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Title: Top 10 research priorities for irritable bowel syndrome: Results of a James Lind Alliance priority setting partnership.

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Irritable bowel syndrome (IBS) is a highly prevalent, chronic, disorder of gut-brain interaction (DGBI), characterised by abdominal pain in association with change in stool form or frequency.¹ It affects 5% of the global population,² and can be difficult to treat, affecting social functioning, ability to work, and quality of life.¹ Impact on quality of life can be worse than other chronic diseases including diabetes, arthritis, and heart failure.³ People would be willing to accept considerable risks from a hypothetical medication in return for cure of symptoms.⁴ The economic impact is substantial, estimated at over £1 billion per year in the UK.⁵ Despite recent successes in the UK, in terms of grant awards to perform clinical trials in the condition,^{6,7} in general, IBS is not viewed as a priority for research funding.⁸

The pathophysiology of, and risk factors for, IBS remain poorly understood.⁹ People living with the condition feel stigmatised due to the potentially embarrassing nature of their symptoms, as well as a lack of understanding from friends, relatives, healthcare professionals, employers, and society as a whole.¹⁰ For example, primary care physicians appear to view IBS as a predominantly psychological disorder.¹¹ There is no biomarker or diagnostic test available for IBS. Instead, a positive diagnosis is made clinically using symptom-based criteria called the Rome criteria, with patients subtyped according to their predominant bowel habit. However, physicians often struggle with this approach, and many still believe IBS is a diagnosis of exclusion.¹² In addition, bowel habit subtypes are unstable; people move between diarrhoea, constipation, or a mixed bowel habit.¹³ Partly because of this, existing drugs are only modestly efficacious,¹⁴ even though they have often been developed to target specific IBS subtypes. Another reason for modest drug efficacy might be because treatment is primarily targeted at bowel symptoms, but IBS is a complex, heterogeneous disorder, with multiple biopsychosocial influences. There may be other subgroups in IBS, beyond those separated according to predominant bowel habit,¹⁵ and these perhaps warrant different treatments. For instance, in people with predominantly bowel symptoms peripherally acting

drugs may be beneficial, but in people in whom psychological symptoms predominate, or in whom both bowel and psychological symptoms coexist and are severe, addressing psychological health at an earlier stage with either gut-brain neuromodulators or behavioural therapies might change the natural history of the disorder and prevent development of refractory symptoms. There is, therefore, an ongoing need for research into the causes of IBS, diagnostic tests for the condition, development of new drugs, or repurposing of existing drugs, and testing more personalised treatment approaches.

Although studies have examined some of these aspects of IBS, the views of people living with the condition are often not considered in such research. One way of addressing this lack of involvement of patients and the public in identifying research priorities is to involve patients, carers, and healthcare professionals caring for people with IBS in a process that puts forward potential future research preferences relevant to all parties and prioritises them. A priority setting partnership dealing with the diagnosis, treatment, and care of people with IBS aged ≥ 16 years was established in cooperation with the James Lind Alliance in the UK in October 2021, funded by Guts UK Charity and the British Society of Gastroenterology.

A modified nominal group method was used, including people living with IBS, their carers, members of patient support groups, and health-care professionals. A steering group was established with equal numbers of people with IBS and their caregivers, as well as professional stakeholders, including nurses, dietitians, psychologists, general practitioners, and gastroenterologists, to decide jointly on all aspects of the priority setting partnership. This included developing a protocol using established James Lind Alliance procedures. The priority setting process was achieved by two public surveys, with 52 UK organisations approached, and efforts made to involve all ethnic and religious groups, followed by a final consensus workshop. In the first survey, from February to April 2022, 3643 respondents,

3362 (92.3%) of whom were people living with IBS or their carers, provided 8638 research questions. These 8638 questions were then processed, with the removal of duplicate or redundant items, questions beyond the scope of the PSP, or suggestions from respondents outside the UK. Following this process, these were distilled into 70 unique questions, and a thorough search of the medical literature was conducted by a trained researcher to confirm these questions remained unanswered by current research. The resulting 65 unanswered questions were listed in a second survey for interim prioritisation, completed between December 2022 and February 2023 by 1784 participants, 1668 (93.5%) of whom were people living with IBS or their carers. The final consensus workshop was held on 2nd March 2023, involving 11 patient representatives, one carer, and 11 health-care professionals. At this conference the 24 questions that received the most votes in the second survey were appraised critically and ranked in three rounds to agree the top 10 research priorities.

These priorities are summarised in Panel 1. They reflect current uncertainties and include questions dealing with how the classification of patients with IBS (beyond changes in stool form or frequency) should be approached when conducting clinical trials, as well as the best treatment(s) for symptoms such as faecal urgency, abdominal pain, and gut sensitivity. All 24 questions, with their ranking, are provided in the Appendix. Effective collaboration between people with IBS, caregivers, patient support organisations, and healthcare professionals, such as this priority setting partnership in IBS, which seeks to answer the questions that are most relevant to the everyday lives of people living with the condition, has the potential to increase quality of care, transform treatment, and improve outcomes in IBS. The top 10 priorities will be publicised widely through the James Lind Alliance, Guts UK charity, and the British Society of Gastroenterology, as well as on social media. It is hoped they will generate considerable interest among researchers and stakeholders in the UK,

leading to grant-giving bodies awarding funding to address these areas of unmet need for people living with IBS and healthcare professionals helping to manage the condition.

ROLE OF THE FUNDING SOURCE

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DECLARATION OF INTERESTS

Christopher J. Black: none. Yvonne A. McKenzie: none. Morgan Scofield-Marlowe: none. Peter Setter: none. Maryrose Tarpey: none. Professor Alexander C. Ford: none.

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Panel: Top 10 Research Priorities for Irritable Bowel Syndrome.

1. Are all forms of IBS the same condition, or are there different types of IBS with different causes and needing different treatments?
2. What causes bowel urgency (a sudden urgent need to go to the toilet) in people with IBS? How is this best treated and managed?
3. What causes pain and/or gut hypersensitivity in people with IBS, including spasms and cramps? Are there better ways to treat and manage these?
4. Could a better understanding of the gut-brain connection in IBS lead to the development of new treatments?
5. Do hormonal changes during the menstrual cycle, pregnancy and menopause affect IBS symptoms? If yes, could this understanding lead to new treatments?
6. How does mental health, particularly anxiety and depression, affect IBS? Do treatments for anxiety/depression reduce or stop IBS symptoms?
7. Are there ways for people with IBS to improve sensitivity in the bowel and/or improve control of their bowels e.g., through training with biofeedback?
8. How can a fast and accurate diagnostic test be developed for IBS? How can different types of IBS be diagnosed more reliably?
9. What changes in diet benefit people with IBS? Which diet is best for the long-term?
10. Are treatments which balance the gut bacteria effective for people with IBS, including faecal transplants? Which prebiotics and probiotics are most effective?