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

0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2013.04.049

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