', and 'uncomfortable'. Although some patients

Table 3 | Example patient descriptions of 'pain' vs. 'discomfort'. Responses are categorized into three qualitative groups, as described further in the text

Pain vs. discomfort: defined as extremes on a shared sensory scale
Pain is more severe. Discomfort is milder.
Discomfort is a mild level of pain.
Discomfort is a slight amount of pain.
Discomfort is mild. Pain is more intense.
Discomfort is milder than pain.
Discomfort is when you're uncomfortable. Pain is when you're in agony.
On a scale of 1 to 5, discomfort to me would be a 1, 2, or 3 while pain would be a 4 or 5.
Pain vs. discomfort: defined as different symptom categories
'Pain' is like a knife twisting. Discomfort is a strong, dull ache throughout my belly.
Belly pain is like sharp, jabbing pain while belly discomfort is more overall aching and upset stomach.
Discomfort is a sense of feeling unwell, uncomfortable. Pain hurts and you want it to be over to stop immediately.
Discomfort is gassy and pain hurts.
Discomfort is just something doesn't feel right and relaxed, as it should, but you can still live your life. Pain is like one step further from discomfort. It feels like a nagging sensation and becomes very difficult to ignore.
Discomfort is a kind of tightness and tenseness in the abdomen.
Discomfort is the pressure, bloating, heaviness, and abnormal sense in the belly. Pain is more associated when 1 have gas, it is more sharp and in one spot. The discomfort is all over my belly and just a general feeling all over.
Discomfort to me is feeling undigested, bloated, full, heavy, all at the same time. Very uncomfortable. Pain is more acute and it hurts. Discomfort is uncomfortable and annoying, but not painful.
I associate pain with cramping and intense shooting or long pain pulses in the abdomen. Discomfort might mean early onset of symptoms or active stomach.
Pain for me is a sharp pain in my lower abdominal area. Discomfort for me is being gassy and bloated.
Pain for me is usually sharp and specific to a location, or a very intense pressure over an area. Discomfort is more dull and unspecific; it's difficult to point out where it ends and difficult to describe how exactly it feels.
Pain hurts. Discomfort just feels like pressure.
Pain hurts... Discomfort is an uncomfortable feeling.
Pain is more shooting, overworked muscles that failed to release any tension in the bowel. I describe discomfort as bloating and feeling 'heavy,' but not painful.
Pain vs. discomfort: defined in terms of varying functional impact
Pain is harder to ignore and more debilitating. Discomfort is more varied in its impact on me.
Discomfort can be bothersome; pain can keep one from daily actions and routines.
Discomfort can be ignored but pain cannot.
Pain is when it's almost debilitating and you can be sitting on the toilet for hours and discomfort is when you can still accomplish tasks, but with some small amount of pain.
Discomfort is bearable and does not stop my day. Pain can often be so bad I am doubled over and will throw up.
Discomfort is something that you can work through and pain stops you from doing anything at all.
Discomfort is tolerable and will pass while pain can be intolerable and sometimes never passes.
Discomfort is unpleasant, but not truly painful. Pain full on hurts and impacts my ability to perform normal tasks.
Discomfort is you are not comfortable but the discomfort is tolerable. Pain hurts and is not tolerable. Like someone is digging a knife in your gut.
Pain interrupts activities while discomfort you ignore to the best of your ability.

described bloating both in terms of look and feel, most patients selected either one or the other category.

Definition of constipation. Consistent with previous work in constipation, patients described constipation using a range of descriptors and sub-symptoms, including: 'hard stools', 'straining to evacuate', 'needing to apply pressure in order to initiate any movement', 'straining on bowel movements', 'infrequent bowel movements', 'inability to have a bowel movement', 'inability to have a bowel movement without a laxative', 'unable to evacuate', and 'incomplete bowel movements'.

Gender differences. As previous data reveal symptom differences between men and women with IBS,[34] we stratified our data by gender (Figure 4). Consistent with a previous meta-analysis from our group,[34] in this study, we found that abdominal pain and constipation were endorsed more frequently in women than in men, whereas diarrhoea and incontinence were more common among men than among women. We did not perform statistical testing on these observations as they emerged from qualitative patient interviews and were not designed for quantitative statistical assessment.

Recall periods. Figure 5 presents data on patient perceptions for the optimal recall period by symptom.

