Meeting Summary

Report From the Multinational Irritable Bowel Syndrome Initiative 2012

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In 2012, a group of 29 internationally recognized experts in the pathophysiology, diagnosis, and treatment of irritable bowel syndrome (IBS) convened to audit the current state of IBS research. The meeting was preceded by a comprehensive online survey that focused on research needs for IBS diagnosis (particularly the strengths and shortcomings of current criteria), definitions used in clinical trials for IBS patients and "healthy controls," potential biomarkers for IBS, and outcome measures in drug trials. While the purpose of the meeting was not to make binding recommendations, participants developed a framework for future questions and research needs in IBS. First, participants indicated the need for revised criteria for the diagnosis of IBS; in particular, inclusion of bloating and de-emphasis of pain as criteria were considered critical needs. Second, participants noted that definitions of normal, healthy controls varied widely among clinical trials; these definitions need to be standardized not only to improve the reliability of results, but also to better facilitate inter-trial comparisons and data synthesis. Third, participants highlighted the need for accurate biomarkers of disease. Fourth and finally, participants noted that further defining outcome measures, so that they are functionally relevant and reflect normalization of bowel function, is a critical need. Together, the discussions held at this workshop form a framework to address future research in IBS.

On May 18, 2012, a group of world leaders in the study of irritable bowel syndrome (IBS) met and contributed to a survey auditing the current state of IBS research. The meeting, called the Multinational IBS Initiative, was composed of clinician researchers and participants from 5 continents (Appendix). Participants were invited if they were clinical scientists-medical physicians and were directly involved in the treatment of IBS patients on a regular basis. In addition, representatives from the United States Food and Drug Administration (FDA), the National Institute of Health (NIH), IBS patient support groups, and pharmaceutical companies with an interest in IBS were also part of the initiative. The purpose of the meeting was to evaluate the current state of IBS diagnosis, study design, and clinical outcome measures and to evaluate international standards for investigation into the pathophysiology and treatment of IBS. This report serves as a summary of the meeting findings and survey results.

Attendees and Survey

A total of 59 IBS clinician-scientists from around the world were invited to participate in the survey and attend the meeting. In some cases, attendees were not attending Digestive Disease Week (DDW), or had a conflicting meeting and could not physically attend the meeting; in total, 29 of the initial 59 clinician-scientists invited to the meeting were able to attend the live meeting. All invitees were also invited to participate in an online survey. A total of 39 IBS clinician-scientists completed the survey. Further, 11 of these 39 surveys were completed by investigators currently or previously involved in the development of the Rome Criteria for IBS.[1] Participants were required to complete the survey in advance of the meeting to avoid having meeting discussion bias the responses. The survey included 9 questions (Table 1). The validity of selected participants was assessed in 2 ways. First, the group's academic merit in the field was assessed quantitatively by the individual number and total sum of publications. Overall, the group is responsible for a total of 884 functional bowel publications in the medical literature. The average number of publications for the group attending the meeting was 27 (median = 11) in functional disease. Thus, participants were truly clinician-scientists with a heavy emphasis on treating patients with IBS. Of note, representatives from the FDA, NIH, and pharmaceutical companies were not asked to complete the surveys because they do not see IBS patients directly, but were active participants in discussions.

IBS Diagnosis

The first point of the discussion by the group was an evaluation of the validity of the current standards for diagnosing IBS. Four survey questions addressed diagnosing IBS. The first question focused on how participants diagnose IBS in their clinic. Table 1 shows the distribution of answers. Most participants (61.5%) indicated that they diagnose IBS at the bedside based on their

