# INPLASY PROTOCOL

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**Support: None**

**Review Stage at time of this submission: The review has not yet started.**

**Conflicts of interest:**
**None.**

## The efficacy and safety of fecal microbiota transplantation in the treatment of systemic sclerosis: a protocol for systematic review and meta analysis

Wang, YG[1]; Zhang, SX[2]; Lv, JJ[3]; Ren, XT[4]; Hao, XY[5]; Zhou, PP[6].

**Review question / Objective:** The objective of this systematic review is to identify, analyze and synthesize research evidence on the effectiveness and safety of fecal microbiota transplantation in the treatment of systemic sclerosis.

**Condition being studied:** Systemic sclerosis is a complex, multi-organ disorder characterized by immune-mediated inflammation, progressive organ fibrosis and vascular pathology.To date, effective treatment alternatives for SSc-related GI disease are lacking and mostly limited to providing partial symptom relief.Fecal microbiota transplantation (FMT) has been utilized sporadically for over 50 years. In the past few years, Clostridium difficile infection (CDI) epidemics in the USA and Europe have resulted in the increased use of FMT, given its high efficacy in eradicating CDI and associated symptoms. As more patients request treatment and more clinics incorporate FMT into their treatment repertoire, reports of applications outside of CDI are emerging, paving the way for the use of FMT in several idiopathic conditions. Interest in this therapy has largely been driven by new research into the gut microbiota, which is now beginning to be appreciated as a microbial human organ with important roles in immunity and energy metabolism. This new paradigm raises the possibility that many diseases result, at least partially, from microbiota-related dysfunction. This understanding invites the investigation of FMT for several disorders, including systemic sclerosis.

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 04 June 2020 and was last updated on 04 June 2020 (registration number INPLASY202060019).

## INTRODUCTION

**Review question / Objective:** The objective of this systematic review is to identify, analyze and synthesize research evidence on the effectiveness and safety of fecal microbiota transplantation in the treatment of systemic sclerosis.

**Rationale:** Currently, there is no systematic review focusing on efficacy of fecal microbiota transplantation in the treatment

of systemic sclerosis , so our meta-analysis aims to comprehensively explore it. Meanwhile we will provide high-quality evidence to help patients, clinicians as well as health policymakers select better treatment strategy of PCOS.

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METHODS

Search strategy: We will search the following sources without restrictions for date, language, or publication status: PubMed, Web of Science,Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Library, EMBASE and China National Knowledge Infrastructure.We will apply a combination of Medical Subject Heading (MeSH) and free-text terms incorporating database-specific controlled vocabularies and text words to implement search strategies. We will also search the

ongoing trials registered in the World Health Organization's International Clinical Trials Registry Platform. Besides, the previous relevant reviews conducted on fecal microbiota transplantation for systemic sclerosis and reference lists of included studies will also be searched.

Participant or population: We will include persons at least 18 years of age with a diagnosis of SSc (diffuse or limited type) as defined by the trial authors, with cutaneous or pulmonary involvement, or both. It will not be necessary that persons fulfil the preliminary American College of Rheumatology (ACR) criteria for scleroderma (ACR 1980); or 2013 ACR/ EULAR Classification Criteria for Scleroderma (van den Hoogen 2013). Trials can include persons with any subset of scleroderma.

Intervention: Systemic sclerosis patients treated with fecal microbiota transplantation.

Comparator: Another standard of care for systemic sclerosis treatment or non-exposure when applicable depending on the study.

Study designs to be included: We will include randomized controlled trials (RCTs).

Eligibility criteria: Only randomized controlled trials are included. Patients with other intestinal diseases, as well as those with other serious diseases will be excluded. Non-randomized controlled trial,self-control, case report, experience summary, animal experiment research, systematic review, and meta-analysis will also be excluded.

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systemic sclerosis and reference lists of included studies will also be searched.

**Main outcome(s):** Efficacy and safety of fecal microbiota transplantation in the treatment of systemic sclerosis.

**Additional outcome(s):** 1) Percent predicted total lung capacity (TLC); 2) Renal function - measured by creatinine clearance, estimated glomerular filtration rate (eGFR), and serum creatinine (percent of persons with a creatinine above normal); 3) Cardiac function - measured by echocardiogram (to detect changes in ejection fraction); 4) Health-related quality of life (HRQOL) - including pain measured by a visual analogue scale (VAS) and the Medical Outcome Survey Short Form (SF-36); 5) Safety outcomes - withdrawals from study and adverse events reported as defined by the authors; 6) Inflammatory markers - measured by erythrosedimentation rate (ESR) or C-reactive protein (CRP), or both.

**Data management:** Two authors will screen the titles and abstracts of the all records retrieved in above electronic databases independently to find potentially eligible reviews. According to the inclusion and exclusion criteria outlined above, the full texts of them will be retrieved for further identification. Any disagreement will be resolved by discussion or by consultation with a third author. Data will be extracted by two reviewers independently using a pre-designed data extraction form. A third reviewer will validate data. The following data will be extracted: General information, Trial characteristics, Intervention(s) and control(s), Participants, Study methodology, Outcomes, Results, etc.

**Quality assessment / Risk of bias analysis:** The methodological quality of eligible studies will be assessed by two review authors independently according to the the Cochrane Handbook for Systematic Reviews of Interventions. The following characteristics will be assessed: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), other bias. Based on the assessments of the studies against these seven domains, they will be classified as being of "low risk", "high risk" or "unclear risk" of bias. Any disagreements will be resolved by discussion or discussed with another reviewer if necessary.

**Strategy of data synthesis:** Meta-analysis was conducted using Review Manager software (version 5.3). Odds ratio (OR) with 95% confidence intervals (CI) was reported for the dichotomous data, and mean differences (MD) with 95% CI for the continuous data. Statistical heterogeneity between studies was tested by calculating Higgins $I^2$ values or using the $\chi^2$ test. $I^2 > 25$ %, $I^2 > 50$ %, and $I^2 > 75$ % were respectively defined to indicate moderate, substantial, and considerable heterogeneity. When the P-value of $\chi^2$ test was < 0.1, an $I^2$ test was carried out. If the $I^2$ test showed a value > 50 %, a random effects model was carried out. Otherwise, a fixed effects model was carried out. A P value lower than 0.05 was considered to be statistically significant.

**Subgroup analysis:** If results of the meta-analysis are significantly heterogeneous, subgroup analyses of the control groups might be performed.

**Sensibility analysis:** If sufficient trials are identified, we plan to conduct a sensitivity analysis comparing the results using all trials with high methodological quality: studies classified as having a 'low risk of bias' versus those identified as having a 'high risk of bias.

**Language:** No.

**Country(ies) involved:** China.

**Keywords:** Fecal microbiota transplantation; Systemic sclerosis; Efficacy; Safety.

**Contributions of each author:** Author 1 - Yan-gang Wang - Conceptualization.

Author 2 - Shixiong Zhang - Data curation,  Writing – original draft.
Author 3 - Jingjing Lv - Formal analysis.
Author 4 - Xuetong Ren - Methodology.
Author 5 - Xinyu Hao - Software.
Author 6 - Pingping Zhou - Software.