

## Consensus report: clinical trial guidelines for pharmacological treatment of irritable bowel syndrome

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### SUMMARY

Appropriate guidelines for clinical trials in irritable bowel syndrome are needed because of the inadequacy of previously performed trials, the use of new and more adequate patient definition, new emerging pathophysiological models and the unique requirements related to the assessment of treatment outcome that, in the absence of a biological marker, can rely only on the evaluation of clinical manifestations. This consensus report highlights the following points. (a) A 4-week period is considered to be adequate to assess drug efficacy for the control of symptoms. (b) For the cyclic and non-life-threatening nature of the disease, a long-term study of 4–6 months or more of active treatment to establish efficacy is considered to be inappropriate in the large majority of patients. (c) In the initial assessment phase of drug efficacy, the withdrawal effect of treatment can be ascertained during a follow-up period prolonged for a sufficient time (4–8 weeks) after stopping treatment. Subsequent trials with proper

withdrawal phase design and duration can then ascertain the drug post-treatment benefit. (d) Considering the intermittent clinical manifestations of irritable bowel syndrome, designing trials with on-demand or repeated cycles of treatment could be envisaged. However, the lack of a definition of what constitutes an exacerbation is a major obstacle to the design of such trials. In the absence of an established gold standard, appropriately justified novel trial designs are welcome. (e) Patients eligible for inclusion should comply with the Rome II diagnostic criteria for irritable bowel syndrome. (f) The main efficacy outcome of the treatment should be based on one primary end-point. (g) The primary efficacy end-point could combine, in a global assessment, the key symptoms (abdominal pain, abdominal discomfort, bowel alterations) of irritable bowel syndrome or rate any single symptom for drugs considered to target specific symptoms. (h) A 50% improvement in the primary efficacy end-point seems to be a reasonable definition of a responder.

### PROCESS FOR THE CREATION OF THE REPORT

The process for the development of this report originated from a project by European academic investigators and

clinicians who reviewed and discussed the 'Points to consider on the evaluation of medicinal products for the treatment of irritable bowel syndrome', released by the European Agency for the Evaluation of Medicinal Products as a draft in April 2002 and as a final document in March 2003.<sup>1</sup>

The six-step process for the creation of this report is outlined below.

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- (a) European academic investigators with clinical and research experience in irritable bowel syndrome, who expressed an interest to submit comments to the above-mentioned draft and document, were invited by E. Corazziari (EC) with the support of the Associazione per la NeUroGastroenterologia e la Motilità Gastrointestinale.
- (b) Each participant submitted independently his/her comments.
- (c) EC then incorporated all comments into a first document based on a literature review with specific reference to published randomized controlled trials, meta-analyses of randomized controlled trials and international consensus reports.
- (d) The European group then met in Rome to discuss and revise the contents of this first document.
- (e) Following this, EC revised the document in accordance with the unanimous consensus achieved during the meeting.
- (f) The document was then resubmitted to all participants of the group for final revision and approval.

All participants have declared, and undersigned, not to have any personal financial interest in this report or in any company involved in trials on irritable bowel syndrome.

## INTRODUCTION

Irritable bowel syndrome is the most common chronic gastrointestinal disorder, with clinical manifestations found in 10–20% of the general population.<sup>2–4</sup>

Although irritable bowel syndrome is not a life-threatening condition, it significantly reduces the quality of life,<sup>5</sup> with a major impact on the well-being and social costs of the community. Direct and indirect medical costs related to the disorder have been found to be considerable.<sup>2, 6</sup> Subjects with irritable bowel syndrome account for a substantial number of physician visits,<sup>3, 7–9</sup> prescriptions,<sup>10</sup> unnecessary tests, inappropriate management and unnecessary surgery.<sup>3, 11</sup>

Pharmacological and non-pharmacological therapeutic options have been shown to have a limited effectiveness on the clinical manifestations of irritable bowel syndrome, and thus there is a real need to improve the efficacy of irritable bowel syndrome treatment.

For the reasons stated above, there has been recent widespread interest in irritable bowel syndrome in the medical community, which has led to standardized

diagnostic criteria, new insight into pathophysiological mechanisms and the development of novel pharmacological therapies. Together with these advances, there has been a parallel increasing need to define appropriate guidelines to assess the efficacy of treatment in clinical trials. The need for appropriate guidelines for clinical trials in irritable bowel syndrome also derives from the analysis of early, inadequately performed, trials<sup>12, 13</sup> and the unique requirements related to the assessment of treatment trials in functional disorders, in which there is a lack of objective outcome measures.