Table 1. Survey Questions and Responses

Survey question	Percentage of responses
1. How many IBS subjects do you see in an average month?	
1–5	6
6–10	14
10–20	29
>20	51
2. What criteria do you use to diagnose IBS in your clinic?	
My own clinical experience	60
Diagnosis of exclusion	23
Manning criteria	14
Kruis criteria	0
Rome I	0
Rome II	11
Rome III	51
3. In your research which criteria do you use to diagnose IBS?	
Manning criteria	0
Kruis criteria	0
Rome I	0
Rome II	31
Rome III	83
4. Do you feel that Rome criteria adequately reflect IBS in your practice/ country?	
Yes	23
No	77
5. What do you feel is the most bothersome symptom among IBS patients you see?	
Abdominal pain	29
Altered bowel habit	17
Bloating	54
Urgency	0
Incomplete evacuation	0
6. Which do you believe?	
IBS is a diagnosis of exclusion	34
IBS is a diagnosis easily made without too many tests	66
7. In case-control studies, how do you define a healthy control when comparing with IBS?	
Subjects who don't have IBS	17
Subjects with no GI disease	20
Subjects with no GI symptoms on a GI checklist	63
Subjects with other GI disorders	0
8. Do you feel we need a new multinational validated criteria for diagnosing IBS?	
Yes	80
No	20
9. Which of the following do you believe would be a good end point in IBS-D trials? (≥1 answer could be selected)	
Unidirectional reduction of stool frequency	20
Normalization of stool form and frequency	77
Reduction of bloating	51
Reduction of abdominal pain	63

own clinical experience. Specifically, few used the standard criteria for IBS. In the second question, investigators were asked which criteria they used most for enrollment in clinical research. In this case, 82.1% stated they used the Rome III Criteria.

The next 2 questions asked the investigators to comment on existing criteria. In the first of these, participants were asked if the existing Rome III Criteria for diagnosing IBS adequately reflect the clinical presentation of IBS in their practice/country. To this question, 79.5% of participants indicated that the current criteria for diagnosing IBS do not reflect IBS as seen in their clinical practices. Interestingly, among investigators previously or currently involved in developing the Rome Criteria, 72.7% felt the existing criteria did not reflect their practice. In the second question about existing criteria, investigators were asked if they felt new criteria were needed (Table 1). From this group, 79.5% of those surveyed felt we need a new international standardized set of diagnostic criteria for IBS. This was followed by 2 additional survey questions. Again, the same 8 of 11 investigators (72.7%) who were/are involved in Rome Criteria effort indicated that new criteria were needed to address significant shortfalls (discussed below).

Formally, the Rome III Criteria require recurrent abdominal pain or discomfort ≥ 3 days/month in the last 3 months associated with ≥2 of the following: 1) improvement with defecation; 2) onset associated with a change in frequency of stool; and 3) onset associated with a change in form (appearance) of the stool.[1] However, one of the pre-meeting survey questions focused on the relative importance of various symptoms of IBS. The response indicated that 53.8% felt that bloating was the most important feature of IBS; only 25.6% felt that abdominal pain was most bothersome.

During discussions regarding the Rome Criteria and the lack of inclusion of bloating, 4 main issues with the current Rome Criteria for IBS were identified. First, and most important, is the lack of multicenter/multinational validation of the criteria. Second, the Rome Criteria do not include bloating, which—as noted above—is considered the most important feature of IBS by many participants. Third, the group consistently indicated that pain is not a primary symptom of IBS. Instead, the group generally agreed that pain is directly linked to the amount of bloating and extent of altered bowel function. The fourth related issue was that current criteria do not include a specific definition of pain or discomfort. Pain cannot be measured directly and must be inferred from self-report and is thus, in the absence of validated pain scales, a necessarily qualitative measure and one that is subject to considerable controversy regarding measurement strategies. How severe does the pain need to be? How often does it need to occur? Participants indicated

that if pain were linked to symptoms (ie, only associated with bloating or bowel function) and not the primary diagnostic indicator, this could be more easily interpreted. The group felt it was ironic that even in the published literature—despite the definition that all IBS subjects must have pain—in many instances bloating was considered the most bothersome symptom.[2, 3] How is it reconcilable that bloating is the most bothersome symptom of IBS, yet it is not included as a primary diagnostic indicator in the Rome III Criteria? While bloating was believed to be the most important symptom, bloating could be as difficult as abdominal pain to quantitate. Impedance plethysmography may be a way to discern bloating from distension, both of which are seen in IBS.[4] In favor of Rome, some participants suggested that the criteria were simple to use in clinical practice, which was felt to be important. However, for research purposes (as opposed to clinical evaluation), participants generally agreed that validation was more important than simplicity.