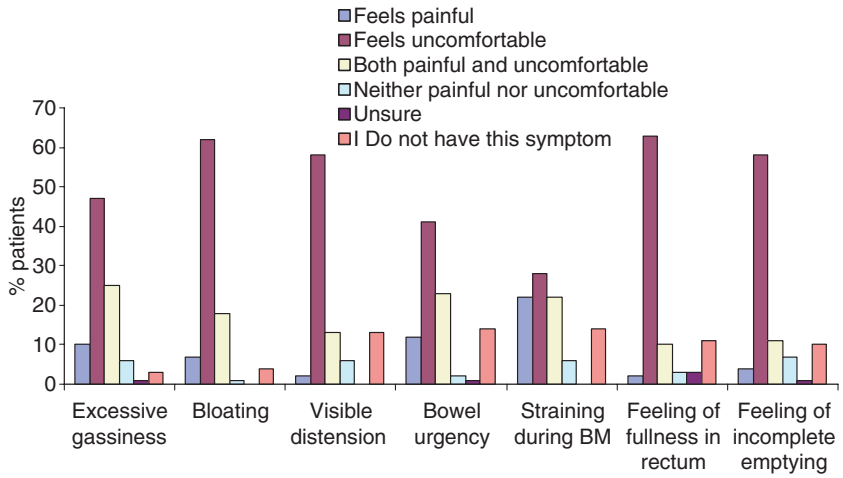

Figure 3 | Patient perceptions of 'pain' vs. 'discomfort' in IBS. Patients were provided a list of cardinal IBS symptoms, and were asked: When you experience each symptom, does it generally feel 'painful', 'uncomfortable', both 'painful' and 'uncomfortable', or neither?.

For most of the symptoms, ≥30% of patients believed that the symptom must be assessed at least daily to capture properly the dynamic shifts in the symptom experience. Defecatory symptoms required less frequent recall periods.

Language cultivation and development of *a priori* scales

Figure 6 presents the conceptual framework that emerged from the data. The framework posits an overall construct of IBS Physical Symptom Experience that is determined by five domains: (i) IBS pain; (ii) IBS gas/bloat; (iii) IBS diarrhoea; (iv) IBS constipation; and (v) IBS extraintestinal symptoms. Each of these domains is discussed further, below.

IBS pain. Irritable Bowel Syndrome pain is manifested by the dimensions of abdominal pain. Most patients stated that their abdominal pain is multifaceted, and that some pain dimensions drive illness severity more than others. Specifically, patients indicated that the intensity, frequency, bothersomeness and predictability (e.g. ability to tell in advance when a pain episode would occur) all contribute towards their IBS pain experience. This is consistent with previous quantitative analyses of data from our PROOF cohort.[35] In addition, many patients believed that the specific location of their pain is important, and that involvement of more abdominal regions was related to a worse overall pain experience.

Many patients endorsed 'cramping' as an important IBS symptom; these patients consistently believed that cramping is a form of pain, not a stand-alone symptom unto itself. On the basis of this feedback, we concluded that cramping is a descriptor of pain that is subsumed within the IBS Pain domain; a separate cramping domain does not appear to be necessary. In addition to cramping, other commonly employed pain descriptors included 'aching', 'burning', 'throbbing', 'squeezing', 'stabbing', 'twisting', 'jabbing', 'spasm', and 'sharp', among others.

IBS gas/bloat. As previously noted, patients referred to bloating in terms its look and feel. Patients also referred to 'flatulence' as a related, but separate symptom that indicated passing gas (in contrast to gas retention with subsequent visible bloating). Flatulence was largely considered a discomfort symptom grouped within the bloating complex rather than as a defecatory symptom, namely because flatulence most often occurs outside the context of bowel movements. Our framework posits that IBS Gas/Bloat consists of three sub-domains: (i) bloating sensation (i.e. feeling pressure or fullness); (ii) bloating appearance (i.e. belly swollen or larger than usual size); (iii) flatulence (i.e. passing gas). These sub-domains comprise individual items capturing the symptom dimensions deemed important by patients in our cognitive interviews.

IBS diarrhoea. Irritable Bowel Syndrome diarrhoea is the first of two defecatory domains in our conceptual framework. The IBS Diarrhoea domain comprises three sub-domains: (i) bowel urgency (i.e. having to rush to the bathroom); (ii) bowel incontinence (i.e. having 'accidents'); and (iii) stool soilage/leakage. The framework includes items capturing the frequency, form, impact, controllability and predictability of urgency. Although bowel incontinence is unusual in IBS, it was reported by some patients in our cohort, typically using the term 'accidents'. Incontinence was uniformly considered to be on a higher level of psychosocial impact compared with urgency alone; patients believed that incontinence should be separated from urgency as a stand-alone symptom. Finally, many patients described soilage or stool leakage as a separate symptom from

Table 4 | Example patient descriptions of 'urgency'. Patients were asked: 'What does "urgency" mean to you?' Responses are categorized into four levels, as described in the text