Clinical trials in irritable bowel syndrome are difficult to design because, unlike organic disease entities, irritable bowel syndrome lacks a biological marker and its diagnosis is based on symptom criteria. In addition, as irritable bowel syndrome is not fatal, treatment outcome cannot be assessed with usual measures, such as mortality, survival times or objective improvement of a biological marker, but relies on the evaluation of clinical manifestations reported by patients. Concerns about clinical trials for irritable bowel syndrome and the need for appropriate and standardized guidelines have recently been expressed, mainly as consensus reports by international groups,<sup>14–16</sup> national gastroenterological societies<sup>17, 18</sup> and government agencies.<sup>1</sup>

Major consensus indications for clinical trials on functional gastrointestinal disorders have been standardized by the Rome II consensus.<sup>14</sup> So far, however, there are no specific guidelines for clinical trials in irritable bowel syndrome that are based on a wide international consensus.

The aim of this report is to provide guidelines on the main and specific aspects pertinent to the clinical investigation of drug treatment in irritable bowel syndrome. The guidelines do not pretend to cover all aspects of clinical trials. They deal mainly with those points considered to have major implications for the application and future development of irritable bowel syndrome trial design which, not being fully established, can take advantage of a consensus document. When available, recommendations are based on published randomized controlled trials on irritable bowel syndrome, meta-analyses of randomized controlled trials and international consensus documents on agreed definitions and criteria. In the absence of published evidence, the guidelines report the consensus of this group of European investigators.

Other non-controversial aspects of clinical trials on functional gastrointestinal disorders that can be applied in irritable bowel syndrome are addressed by the Rome II consensus.<sup>14</sup>

## DEFINITION OF IRRITABLE BOWEL SYNDROME

### *Irritable bowel syndrome and functional bowel and abdominal disorders*

Irritable bowel syndrome is defined as a condition comprising a group of functional bowel disorders in which abdominal discomfort or pain is associated with defecation or a change in bowel habit with features of disordered defecation.<sup>3</sup>

Functional bowel disorders in the absence of abdominal pain/discomfort (i.e. functional diarrhoea, functional constipation, unspecified functional bowel disorders and pelvic floor dyssynergia) and abdominal pain/discomfort in the absence of bowel disorders (i.e. functional abdominal pain and functional abdominal bloating) are viewed as separate diagnostic categories by the Rome II consensus<sup>3</sup> and unanimously by this European group.

The three pain-related clinical manifestations — pain relieved with defecation, pain onset associated with looser stools and pain onset associated with increased bowel frequency — are identified by factor analysis as the principal symptom associations in irritable bowel syndrome and are equally reliable in both genders.<sup>19, 20</sup>

The other symptoms — abdominal distension, mucus per rectum and a feeling of incomplete emptying — are less commonly expressed by males than females,<sup>21</sup> and are not identified as principal symptoms of irritable bowel syndrome by factor analysis.<sup>19, 20</sup>

In addition, abdominal pain alone (i.e. not associated with defecation and bowel alterations) or abdominal pain not closely time-related to defecation or bowel alterations may imply a different pathophysiological mechanism and/or an origin other than intestinal.

Thus, strict criteria are necessary to properly discriminate between irritable bowel syndrome and other functional abdominal and bowel alterations.

### *Irritable bowel syndrome subtypes*

Irritable bowel syndrome itself is a heterogeneous condition which, according to the modality of bowel

alterations, comprises three main subtypes of presentation: alternating predominant, diarrhoea predominant and constipation predominant. However, most diarrhoea- or constipation-predominant patients will be found to alternate if followed for a sufficient length of time.<sup>3</sup>

Considering the heterogeneity of clinical presentations and of the underlying pathophysiological mechanisms, it is unlikely that any single drug will be effective for irritable bowel syndrome in general, or in patients with functional bowel disorders not meeting the irritable bowel syndrome definition.

A strict classification criterion of irritable bowel syndrome is thus essential to recruit homogeneous patients for trials. There is evidence to indicate that a positive irritable bowel syndrome diagnosis based on symptoms can be reliably made using Manning,<sup>22, 23</sup> Rome I<sup>24, 25</sup> and Rome II criteria.