A few final important comments were made by the group. First, advisors suggested that in many clinical studies, subjects with severe diarrhea (ie, >10 bowel movements per day) may not have had IBS; instead, these subjects may have conditions that mimic IBS with diarrhea but are not amenable to conventional modalities for the treatment of IBS-D. Notably, current Rome Criteria for IBS do not set upper limits on the number of bowel movements per day. Since clinical trials do not require colon biopsies to rule out microscopic colitis, it was felt that either studies should require colon biopsies to exclude microscopic colitis, or IBS severity should have defined limits to avoid enrollment of inappropriate patients.

Participants also noted that most IBS seen in the clinic has mixed features. Recent studies suggest that IBS with constipation and IBS with diarrhea have opposite features, and perhaps mixed features are a hallmark of IBS.[5,6] Another problem that was discussed was the lack of a definition for normal bowel habits. Some participants suggested that a clear definition of normal would help identify patients who are abnormal in the context of functional disease.

The Definition of Normal

The pathophysiology of IBS is complex and its potentially multifactorial nature adds a layer of complexity to its study. For this reason, standardizing the design of clinical trials in IBS, particularly the definition of normal, is critical for assessing the reliability of study results as well as facilitating inter-trial comparison. One of the classic methods for studying IBS pathophysiology is through case-control studies, in which IBS patients are compared with a control group. In the pre-meeting survey, 61.5% of investigators felt that healthy controls should be defined prospectively through the completion of a thorough survey that clearly indicates a lack of symptoms consistent with IBS. However, a recent review of the literature suggested that few case-control studies in IBS or functional disease defined their controls appropriately.[7] Most studies simply stated "healthy subjects," "controls," "did not have IBS," "did not meet Rome Criteria," or other equally vague definitions. The failure to adequately define control groups in IBS trials has significant implications, particularly for inter-trial comparisons. For example, if 2 studies were completed examining the role of serotonin in IBS compared with controls (1 study showing a difference and the other no difference), there would be no way of comparing the 2 studies as the controls could be entirely different. The advisors unanimously agreed that a clear definition for "healthy controls" is imperative for publishing studies in IBS since functional symptoms that are sub-diagnostic for IBS are common. Participants generally agreed that there should be a uniform approach to the recruitment of healthy controls so that studies could be relied upon to be comparable. Furthermore, if a true underlying pathophysiology of IBS is to be identified, initial case-control studies should include "super-healthy" subjects, (ie, subjects with a complete absence of functional symptoms). Subsequent studies could then proceed with the study of IBS compared with subjects who might have functional symptoms but who do not seek medical attention. Such studies would focus on examining symptom severity, healthcare-seeking behavior, and similar issues of critical importance.

In the absence of a well-defined control population that is used universally in clinical trials of IBS, all participants agreed that studies that do not accurately define controls should not be published without explicitly defining the control population in detail. It is clearly inadequate to simply state that "healthy subjects were enrolled" in case-control studies of functional bowel diseases.

Biomarkers

The discussion continued with a focus on biomarkers for IBS. The group unanimously agreed that a biomarker was needed; if identified, a biomarker would validate the condition, and legitimize patient complaints. Two approaches to biomarkers were discussed. First, identification of a direct marker for IBS is clearly the most desirable approach, and steps have been taken in this direction. Second, use of biomarkers to exclude other diseases, such as inflammatory bowel disease, microscopic colitis, and celiac disease, would also provide a route, albeit less direct, to a more accurate diagnosis of IBS.[8]

Table 2. Meeting Summary Points

Category	Issues raised
Diagnosis of IBS	• Criteria for the diagnosis of IBS are subjective and have not undergone multicenter/multinational validation • Pain was not felt to be the most important component of the IBS symptom complex. Instead, participants felt that bloating was felt to be more important than pain and needs to be incorporated in any diagnostic approach
Outcome measures	• Study outcome measures set by the FDA are based on current understanding and it is our prerogative to better define outcomes to guide the FDA • Unidirectional outcome measures in drug development are not sufficient. Better outcome measures would involve normalization of bloating and bowel function (eg, not conversion of constipation to diarrhea)
Defining normal	• In pathophysiology studies of IBS, the definition of the control group must be stated. This includes questionnaires to qualify control groups for enrollment since functional symptoms are common • "Super-healthy" controls may be needed in some studies to better define pathophysiology
Enrolling IBS subjects in study	• It was felt that extreme IBS symptoms might represent undiagnosed conditions such as microscopic colitis. Studies should limit enrollment to less severe symptoms or consider colonic biopsy in the study

Outcome Measures in Drug Trials

The definition of appropriate outcome measures for IBS was a topic of considerable debate. The current FDA guidance on outcomes in IBS clinical trials focuses on stool frequency for IBS-C and IBS-D as follows:[9]

- **IBS-C:** A Stool Frequency Weekly Responder is defined as a patient who experiences an increase of at least one complete spontaneous bowel movement per week from baseline.