Level 1: Description of bowel urgency and its sensory experience
Need to get out the stool that is associated with the pain, once it's evacuated the pain stops.
Diarrhoea.
Feeling like my gut is going to explode.
Feeling that faeces is about to explode out of my rectum.
Sweating and shaking.
Level 2: Emphasis on immediacy
Dropping everything and getting to the bathroom immediately.
Feeling like I have to get the bathroom right now.
Feeling like I need to use the restroom now and if I don't use it I will have an accident.
Have to use the bathroom immediately.
I suddenly have to go without warning and often can't make it to the bathroom in time.
Must go to bathroom immediately.
Needing to find a toilet within a short amount of time frame, like within 1 min.
Rushing to the toilet all the time.
Feeling that I have to go all of a sudden, with no warning.
The immediate need to go to the bathroom.
The need to go immediately.
Running to find a bathroom.
Must run to the nearest clean toilet.
Pain for me is a sharp pain in my lower abdominal area. Discomfort for me is being gassy and bloated.
Pain for me is usually sharp and specific to a location, or a very intense pressure over an area. Discomfort is more dull and unspecific; it's difficult to point out where it ends and difficult to describe how exactly it feels.
Pain hurts. Discomfort just feels like pressure.
Pain hurts... Discomfort is an uncomfortable feeling.
Pain is more shooting, overworked muscles that failed to release any tension in the bowel. I describe discomfort as bloating and feeling 'heavy,' but not painful.
Level 3: Immediacy impacts controllability
Accidents. I have had near accidents and have had accidents because I could not get to the bathroom in time.
Feeling like I can't stop a bowel movement from coming before I reach the bathroom.
Feeling like I need to use the restroom now and if I don't use it I will have an accident. There have been several times where I have had to stop before my destination to find a restroom.
Often can't make it to the bathroom in time.

Table 4 | (Continued)

Feeling of 'I can't hold it'.
Short lead time to get to a toilet, no control.
That I have just moments to get to a toilet or I will have an accident.
Need to go to the bathroom. Almost uncontrollable.
Level 4: Immediacy and controllability impact psychosocial functioning
Fear of not getting there in time.
It means no travelling or just going out of the house.
It means the stress of having to know where a bathroom is at every location. I have not made it before, which was quite frankly, disturbing, and caused post traumatic stress for sure.
Sitting in traffic is sometimes a scary thing. Travel in general is nerve racking.
Worry that I can't reach the bathroom in time.

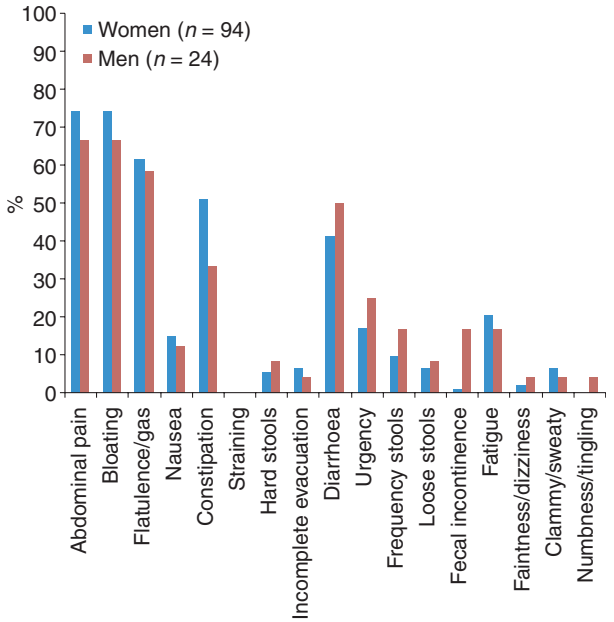

Figure 4 | Symptom endorsement stratified by gender.

urgency or incontinence. These patients explained that soilage in their underpants, for example, was a troublesome symptom that often occurs independent of incontinence or urgency.

IBS constipation. Irritable Bowel Syndrome constipation is the second defecatory domain. It includes items capturing the cardinal sub-symptoms of incomplete evacuation, straining, infrequent stools and hard stools. These symptoms are all included in the Rome III diagnostic battery for constipation,[1] and were independently