The Rome I criteria are more selective than the Manning criteria and identify a subset of patients belonging to the latter group.<sup>26</sup> In comparison with the Rome I criteria, the Rome II criteria are more selective as they identify a subset of the Rome I irritable bowel syndrome patients, mainly affected by functional constipation, and discriminate between them and the remaining patients.<sup>27</sup> Thus, the Rome II irritable bowel syndrome criteria identify a more homogeneous group of patients than the Manning or Rome I criteria.

Classification into constipation- and diarrhoea-predominant subtypes may be relevant when clinical trials attempt to identify a treatment that targets a specific subgroup of irritable bowel syndrome patients and/or require the exclusion of those patients who do not benefit or risk adverse effects from drugs acting on either diarrhoea or constipation. Division into subgroups is likely to prove fruitful, as shown by published trials on diarrhoea-predominant irritable bowel syndrome<sup>28</sup> and constipation-predominant irritable bowel syndrome.<sup>29</sup> Clinical trials should therefore clearly define the subtype(s) of irritable bowel syndrome patients who are eligible in accordance with the Rome II diagnostic criteria.<sup>3</sup>

### *The role of psychosocial co-morbidity*

The majority of irritable bowel syndrome patients seeing a physician for abdominal symptoms are mainly concerned with gastrointestinal disturbances, particularly

abdominal pain.<sup>30</sup> Irritable bowel syndrome patients, however, report more non-gastrointestinal symptoms than the general population,<sup>31</sup> and this behaviour has been related to psychosocial co-morbidity.<sup>20, 32</sup>

Co-morbid psychological status has been found to affect irritable bowel syndrome patients to a variable extent, mostly related to the clinical setting from which the patients are recruited. A co-morbid psychological status has been reported in as many as 60% of irritable bowel syndrome patients in tertiary care centres, and in as few as 16% of irritable bowel syndrome patients diagnosed in general practice.<sup>33</sup>

The presence of a co-morbid psychological status is shared by all chronic disorders, irrespective of whether they are organic or functional,<sup>34</sup> and is expected in 24% of patients with organic gastrointestinal disorders.<sup>35</sup> In inflammatory bowel disease, gastrointestinal and non-gastrointestinal symptoms were reported to be more frequent and more severe by patients with a co-morbid psychological status in comparison with those without.<sup>36</sup>

The observation that chronic irritable bowel syndrome clinic attendees report more severe gastrointestinal and non-gastrointestinal symptoms than recent attendees may reflect the co-morbid psychological status but also, or alternatively, one aspect of illness behaviour.<sup>37</sup> In addition, the disabling effect of a chronic physical illness itself may induce symptoms (such as inability to work or sleep loss), which may be interpreted, especially when assessed with psychosocial evaluation instruments, as being due to a co-morbid psychological status.<sup>38</sup>

It would therefore appear that, in chronic gastrointestinal disorders, including irritable bowel syndrome, the role played by psychological factors in determining clinical manifestations has not been fully established and remains questionable; instead, there is substantial and converging evidence that a co-morbid psychological status, such as increased anxiety or somatization, may determine the care-seeking behaviour.<sup>20, 32, 39</sup>

## THERAPEUTIC OPTIONS

An effective physician–patient relationship, patient education, reassurance and judicious dietary instructions are prerequisites for any treatment of irritable bowel syndrome. Many treatments, both pharmacological and non-pharmacological, have been proposed for irritable bowel syndrome. However, the efficacy of

current therapeutic options is not satisfactory for the following reasons: (i) benefit has been poorly documented for the majority of proposed treatments; (ii) when documented, the benefit is often limited to specific irritable bowel syndrome symptoms, such as diarrhoea, constipation or pain; and (iii) benefit occurs in a limited number of patients, usually not exceeding 10–20%.

### *Non-pharmacological options*

Non-pharmacological options include changes in the fibre content of the diet, both increases and decreases, biofeedback and psychological treatment.

