INPLASY PROTOCOL

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The authors declare that there are no conflicts of interest regarding the publication of this paper.

Probiotics, Prebiotics, Antibiotic, Chinese Herbal Medicine, and Fecal Microbiota Transplantation in Irritable Bowel Syndrome: Protocol for a Systematic Review and Network Meta-analysis

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Review question / Objective: **This study is to systematically evaluate the efficacy and safety of five approaches for the treatments of irritable bowel syndrome (IBS), including probiotics, prebiotics, antibiotic, Chinese herbal medicine, and fecal microbiota transplantation. The network meta-analysis will be used to indirectly compare the five treatments to find out the optimal treatment plan for IBS and to provide evidence-based medicine for clinical decision-making. Only randomized controlled trial will be included, and the control is placebo or other one of the five treatments mentioned above.**
Condition being studied: **IBS is a common functional gastrointestinal disorder (FGIDS). Gut is the largest reservoir of bacteria in the body. More and more evidences show that there is a close relationship between intestinal flora and IBS. At present, many therapy to treat IBS are related to the regulation of intestinal flora, and probiotics, prebiotics, antibiotic, Chinese herbal medicine, and fecal microbiota transplantation are the representative therapies. Therefore, it is very important to evaluate the safety and effectiveness of these five treatment methods, and use meta-analysis to carry out indirect comparison of these five treatments.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 May 2020 and was last updated on 12 May 2020 (registration number INPLASY202050047).

INTRODUCTION

Review question / Objective: **This study is to systematically evaluate the efficacy and safety of five approaches for the treatments of irritable bowel syndrome (IBS), including probiotics, prebiotics, antibiotic, Chinese herbal medicine, and fecal microbiota transplantation. The network meta-analysis will be used to indirectly compare the five treatments to find out the optimal treatment plan for IBS**

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Rationale: Meta analysis summarizes the results of multiple independent studies of the same kind to achieve the purpose of increasing the sample size and improving the test efficiency. Ordinary meta analysis can only achieve pairwise comparison, but network meta analysis can achieve indirect comparison of a variety of different intervention approaches, so that some treatment methods that are not directly compared can be indirectly compared to choose the best plan.

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METHODS

Search strategy: The search strategy will include medical subject headings (MeSH) and key words associated with prebiotics, probiotics, antibiotics, FMT, and CHM in the treatment of IBS. All databases will be searched from inception to June.

Participant or population: IBS patients and the diagnostic criteria must meet Manning criteria, Rome I, Rome II, Rome III, Rome IV criteria, or the Kruis score. Subjects are adults aged ≥ 18 years.

Intervention: Oral Chinese herbal medicine treatment under the guidance of syndrome differentiation, and no restrictions on dosage forms, probiotics, prebiotics, antibiotics, fecal transplantation via oral route.

Comparator: Placebo or other intervention in the five treatments mentioned above (Chinese herbal medicine, probiotics, prebiotics, antibiotics, and fecal microbiota transplantation).

Study designs to be included: Study designs to be included is randomised controlled trials.

Eligibility criteria: 1. Types of Study: Randomised controlled trials (RCTs). 2. Participants: We will include studies in which the diagnostic criteria for IBS patients must meet Manning criteria, Rome I, Rome II, Rome III, Rome IV criteria, or the Kruis score. Subjects are adults aged ≥ 18 years. 3. Interventions: Treatment strategies include the following five: probiotics, prebiotics, antibiotic, Chinese herbal medicine, and fecal microbiota transplantation. No restrictions on dosage forms. All 5 methods listed above can be used as monotherapy or combined treatments. Controlled interventions will include placebo or another intervention in the five treatments mentioned above. Studies that do not meet the inclusion criteria or that are difficult to extract data from will be excluded.

Information sources: The following electronic databases will be searched: Embase, Pubmed, Cochrane Central Register of Controlled Trials (CENTRAL), and Chinese Biomedical Literature Database (CBM). We will also search other trial databases, including WHO International Clinical Trials Registry Platform (apps. who.int/ trialsearch/), and ClinicalTrial.gov (www.clinicaltrials.gov) to collect to collect studies.

Main outcome(s): Efficacy assessments of global symptoms cure or improvement.

Additional outcome(s): Effect of therapy on individual IBS symptom scores (abdominal

pain, distension, and urgency), adverse events, etc.

Data management: We will import all retrieved studies into EndNote and then remove any duplicates. Two researchers (WW and RX) will first scan the title and abstract then the full articles will be read when the abstracts lack of the information. The articles will be screened according to the pre-established inclusion and exclusion criteria. Any disagreement will be resolved through discussion, or underwent third-party adjudication.

Quality assessment / Risk of bias analysis: The risk of bias for each study included will be assessed independently by two researchers on the basis of the Cochrane risk-of-bias tool. Disagreement will be resolved by a third party.

Strategy of data synthesis: 1. Direct meta-analysis; 2. Network meta-analysis; 3. We will combine the data based on the random-effect model. We will use relative risk (RR) for the dichotomous data, and use standard mean differences (SMD) for the continuous outcome.

Subgroup analysis: Subgroup analyses will be conducted with different types of IBS, etc.

Sensibility analysis: In the direct comparison, if there is a large heterogeneity and the number of studies included is enough, we will use the method of meta regression for sensitivity analysis, otherwise we will exclude the studies one by one for sensitivity analysis.

Language: No language restrictions.

Country(ies) involved: China.

Keywords: Probiotics; Prebiotics; Antibiotic; Chinese herbal medicine; Fecal Microbiota Transplantation; Network meta-analysis; Protocol.

Dissemination plans: Ethical approval is not required for this study, as all analyses were based on previously literature. The findings will be disseminated through conference presentations, media, and peer-reviewed journals.

Contributions of each author:

Author 1 - Ying He - Author 1 drafted the manuscript, responsible for research design, and data retrieval.

Author 2 - Rui Xu - The author provided statistical expertise and contributed to the extraction of research data and evaluation of bias.

Author 3 - Wei Wang - The author contributed to the extraction of research data and evaluation of bias.

Author 4 - Jie Zhang - The author contributed to data verification and analysis.

Author 5 - Xiao-Yu Hu - The author read, provided feedback and approved the final manuscript.