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STUDY PROTOCOL

REVISED Fecal microbiota transplantation for treatment of moderate to severe ulcerative colitis: a living systematic review protocol

[version 2; peer review: 1 approved, 1 approved with reservations]

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Abstract

Background: Primary studies and systematic reviews assessing the safety and effectiveness of fecal microbiota transplantation as a treatment for ulcerative colitis are being continuously published. The objective of this review is to synthesize and keep updated the evidence about the efficacy and safety of fecal microbiota transplantation for adult patients with moderate or severe ulcerative colitis through a living systematic review.

Methods: We will carry out a living systematic review including only randomized controlled trials irrespective of publication type, year and language of publication. To prioritize the fecal microbiota transplantation administration route, comparators and outcomes more relevant for supporting the clinical decisions in the treatment of ulcerative colitis patients, we will perform a Delphi process conducted by an expert panel in the field of gastroenterology and colorectal surgery. Searches will be performed in Epistemonikos database and results will be incorporated into the L·OVE platform identified as "Fecal microbiota transplant in ulcerative colitis". We will evaluate the risk of bias of the included randomized trials using the ROB-2 tool and assess the certainty of evidence using the GRADE approach.

We will monitor the L ·OVE platform every two months searching for

Open Peer Review

Approval Status ✓ ?

	1	2
version 2 (revision) 03 May 2022		? view
version 1 07 Feb 2022	✓ view	? view

1. **Andrés Gempeler**, Fundación Valle del Lili, Cali, Colombia

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Any reports and responses or comments on the article can be found at the end of the article.

relevant trials that could imply changes in the available evidence. The living process will end after 12 months of surveillance.
PROSPERO registration: CRD42021257579 (29/10/2021).

Keywords
Fecal microbiota transplant, Living systematic review, living evidence synthesis



This article is included in the Horizon 2020 gateway.



This article is included in the Marie-Sklodowska-Curie Actions (MSCA) gateway.



This article is included in the Clinical Medicine gateway.



This article is included in the Disease Management and Treatment collection.

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Author roles: Correa-Pérez A: Investigation, Methodology, Writing – Original Draft Preparation; **Guijarro JdV**: Investigation, Writing – Original Draft Preparation; **Gaetano Gil A**: Investigation, Methodology, Writing – Original Draft Preparation; **Ocaña Jiménez J**: Investigation, Writing – Original Draft Preparation; **Luengo González R**: Investigation, Writing – Original Draft Preparation; **Rigau Comas D**: Supervision, Writing – Review & Editing; **Bendersky J**: Supervision, Writing – Review & Editing; **Rojas Reyes MX**: Project Administration, Supervision, Writing – Review & Editing; **Plana Farrás MN**: Conceptualization, Investigation, Methodology, Writing – Original Draft Preparation

Competing interests: No competing interests were disclosed.

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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REVISED **Amendments from Version 1**

In this new version, we have made the following minor changes to the manuscript according to the peer reviewer's comments:

1) Rewording of the abstract, regarding the objective and methods of the study.

2) To improve readability, the use of acronyms for fecal microbiota transplantation (FMT) and ulcerative colitis (UC) has been removed.

3) Clarification of the plan to consult the expert panel for the revisitation of the PICO question and selection criteria.

4) Justification of the maintenance of evidence surveillance.

Any further responses from the reviewers can be found at the end of the article

Plain language summary

Evidence assessing the safety and effectiveness of fecal microbiota transplantation as a treatment for ulcerative colitis are being continuously published. The objective of this review is to synthesise and keep updated the evidence about the efficacy and safety of fecal microbiota transplantation for adult patients with moderate or severe ulcerative colitis through a living systematic review.

The research question will be defined by an expert panel in the field of gastroenterology and colorectal surgery. We will search for randomized controlled trials that answer the research question. We will search for them in the database Epistemonikos and select the studies that meet our criteria for inclusion. We will evaluate the risk of bias of the selected studies and assess the certainty of the evidence using specific tools. We will monitor the new published evidence every two months, searching for relevant studies that could indicate changes in the available evidence. This monitoring process will last 12 months.

Introduction

Condition being studied

Ulcerative colitis (UC) is a chronic inflammatory disease that mainly affects the large intestine and rectum, causing ulcers and other damage to the tissue[1]. Typical intestinal symptoms of the disease are abdominal pain and bloody diarrhea. Other symptoms associated with the disease are the presence of tenesmus or urgency, weight loss and fever[1]. Etiology and pathogenesis are not completely understood. Different studies propose that the disease could be the result of the interaction of different factors: a genetic predisposition, changes in the composition of the intestinal microbiota and an abnormal immune response to environmental exposures, mainly microbial[2–4]. Ulcerative colitis has two incidence peaks: between 15 and 25 years of age, and between 55 and 65 years of age[1,5]. The disease alternates symptomatic episodes with periods of clinical remission or mild activity[2]. Approximately 15% of patients may experience an aggressive course, of which up to 20% may require hospitalization[6]. Despite recent advances in overall disease management and improved therapeutics, patients with inflammatory bowel diseases still experience a substantial disease burden[5].