Increasing fibre in the diet and the use of bulking agents have been shown to improve bowel movements in functional constipation without any beneficial effect on abdominal symptoms;<sup>40</sup> their efficacy in irritable bowel syndrome patients has not been clearly established.<sup>41</sup> In addition, a high-fibre diet does not apply in diarrhoea-predominant irritable bowel syndrome and is poorly tolerated by the majority of irritable bowel syndrome patients. In fact, dietary fibre supplements may worsen abdominal discomfort,<sup>42</sup> and some patients benefit from exclusion diets which reduce the fibre content substantially.<sup>43</sup>

Psychological treatment involving psychotherapy, hypnotherapy and relaxation techniques, including biofeedback procedures aimed at managing stress, have been reported to improve some of the symptoms of irritable bowel syndrome.<sup>44–46</sup> However, they have no effect on the symptoms of constipation and constant abdominal pain. The favourable effects of psychological treatment are more evident in patients with overt psychiatric disorders and those with stress-exacerbated symptoms.<sup>47</sup> In addition, psychological treatments have mainly been studied in selected tertiary care patients who have not responded to standard management. Two systematic reviews of the literature have concluded that the efficacy of psychological treatments has not been established<sup>41, 48</sup> and, in any case, they should best be regarded as treatment options in the case of pharmacotherapy failure or as an adjunct to pharmacotherapy.

### *Pharmacological options*

Pharmacological options aim to control irritable bowel syndrome symptoms, bowel alterations and abdominal

pain with drugs mainly targeted to the gastrointestinal tract or the central nervous system.

The majority of the available drugs have been tested and are used in the management of individual symptoms, and not to control the whole range of symptoms inherent in the complex irritable bowel syndrome. Loperamide has been shown to be effective in the control of functional diarrhoea, and osmotic and contact laxatives and polyethylene solution in the control of functional constipation. These agents, however, have no effect on, or may even aggravate, other symptoms, such as pain and bloating.<sup>49, 50</sup> In addition, their use is indicated only as a symptomatic, on-demand treatment in selected patients, as their effect may be unpredictable or even undesirable in the majority of irritable bowel syndrome patients who present with an alternating bowel pattern.

The smooth muscle relaxants, cimetropium bromide, pinaverium bromide, octilonium bromide, trimebutine and mebeverine, have been shown to be more effective than placebo in three meta-analyses.<sup>41, 51, 52</sup> On average, the global symptom improvement with myorelaxants exceeded that of placebo by 22%. However, the benefit was due essentially to their effect on abdominal pain and abdominal distension (18% and 14% over placebo, respectively) with no effect on bowel alterations.<sup>52</sup>

Besides being of limited value, the therapeutic benefit of myorelaxants was demonstrated in clinical trials that were hampered by methodological problems. The trials were performed in non-homogeneous groups of patients who presented with different types of functional bowel alterations and were not selected on the basis of standardized irritable bowel syndrome symptom-based criteria.

Psychotropic drugs, mainly low-dosage tricyclic antidepressants, have been used in non-constipated irritable bowel syndrome patients with abdominal pain as the chief complaint. A meta-analysis based on a few uncontrolled trials indicated that they were useful in about one-third of patients.<sup>53</sup> However, their efficacy has not been assessed in randomized, double-blind, placebo-controlled trials.\*

\*After submission of this article, a randomised, double-blind, placebo-controlled trial has been published showing that the tricyclic antidepressant desipramine may be effective in clinical subgroups of patients with functional bowel disorders (Drossman DA, Toner BB, Whitehead WE, *et al.* Gastroenterology 2003; 125: 19–31.

## GUIDELINES FOR CLINICAL TRIALS

### *Pre-trial baseline observation period*

A baseline observation period is relevant to: (i) assess the severity and duration of irritable bowel syndrome so that they can be compared in active and placebo groups; (ii) regularize eating times and diet; (iii) become familiarized with systems of data collection (e.g. diary cards, electronic diary, etc.); and (iv) assess the psychosocial status with validated instruments, as this may be related to the outcome of treatment.

A lack of knowledge about the natural history of irritable bowel syndrome and the unpredictable fluctuation of symptoms make the choice of duration of the baseline period difficult. The majority of published randomized controlled trials on irritable bowel syndrome treatment have employed a 2-week baseline phase mainly used as a washout, placebo run-in, period.