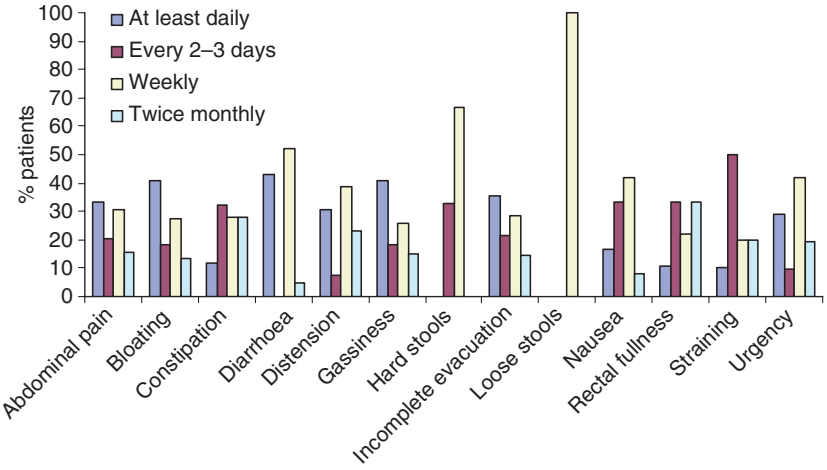

Figure 5 | Patient perceptions of optimal recall period for individual IBS symptoms. Patients were asked: 'If we needed to understand what was going on with your typical [symptom X] over a 1-week period, how often would we need to ask you about this?'.

endorsed by the patients in our cognitive interviews without specific prompting.

IBS extraintestinal symptoms. In addition to GI symptoms, patients endorsed a range of common extraintestinal symptoms attributable to IBS. The most frequently referenced symptoms were the presence of 'fatigue', 'tiredness', feeling 'clammy' or 'sweaty', 'faintness', and 'dizziness'. IBS-D patients, in particular, reported episodes of sweatiness during bouts of urgency, often followed by feeling tired and, in some cases, having to take an unscheduled nap. It is notable that these symptoms may occur in the absence of IBS, yet patients were able to specifically attribute these symptoms to their IBS in particular, as opposed to other conditions or to life in general.

DISCUSSION

There are ongoing efforts to develop a valid and meaningful PRO in IBS.[2] Yet, to date, there are no PROs that meet the guidance set forth by the FDA.[6] In this study, we have laid the groundwork for a future PRO by developing a conceptual framework for measuring IBS symptoms based on the systematic, patient-driven approach required by the FDA and PROMIS. Our study has six main results:

First, on the basis of a systematic review of existing PROs, input from key opinion leaders and open-ended feedback from over 123 IBS patients, we developed a conceptual framework for IBS Physical Symptom Experience (Figure 5). The framework posits that the physical symptom experience comprises two abdominal symptom domains (IBS pain, IBS gas/bloat), two defecatory domains (IBS diarrhoea, IBS constipation) and one IBS extraintestinal symptom domain. Future PRO development will evaluate whether this *a priori* structure is supported by empirical data.

Second, we found that patients perceive their IBS symptoms to be multi-dimensional. This has implications for PRO development. When developing a PRO, it is often unclear whether to measure individual symptoms in terms of frequency (i.e. how often?), intensity (i.e. how bad or severe?), or impact (i.e. how much does it interfere with daily functions?). Rather than arbitrarily selecting a symptom dimension, it is preferable to determine the importance of each dimension using data from patients themselves. Our framework outlines the dimensions patients perceive to be important for each of the cardinal IBS symptoms (Figure 5). For example, we found that abdominal pain is multifaceted in IBS, and that some pain dimensions may drive the illness experience more than others. To understand fully the impact of IBS pain on the overall symptom experience, trialists may need to measure various dimensions of pain including intensity (e.g. using 0–10 point numeric rating scale[22] to measure the lowest, highest and mean daily pain levels), frequency, impact (e.g. 'How much did your pain impact your quality of life today?'), predictability (e.g. 'How well can you tell in advance when you will have pain?'), bothersomeness and location. This approach of measuring several dimensions is consistent with guidance in other chronic pain disorders that emphasize the multi-dimensionality of pain.[36, 37]

Third, we found that patients do not believe that pain and discomfort are the same. This is in contrast to both the Rome diagnostic criteria and IBS PROs that combine pain and discomfort within one symptom category.[1] The FDA recognizes that although clinical trials have employed PROs that group pain and discomfort,[5, 38] it remains unclear if these terms are perceived by patients to be synonymous or different. Understanding this distinction is essential for valid measurement. We therefore elicited IBS patients' understanding of pain vs. discomfort, and found