- **IBS-D:** 50 percent or greater reduction in the number of days per week with at least one stool that has a consistency of Type 6 or 7 compared with baseline.

To address this outcome, in the pre-meeting survey, investigators were asked what they felt was the best outcome measure for drug trials in IBS (responses could include ≥1 outcome measure). Normalization of stool form/function was selected by 76.9% of participants, 61.5% suggested improvements in pain, and 48.7% suggested improvements in bloating. However, 82.1% indicated that outcomes that describe a unidirectional improvement are unacceptable. For example, in IBS-D, registered trials require "adequate relief of IBS-D" with a decrease in bowel frequency. However, if the drug constipates subjects (in essence a conversion from IBS-D to IBS-C), this would still indicate a successful outcome. Instead, the group indicated that it is of critical importance to develop outcome measures that evaluate the ability of a drug to return patients to normal bowel function. Again, participants emphasized that outcome measures should include bloating, which was felt to be more important than abdominal pain. While there was criticism of these outcomes, the FDA representative pointed out that it was the responsibility of the agency to provide guidance on study outcomes based on the literature. The challenge in IBS pointed out by the FDA was that we have in general done a poor job defining and validating end points. Thus, the FDA uses best judgment to provide draft guidance. The agency was open to new suggestions with proper validation.

Summary and Conclusions

While the purpose of the meeting was not to make binding recommendations, there were many issues raised that require standardization and attention (Table 2). A more scientific, rigorous approach to the study of IBS is needed; in particular, validation of diagnostic criteria is of critical importance. The FDA has defined outcomes of clinical trials based on the literature, because in many cases outcome measures are poorly defined. The FDA has proactively constructed the best possible outcomes given the data.

It is our responsibility as IBS investigators to improve our validation and assist the FDA with better guidance in these matters. Unidirectional outcomes were considered a treacherous approach at best because of the laxative and prokinetic approach to IBS-C and IBS-D, respectively, which fail to address pathophysiology. Bloating is an important symptom in IBS and must be part both of the symptom complex and of the outcome measures of drug trials. Finally, if biomarkers for IBS and the pathophysiology of IBS are to be further elucidated, a uniform approach to selecting control groups is critical.

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Appendix

Participants in the Multination Meeting/Survey

FDA, Rui He; **NIH,** Frank Hamilton; **IBS Investigators,** *Europe:* Giovanni Barbara (Italy), Michele DiStefano (Italy), Jan Tack (Belgium), Lars Agreus (Sweden), Eamonn M. Quigley (Ireland), Lionel Bueno (France), Claudia Defilippi (Italy); *Central/South America:* Hani Albis (Colombia), Carolina Olano (Uruguay), Romulo Vargas (Venezuela), Ana Maria Madrid (Chile), Maria Galiano (Colombia); *Asia:* Varocha Mahachai (Thailand), Sinn Anuras (Thailand), Hyo-Jin Park (South Korea), Reuben Wong (Singapore), Ala Sharara (Lebanon), Seung-Jae Myung (South Korea); *North America:* Max Shmulson (Mexico), Yehuda Ringel (US), Anthony Lembo (US), Baharak Moshiree (US), Mark Riddle (US), William Chey (US), Lin Chang (US), Philip Schoenfeld (US), Christopher Chang (US), Edy Soffer (US), Jeffrey Conklin (US), Paul Moayyedi (Canada), Miguel A. Valdovinos (Mexico), Javier Preciado (Panama), Michael Camilleri (US), Brooks Cash (US), Filippo Cremonini (US), Glenn L. Gordon (US), Yuri Saito (US), Mark Pimentel (US); *Australia:* Nicholas J. Talley.