A 2-week baseline period may be regarded as sufficient time to include patients with minimal severity requirements before randomization. However, although the assessment of a baseline value may be important to demonstrate that various groups have similar disease activities at entry, it should be noted that a placebo run-in is not appropriate as it may result in an undesirable selection bias for many reasons: (i) dropouts due to rapid improvements in symptoms; (ii) different responses of dropouts relative to those entering the trial; (iii) study refusal due to an unwillingness to receive no active medication for a period of time; and (iv) unpredictable prolongation of the placebo effect during the trial period.

### *Timing of the intervention*

This should be carefully considered and standardized so that randomization is not carried out immediately after the performance of reassuring diagnostic investigations. On the other hand, delaying randomization for too long may lead patients to withdraw from the trial.

In addition, whenever possible, diagnostic testing (e.g. colonoscopy), which may affect a patient's perception of his/her complaints, should be avoided immediately before randomization, even if therapy is normally administered immediately after diagnostic tests. However, any change in symptoms during the baseline period, directly related to the patient's knowledge of the results of diagnostic testing, will not introduce bias into

the assessment of the effect of the active treatment, as both the placebo and active treatment groups will be affected in a similar way by these changes and the treatment is evaluated using a direct comparison of these two groups.

A practical solution when diagnostic studies are necessary is to perform them before the 2-week baseline observation period.

#### *Design of the trial*

Considering the absence of a current standard of care, the high placebo response and the time variability of symptoms, it is advisable to design double-blind, placebo-controlled, parallel group trials in irritable bowel syndrome. Trials comparing a new intervention with an established medication may be advisable in the case of treatment aimed at a specific predominant symptom, and when drugs become available with established efficacy in the control of both abdominal pain and disturbed bowel function. A detailed analysis of study designs can be found in the Rome II consensus report.<sup>14</sup>

#### *Duration of the trial*

The duration of the trial, whether short or long, should depend on the expected effect of the drug. However, the spontaneous fluctuations in symptom severity and symptom variability over time make the determination of treatment duration difficult. A study duration of 1–3 months can be considered to be sufficient for most efficacy trials.

More recent trials have used a duration of 12 weeks as recommended by the Rome II international consensus. This duration can be considered to be suitable for the demonstration of the efficacy and safety of a proposed drug.

However, there is no evidence that 12-week trials offer more reliable indications of the efficacy of drugs in irritable bowel syndrome than shorter trials. Klein's critical comments on short trials were not based on published data, but on the reasoning that, as longer irritable bowel syndrome trials showed a decline in treatment efficacy, shorter trials would be even less reliable with regard to the placebo response,<sup>12</sup> which, in the 1980s, was regarded to last, and to be at a maximum, during the first 4 weeks of treatment.

On the contrary, it has been shown that the placebo response increases from the beginning of the trial,

reaches a maximum at between 6 and 12 weeks, decreases and then disappears after 6 months.<sup>13</sup> In addition, three meta-analyses have shown that short- and long-term trials discriminated equally well between active drugs and placebo.<sup>41, 51, 52</sup> It therefore appears that a short-term period of 4 weeks is sufficiently valid to assess the efficacy of a drug in irritable bowel syndrome, as prospective studies have shown that symptoms occur rather predictably more than 50% of the time.<sup>54</sup>

The assessment of drug efficacy in irritable bowel syndrome over a brief period is also clinically sound because a drug that takes a long time to act would not be regarded as therapeutically useful for most irritable bowel syndrome patients. Such a suggestion is also supported by the Rome II consensus: 'It is not unreasonable for studies of short duration to be done first, as one may want to have some evidence of potential efficacy before studies of longer duration are conducted.'<sup>14</sup>

Prolonging the trial period from 4 to 12 weeks will not decrease the placebo response, whereas the intermittent irritable bowel syndrome time course, the level of compliance and the dropout rate may affect the interpretation of drug efficacy in long-term trials. Considering the cyclic and non-life-threatening nature of the disease, a long-term study of 4–6 months or more of active treatment to establish efficacy is considered to be inappropriate in the large majority of patients. It is acknowledged that there is a small subgroup of patients who may require prolonged treatment, but they are likely to be atypical, have a more severe condition and be refractory to most treatment approaches.

Moreover, a long-term study would be likely to pose major problems. It would be hard to persuade a patient to accept the possibility of taking a placebo for a long period. Prolonged placebo treatment may also pose ethical problems. Furthermore, this type of trial is unlikely to determine whether any response is sustained because of the following: (i) the natural variation in symptom severity; (ii) the expected high dropout rate; and (iii) the expected low compliance with drug intake.