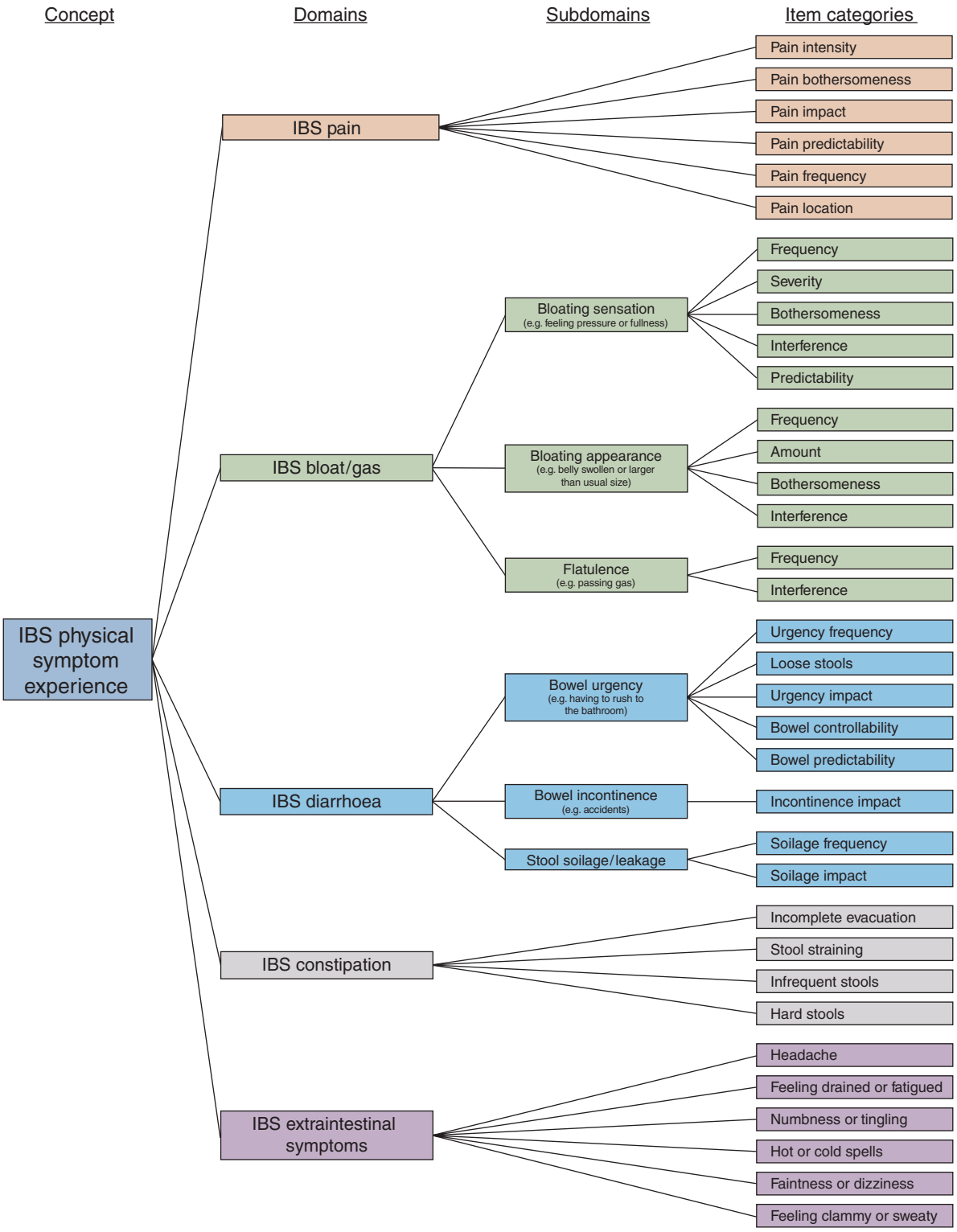

Figure 6 | Conceptual framework of IBS physical symptom experience. The framework proposes that the IBS physical symptom experience is determined by five major domains: IBS pain, IBS gas/bloat, IBS diarrhoea, IBS constipation and IBS extraintestinal symptoms.

that the symptoms are indeed perceived as different by most (88%) patients. Furthermore, we found that discomfort encompasses a range of symptoms such as bloating, gas, fullness, flatulence, sensation of incomplete evacuation and urgency. When asked to explain the difference, patients exhibited wide variations in their understanding. In short, asking patients about discomfort alone is nonspecific because it covers many symptoms and concepts. Future iterations of IBS diagnostic criteria and PROs should distinguish pain from discomfort and further delineate individual discomfort symptoms rather than aggregating under the shared discomfort construct.

Fourth, we found that many IBS-D and IBS-M patients spontaneously use the word 'urgency' to describe their bowel habits; that is, the term is not merely a clinical contrivance. However, all of the subjects had sought health care for their symptoms and it is not known if the term urgency was secondarily adopted by the patient from the providers' terminology. When asked to define urgency, patients described four hierarchically related scales: (i) symptom description stratified by urgency attributes; (ii) immediacy; (iii) controllability; and (iv) psychosocial impact. Moreover, we found that urgency is multifaceted with some symptom attributes driving the illness experience more than others; urgency is not a unidimensional symptom.