It is usual for a period of symptom activity to alternate with a period of inactivity. This time sequence confounds the interpretation of the placebo response. The apparent placebo effect contains two components: spontaneous improvement and the true placebo effect. Spontaneous improvement occurs because, at the start

of the trial, patients will be at the summit of their complaints for two reasons. First, patients present themselves for treatment, and hence inclusion in the trial, when symptoms are at their worst. Second, a minimal severity of symptoms is usually required to qualify for the trial. This well-known phenomenon, called 'regression towards the mean', explains why the level of symptoms does not return to baseline after the end of placebo treatment in most trials.

Due to the increasing spontaneous improvement, the therapeutic gain by the tested drug will be underestimated [therapeutic gain equals (improvement during drug treatment) minus (improvement during placebo treatment)], because both improvements are determined relative to baseline at the start of double-blind treatment. However, this baseline becomes less and less valid, the more spontaneous improvement occurs. Hence, the longer the trial, the more the therapeutic gain is underestimated.

The number of dropouts increases and drug compliance declines with increasing length of the trial, both largely due to a lack of therapeutic effect.<sup>55-57</sup>

In addition, the high degree of statistical compensation for missing data (using imputation techniques), required by the expected large number of dropouts, will lead to an insufficiently robust statistical evaluation of treatment.

The lack of clinical interest and the difficulty in performing such studies are indicated by the fact that there is no experience with 6-month controlled trials in irritable bowel syndrome.

#### *Withdrawal extension phase*

Considering the chronic nature of irritable bowel syndrome, it is of great relevance to determine the long-term efficacy of treatment after the intervention is stopped. However, without knowing a priori the long-term effect of the treatment, serious problems may be encountered in the design of an appropriate withdrawal extension phase.

Re-randomization of all patients to placebo or active treatment at the end of the initial double-blind study has several limitations because: (i) the analysis of efficacy may be limited by the carry-over effect in those patients who cross-over from active drug to placebo; and (ii) any drug effect will be minimized, even a drug with initial superior efficacy, if patients spontaneously improve.

By re-randomization of responders to the active drug only, it would be possible to detect a difference between re-randomization treatments, but there are several methodological limitations.

To incorporate such a randomized withdrawal phase without knowing the duration of the carry-over effect, there is no indication a priori of the duration of the re-randomization period. It would therefore require an undefined extension of a randomized controlled trial to accommodate the unknown duration of carry-over effects, with the inherent practical problems discussed previously. In addition, treatment effects observed in the randomized withdrawal phase may be larger than those seen in an unselected population because the group of patients included in this phase is enriched with responders.

Another possible problem is unblinding of the trial, as patients may recognize that the second treatment has identical side-effects or, on the contrary, lacks the specific side-effects of the first treatment, thus affecting their response to therapy.

To overcome the above-mentioned limitations in the initial assessment phase of drug efficacy, the withdrawal effect of treatment can be ascertained during a follow-up period with no active treatment prolonged for a sufficient time (4-8 weeks) after stopping treatment. Subsequent trials with appropriate withdrawal phase design and duration can then be used to ascertain the drug post-treatment benefit.

#### *On-demand and repeated cycles of treatment*

It is conceivable that, in the future, there may be compounds available for the acute control of symptoms, which can be administered on demand, and for the prevention of relapses.

Considering the intermittent clinical manifestations of irritable bowel syndrome, with periods of well-being alternating with relapses, the design of trials with repeated cycles of treatment may be envisaged.

However, there are, at present, no established formally structured experimental designs for repeated cycles of treatment in irritable bowel syndrome. The most probable major obstacle to the design of trials with drug treatment that can be repeated, as with on-demand or cyclical administration, or given to prevent relapse is the lack of a definition of what constitutes an exacerbation.

In addition, the high degree of patient variation in symptom severity and symptom time patterns (i.e. the

cyclical nature of irritable bowel syndrome), the unpredictability of irritable bowel syndrome, the possible 'carry-over' effects of a treatment of unknown duration, the placebo response, and the decline in compliance and increase in the attrition rate over time all have serious implications for the accurate assessment of treatment effects relative to placebo. Furthermore, if patients are re-randomized between treatment cycles, there will be the risk of unblinding the trial. In addition, the timing of the second treatment cycle is still unclear. The course of exacerbations may be very different after placebo and active treatments, leading to unbalanced groups, and, as mentioned above, there is a risk of unblinding the trial.