Fifth, patients refer to bloating in terms of its look and its feel. The look of bloating is described as 'swollen', 'full of air', and 'looking fat', among other terms. Of note, the words distension and distended, which are commonly employed in both clinical practice and clinical trials, were not widely recognized by patients in our cognitive interviews. The feeling of bloating was variably described as 'tightness', 'feeling full of air', and 'feeling pressure', among other terms. Future PROs should distinguish the look vs. feel of bloating, and should avoid using the term distension as it is not widely employed by patients despite its common use among clinicians.

Last, we found that many IBS patients believe that symptoms must be measured at least daily in order to capture the dynamic nature of their illness experience. This is consistent with the recent FDA recommendation that IBS PROs include daily symptom assessments.[6] Although some symptoms might be measured less frequently (e.g. constipation symptoms), others should probably be measured at least daily (e.g. pain). As the lowest common denominator is daily measurements, future PROs may need to be administered daily until empirical data support less frequent administration. This could be accomplished either by scheduled once-daily questionnaire administrations, or even by momentary assessments at random times of day with a personal digital assistant (PDA) or interactive voice response system (IVRS), as has been recently evaluated by Weinland and colleagues in patients with IBS.[39, 40] Additional research will evaluate the correlations between daily and weekly IBS symptom assessments, as has been performed extensively by Stone and colleagues for somatic pain.[41, 42] It may be that less frequent administration will also be adequate for measuring many physical symptoms in IBS, but before deviating from FDA guidance, we will need empirical data to support alternative schedules. Certainly global endpoints, such as HRQOL, daily functioning, or work productivity, will not require daily administrations – but the FDA guidance is not currently focused on these types of endpoints as primary outcome measures.

Our qualitative analyses have several strengths. We have attempted to follow the FDA PRO guidance[4] explicitly, and have bolstered this with techniques supported by the PROMIS consortium.[8, 17] We began with a literature search using a validated PROMIS search strategy[16] and coupled with input from an expert panel. We relied upon patients with demographic and illness severity variations to maximize the generalizability of our sample. We performed open-ended interviews for cognitive interviews. And we bolstered our one-on-one interviews with a larger sample of online elicitations using 'virtual cognitive interviews'[21] – a process that yielded extensive and detailed responses and helped to achieve thematic saturation.

As with any qualitative effort, our study has important limitations. Although our conceptual framework is explicitly portrayed (Figure 5), its structure must be verified through empirical testing – only time and data will tell. In addition, we did not focus on a single IBS sub-type, but instead included representation from multiple types of IBS, including IBS-D, IBS-C, and IBS-M. However, all IBS groups share the pain, gas/bloat, and extraintestinal symptom domains; they vary only in terms of defecatory symptoms. We found that IBS patients share more symptoms in common than not, and that the pain and gas/bloat domains fall in the centre of the Venn diagrams among symptom groups. A future PRO must be flexible to capture variations in defecatory symptoms among groups, but otherwise should measure common symptoms among groups – there is no strong need to develop independent PROs for different subgroups as this would be contrary to what we have observed in this research. Nonetheless, although IBS sub-types share more symptoms in com-

mon than not, there remain differences among subtypes in terms of the physical, cognitive, and emotional illness experiences of IBS. The PRO development process may benefit from additional research targeting differences in the patient report by sub-type.

Our framework may also be criticized for including extraintestinal symptoms. Extraintestinal symptoms may not be directly attributable to IBS itself, and may also be difficult to impact with gut-directed therapies. However, the FDA and PROMIS emphasize the importance of capturing the illness experience without considering the mechanism of action (MOA) of current or future therapies – PRO development and MOA considerations must be strictly separated. And although IBS is generally conceived as a bowel disorder, as implied by its very name, patients tell us that IBS goes beyond the bowels in its symptom expression. This may ultimately have pathophysiological implications, but we cannot address mechanistic questions at all in this study. However, we can address the IBS illness experience, and our patients indicate that IBS symptoms go beyond the intestines. Moreover, patients believe that these extraintestinal symptoms can be attributed to IBS itself, as opposed to other health conditions or to life in general. Thus, it may be shortsighted to remove the extraintestinal symptoms from an IBS PRO summarily, especially if the rationale is convenience rather than to reflect the patient experience. Ultimately empirical testing will determine whether this domain has a place in the framework.

In conclusion, we have applied mixed-methods qualitative techniques to develop a conceptual framework for measuring the physical symptom experience in IBS. Our model suggests that the symptom experience comprises pain, gas/bloat, diarrhoea, constipation and extraintestinal symptom domains. This framework can now be applied to develop and initially validate a novel PRO for use in future IBS clinical trials.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Search strategy for legacy instruments including items pertaining to IBS symptoms.

Appendix S2. Script for PROOF-Q development patient cognitive interviews.