In any case, designs for this purpose have not yet been fully evaluated, and the recommendation for repeated cycles of treatment should not be regarded as pivotal for trial design at present. So far, to our knowledge, no randomized controlled trials have been performed with on-demand or relapse-prevention designs. If such compounds become available, as there are no established gold standard designs, investigators should be free to choose novel trial designs that are appropriately justified.

#### *Patient population*

Participants from primary, secondary and tertiary care settings may represent different types of patient and may show different responses to treatment.<sup>30, 58, 59</sup>

Thus, the recruitment of patients from all sources of health-care setting, determined proportionally to the prevalence rate in the different (usually three) levels, is ideal for assessing the efficacy of a drug for universal use.

In this case, the effect of recruitment source on the response may be assessed by secondary multivariate analysis. Alternatively, recruitment of patients from only one health-care setting may introduce problems when generalizing the results to patients in other health-care settings.

The recruitment of respondents from newspaper advertisements is not appropriate as these subjects may show different demographic and cultural characteristics from primary care and referred patients.<sup>30</sup>

#### *Inclusion and exclusion criteria*

Patients eligible for inclusion should: (i) comply with the Rome II irritable bowel syndrome diagnostic criteria (Table 1)<sup>3</sup> and have (ii) a negative physical examina-

tion; (iii) normal complete blood count and sedimentation rate; (iv) absence of ova and parasites in the stool; (v) no fever; and (vi) negative findings at colonoscopy or sigmoidoscopy and double-contrast enema, performed after the onset of irritable bowel syndrome symptoms and within the previous 5 years.

Also eligible for inclusion are patients with the alarm symptom of weight loss, nocturnal symptoms, progressive deterioration of symptoms or a family history of colorectal cancer or inflammatory bowel disease, in whom an appropriate work-up has excluded organic disease and confirmed a diagnosis of irritable bowel syndrome.

When indicated, the Rome II diagnostic criteria can be used to subclassify and include irritable bowel syndrome patients with predominant diarrhoea, predominant constipation or alternating bowel pattern.<sup>3</sup>

The main indications for exclusion are as follows: (i) patients over 50 years of age who have not had a colonoscopy and patients of 50 years or younger who have not had a colonoscopy or sigmoidoscopy (thus excluding organic disease) after the onset of irritable bowel syndrome symptoms and within the previous 5 years; (ii) patients with relevant abnormalities on physical examination that are related to or can explain the irritable bowel syndrome symptomatology; (iii) patients with abnormal blood count or elevated sedimentation rate, presence in the stool of occult blood, and, according to the geographical area, ova and parasites; (iv) patients with clinically evident disturbed behaviour and those affected by major psychiatric disorders; (v) female patients whose symptoms are suggestive of an underlying gynaecological disorder, but including women with symptoms predominantly related to menstruation, as in many women irritable bowel syndrome tends to fluctuate with the menstrual cycle;<sup>60</sup> (vi) patients with suspected lactose intolerance in whom symptoms are resolved on a lactose-free diet; a systematic assessment of lactose intolerance using a lactose tolerance test when screening for irritable bowel syndrome trials is not recommended because the yield is low,<sup>61</sup> and a positive lactose tolerance test does not rule out irritable bowel syndrome as it is performed with more lactose than would normally be ingested;<sup>62</sup> only symptoms that are resolved on a lactose-free diet are likely to be due to lactose malabsorption; (vii) as coeliac disease may produce symptoms consistent with irritable bowel syndrome and has been reported to have a prevalence rate as high as 1 : 111 and 1 : 250,

Table 1. Rome II diagnostic criteria for irritable bowel syndrome

At least 12 weeks or more, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two out of three features:

- 1 Relieved with defecation; and/or
- 2 Onset associated with a change in frequency of stool; and/or
- 3 Onset associated with a change in form (appearance) of stool

To identify irritable bowel syndrome subtypes, refer to the following features:

- 1 Fewer than three bowel movements a week
- 2 More than three bowel movements a day
- 3 Hard or lumpy stools
- 4 Loose (mushy) or watery stools
- 5 Straining during a bowel movement
- 6 Urgency (having to rush to have a bowel movement)
- 7 Feeling of incomplete bowel movement
- 8 Passing mucus (white material) during a bowel movement
- 9 Abdominal fullness, bloating or swelling

Diarrhoea-predominant: one or more of 2, 4 or 6 and none of 1, 3 or 5; or two or more of 2, 4 or 6 and one of 1 or 5 (hard or lumpy stools do not qualify).