Appendix S3. Symptoms identified by patients in online and one-on-one cognitive interviews.

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REFERENCES

1. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology* 2006; **130**: 1480–91.
2. Chang L, Drossman DA. Rome Foundation Endpoints and Outcomes Conference 2009: optimizing Clinical Trials in FGID. *Am J Gastroenterol* 2010; **105**: 722–30.
3. Burke LB, Kennedy DL, Miskala PH, Papadopoulos EJ, Trentacosti AM. The use of patient-reported outcome measures in the evaluation of medical products for

regulatory approval. *Clin Pharmacol Ther* 2008; **84**: 281–3.
4. *Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*. Silver Spring, MD: Services USDoHaH, 2009.
5. Camilleri M, Mangel AW, Fehnel SE, Drossman DA, Mayer EA, Talley NJ. Primary endpoints for irritable bowel syndrome trials: a review of performance of endpoints. *Clin Gastroenterol Hepatol* 2007; **5**: 534–40.
6. Trentacosti AHR, Burke L, Griebel D, Kennedy D. Evolution of clinical trials for Irritable Bowel Syndrome: issues in endpoints and study design. *Am J Gastroenterol* 2010; **105**: 731–5.
7. Reeve BB, Hays RD, Bjorner JB, *et al.* Psychometric evaluation and calibration of health-related quality of life item banks: plans for the Patient-Reported Outcomes Measurement Information System (PROMIS). *Med Care* 2007; **45**: S22–31.
8. Cella D, Yount S, Rothrock N, *et al.* The Patient-Reported Outcomes Measurement Information System (PROMIS): progress of an NIH Roadmap cooperative group during its first two years. *Med Care* 2007; **45**: S3–11.
9. ACG. An evidence-based position statement on the management of irritable bowel syndrome. *Am J Gastroenterol* 2009; **104**: S1–35.
10. Grover M, Herfarth H, Drossman DA. The functional-organic dichotomy: postinfectious irritable bowel syndrome and inflammatory bowel disease-irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2009; **7**: 48–53.
11. Long MD, Drossman DA. Inflammatory bowel disease, irritable bowel syndrome, or what?: a challenge to the functional-organic dichotomy. *Am J Gastroenterol* 2010; **105**: 1796–8.
12. Patrick DL, Drossman DA, Frederick IO, DiCesare J, Puder KL. Quality of life in persons with irritable bowel syndrome: development and validation of a new measure. *Dig Dis Sci* 1998; **43**: 400–11.
13. Labus JS, Bolus R, Chang L, *et al.* The Visceral Sensitivity Index: development and validation of a gastrointestinal symptom-specific anxiety scale. *Aliment Pharmacol Ther* 2004; **20**: 89–97.
14. Dean BB, Aguilar D, Barghout V, *et al.* Impairment in work productivity and health-related quality of life in patients with IBS. *Am J Manag Care* 2005; **11**: S17–26.
15. Bijkerk CJ, de Wit NJ, Muris JW, Jones RH, Knottnerus JA, Hoes AW. Outcome measures in irritable bowel syndrome: comparison of psychometric and methodological characteristics. *Am J Gastroenterol* 2003; **98**: 122–7.
16. Terwee CB, Jansma EP, Riphagen de Vet HC II. Development of a methodological PubMed search filter for finding studies on measurement properties of measurement instruments. *Qual Life Res* 2009; **18**: 1115–23.
17. DeWalt DA, Rothrock N, Yount S, Stone AA. Evaluation of item candidates: the PROMIS qualitative item review. *Med Care* 2007; **45**: S12–21.
18. Brandt LJ, Chey WD, Foxx-Orenstein AE, *et al.* An evidence-based position statement on the management of irritable bowel syndrome. *Am J Gastroenterol* 2009; **104**(Suppl. 1): S1–35.
19. Ericsson A, Simon H. *Protocol Analysis: Verbal Reports as Data*. 2nd ed. Cambridge, MA: MIT Press, 1993.
20. Willis G. *Cognitive Interviewing and Questionnaire Design: A Training Manual*. Washington, DC: National Center for Health Statistics, 1994.
21. Spiegel BM, Bolus R, Han S, *et al.* Development and validation of a disease-targeted quality of life instrument in chronic hepatitis B: the hepatitis B quality of life instrument, version 1.0. *Hepatology* 2007; **46**: 113–21.
22. Spiegel B, Bolus R, Harris LA, *et al.* Measuring IBS patient reported outcomes with an abdominal pain numeric rating scale: results from the proof cohort. *Aliment Pharmacol Ther* 2009; **30**: 1159–70.
23. Spiegel B, Harris L, Lucak S, *et al.* Developing valid and reliable health utilities in irritable bowel syndrome: results from the IBS PROOF Cohort. *Am J Gastroenterol* 2009; **104**: 1984–91.