Constipation-predominant: one or more of 1, 3 or 5 and none of 2, 4 or 6; or two or more of 1, 3 or 5 and one of 2, 4 or 6.

Alternating-predominant: the alternating presence of the two above conditions.

according to the geographical area,<sup>63, 64</sup> screening patients eligible for irritable bowel syndrome trials with serological markers seems relevant in countries with a high prevalence rate; a cost-effective protocol is to exclude patients who, being positive at anti-transglutaminase antibody screening, are positive to anti-endomysial antibodies.<sup>65</sup>

#### *Concomitant medications*

A large proportion of irritable bowel syndrome patients have simultaneous anxiety or depressive disorders. It appears to be inappropriate to withdraw medications needed by these patients or to exclude them from participation in a trial. Patients with concomitant medications are eligible to participate in a trial if: (i) concomitant medications are needed; (ii) their use has been stable for at least several weeks; (iii) they do not interfere with the drug under investigation; and (iv) symptoms do not coincide with the start of concomitant medical therapy.

#### *Primary efficacy end-point*

The main efficacy outcome of the treatment assessed in the trial should be based on one primary end-point.

Due to the lack of a biological marker, the most important efficacy end-points in the treatment of

irritable bowel syndrome are symptoms. Drugs in irritable bowel syndrome trials can be targeted to: (i) abdominal pain/discomfort associated with bowel dysfunction; or (ii) specific symptoms, such as pain, bloating or bowel alterations.

However, currently, there are no validated measurements or consensus agreement<sup>66</sup> for the assessment of the symptoms of irritable bowel syndrome. In accordance with the Rome II consensus recommendations,<sup>14, 66</sup> the primary efficacy end-point could combine, in a global assessment, the key symptoms (abdominal pain, abdominal discomfort, bowel alterations) of irritable bowel syndrome. As abdominal pain and discomfort are, by definition, necessarily present and associated with a variable expression of bowel alterations, the global assessment will be indicative, in most cases, of the treatment effect on abdominal pain or discomfort when of mild to moderate severity. However, it is worth considering that subgroups of irritable bowel syndrome patients may predominantly complain of abdominal pain or discomfort, and others of an altered defecation pattern. New drugs that relieve specific symptoms (e.g. normalize defecation patterns or relieve abdominal discomfort or pain) may offer significant advantages, even though they may have only minor or no effect on the other key symptoms.

In the case of drugs targeted to one of the specific key symptoms of irritable bowel syndrome, the primary

end-point should be chosen accordingly. This will depend on the aim of the particular treatment and should be justified accordingly.

Other relevant measurements, such as quality of life, psychological status and physiological parameters, which do not reflect a patient's symptoms, may be considered as secondary outcome measures useful for explaining the therapeutic effect.

#### *Outcome measure and definition of a responder*

The use of a global outcome measure of symptom severity, which assesses the combination of pain and bowel alterations, is now well established in irritable bowel syndrome trials.

A specific rating of any single symptom may be appropriate for drugs considered to target this symptom.

The outcome measure should be sensitive to change in the patient's condition so as to detect a variation (deterioration, no change or improvement) in the primary end-point during the trial. Conversely, the change should not be assessed by asking the patient to compare his/her present status to a previous one.

In a condition in which there is very little successful treatment, a 50% improvement in the primary efficacy end-point seems to be a reasonable definition of a responder. A 10–15% improvement of the global outcome measure over placebo could be considered as a clinically significant therapeutic gain.

The analysis of the proportion of responders is a useful way to examine the clinical value of a treatment effect but, by itself, can be misleading if the treatment increases the variance of outcome, e.g. an improvement is obtained in a proportion of patients equal to or less than the proportion deteriorating. It is not possible to rely on the analysis of the proportion of responders without also examining the mean change in score, which provides confirmation that the overall treatment effect is in a beneficial direction, taking the size of all changes into account.

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