24. Svedlund J, Sjodin I, Dotevall G. GSRS–a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. *Dig Dis Sci* 1988; **33**: 129–34.
25. Francis CY, Morris J, Whorwell PJ. The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. *Aliment Pharmacol Ther* 1997; **11**: 395–402.
26. Drossman DA, Li Z, Toner BB, *et al.* Functional bowel disorders. A multicenter comparison of health status and development of illness severity index. *Dig Dis Sci* 1995; **40**: 986–95.
27. Goka AKSJ. Development and validation of an IBS symptom questionnaire and the relevance of the Rome Criteria to selection of patients for IBS clinical trials. Proceedings of the MWT symposium "Definition of a Responder in Clinical Trials for Functional Bowel Disorders." Vienna, 1998.
28. Longstreth GF, Bolus R, Naliboff B, *et al.* Impact of irritable bowel syndrome on patients' lives: development and psychometric documentation of a disease-specific measure for use in clinical trials. *Eur J Gastroenterol Hepatol* 2005; **17**: 411–20.
29. Talley NJ, Boyce PM, Owen BK, Newman P, Paterson KJ. Initial validation of a bowel symptom questionnaire and measurement of chronic gastrointestinal symptoms in Australians. *Aust N Z J Med* 1995; **25**: 302–8.
30. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol* 1997; **32**: 920–4.
31. Leibbrand R, Cuntz U, Hiller W. Assessment of functional gastrointestinal disorders using the gastro-questionnaire. *Int J Behav Med* 2002; **9**: 155–72.
32. Chassany O, Marquis P, Scherrer B, *et al.* Validation of a specific quality of life questionnaire for functional digestive disorders. *Gut* 1999; **44**: 527–33.
33. Roalfe AK, Roberts LM, Wilson S. Evaluation of the Birmingham IBS symptom questionnaire. *BMC Gastroenterol* 2008; **8**: 30.
34. Adeyemo MA, Spiegel BM, Chang L. Meta-analysis: do irritable bowel syndrome symptoms vary between men and women? *Aliment Pharmacol Ther* 2010; **32**: 738–55.
35. Spiegel BM, Bolus R, Harris L, *et al.* Characterizing abdominal pain in IBS: guidance for study inclusion criteria, outcome measurement and clinical practice. *Aliment Pharmacol Ther* 2010 [Epub ahead of print].
36. Turk DCDR, Allen RR, Bellamy N, *et al.* Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2003; **106**: 337–45.
37. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. *Pain* 1975; **1**: 277–99.
38. Spiegel B, Camilleri M, Bolus R, *et al.* Psychometric evaluation of patient reported outcomes in irritable bowel syndrome randomized controlled trials: a Rome Foundation report. *Gastroenterology* 2009; **137**: 1944–53, e1–3.
39. Weinland S, Morris CB, Hu YJ, *et al.* Pain and bloating symptoms decrease after bowel movements in IBS: a reaffirmation of ROME criteria. *Gastroenterology* 2009; **136**: M1229.
40. Weinland S, Morris CB, Hu YJ, *et al.* Episodes of irritable bowel syndrome – a quantitative examination of IBS-D, C & M symptoms using ecological momentary assessment. *Gastroenterology* 2009; **136**: M1222.
41. Stone AA, Broderick JE, Shiffman SS, Schwartz JE. Understanding recall of weekly pain from a momentary assessment perspective: absolute agreement, between- and within-person consistency,

and judged change in weekly pain. *Pain* 2004; **107**: 61–9.
42. Stone AA, Schwartz JE, Broderick JE, Shiffman SS. Variability of momentary pain predicts recall of weekly pain: a consequence of the peak (or salience) memory heuristic. *Pers Soc Psychol Bull* 2005; **31**: 1340–6.
43. Slappendel R, Simpson K, Dubois D, Keininger DL. Validation of the PAC-SYM questionnaire for opioid-induced constipation in patients with chronic low back pain. *Eur J Pain* 2006; **10**: 209–17.
44. Frank L, Kleinman L, Farup C, Taylor L, Miner P Jr. Psychometric validation of a constipation symptom assessment questionnaire. *Scand J Gastroenterol* 1999; **34**: 870–7.
45. Rentz AM, Yu R, Muller-Lissner S, Leyendecker P. Validation of the bowel function index to detect clinically meaningful changes in opioid-induced constipation. *J Med Econ* 2009; **12**: 371–83.
46. Toner BB, Stuckless N, Ali A, Downie F, Emmott S, Akman D. The development of a cognitive scale for functional bowel disorders. *Psychosom Med* 1998; **60**: 492–7.