Why it is important to do this review

Fecal microbiota transplantation (FMT) consists of the instillation of a fecal solution from a healthy donor to the gastrointestinal tract of a diseased recipient. Thus, natural bacteria are transferred in order to replace other pathological microbiota. It can be performed through different techniques such as colonoscopy, enema, upper endoscopy and nasojejunal or nasogastric tube. Fecal microbiota transplantation is an alternative treatment option for patients with multiple recurrences of clostridium difficile infection for whom appropriate antibiotic treatment has failed[7]. In theory, every disease associated with the impairment of intestinal microflora might benefit from the therapeutic modulation of the gut microbiota. In this regard, several primary studies and systematic reviews (SRs) have been published over the past 10 years to assess the safety and effectiveness of FMT as a treatment for ulcerative colitis. We performed an initial tiered search strategy, beginning with the identification of SRs included in the Epistemonikos Database[8] for mapping the available evidence about this topic. We identified 16 SRs conducted during 2014 and 2021, that assessed the effect of FMT in inflammatory bowel diseases including ulcerative colitis. Based on these SRs we developed an evidence matrix that revealed 45 primary studies that have been included in the published reviews, but no review has included all of them[9]. The most recently published SRs, Zhou 2020[10] and Liu X 2021[11], included 5 and 11 studies, respectively. The primary studies included in these SR show a great variability in fecal microbiota transplantation delivery methods, type and dose of microbiota, target population and outcomes of interest.

Considering the wide variability of the available evidence, and taking into account that the evidence on this therapy is on the rise (i.e. new studies have been published recently and other studies are going to be published in the near future), we propose to carry out a living systematic review with the aim of updating the estimates of the effect of the FMT on ulcerative colitis patients once new evidence emerges. This SR will be developed as part of the *Living Evidence to Inform Health Decisions* project, which supports health system organizations in the implementation of the living evidence model for the development of evidence synthesis to inform health decisions[12].

Objective

To evaluate the efficacy and safety of fecal microbiota transplantation for patients with moderate or severe ulcerative colitis.

Methods

As part of the Living Evidence to Inform Health Decisions Project[12], a common methodological protocol has been defined for developing multiple living systematic reviews and living overviews of reviews. This protocol is reported in line with the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) guidelines[13]. The systematic review has been registered on PROPSERO (CRD42021257579) on 29th October 2021.

PICO question

To define the research question most relevant to support the clinical decisions in patients with UC, we will ask a convenience

sample of national experts in the field of gastroenterology and colorectal surgery to compose a panel to select the population, intervention, comparators, and outcomes.

We will perform a one-round consultation, following a modified Delphi process[14]. First, we will elaborate an online questionnaire including different UC diagnostic criteria, TFM administration routes, comparisons and outcomes as described in the *Extended data*[13].

Second, we will ask to the panel to rate each item, from 1 to 9 points as follows: low importance (score: 1–3), important but non-critical (score: 4–6), and critical (score: 7–9). The items rated as critical will define the final PICO question.

Eligibility criteria

Types of studies to be included. We will include randomized controlled trials (RCTs).

Types of participants. Adult patients (>18 years old) diagnosed with moderate or severe ulcerative colitis using the diagnosis criteria selected by the panel.

Setting. Studies including patients in any setting (hospital or community dwelling). No distinctions will be made based on the income of the countries in which the studies were carried out.

Intervention. Treatment with fecal microbiota transplantation for ulcerative colitis including any frequency of administration, or treatment duration, and the administration route selected by the panel.

Comparator. The comparator (placebo, pharmacological treatment, or no treatment) selected by the panel.

Types of outcome measures. We will not consider the outcomes as an inclusion criteria. We will include the studies independently of the reported outcomes.

Methods for identification of studies

The main search source will be the Epistemonikos database, a comprehensive database of systematic reviews and other types of evidence, maintained by screening multiple information sources to identify systematic reviews and their included primary studies, including Cochrane Database of Systematic Reviews, MEDLINE, EMBASE, CINAHL, PsycINFO, LILACS, DARE, HTA Database, Campbell database, JBI Database of Systematic Reviews and Implementation Reports, EPPI-Centre Evidence Library[8].

An additional search will be performed on MEDLINE in order to identify randomized trials/primary studies not included in reviews. The searches will cover from the inception date of each database. No publication status or language restriction will be applied to the searches in Epistemonikos. We will apply validated filters to identify clinical trials in the MEDLINE database.

Results from these searches will be automatically included in the L.OVE platform of the Epistemonikos Foundation[15]. This platform has been validated showing to be highly comprehensive source of evidence[16,17].

Our literature search will be devised by the team maintaining the Epistemonikos-L·OVE platform, using the following approach:

1. Identification of terms relevant to the population and intervention components of the search strategy, using Word2vec technology[10] to the corpus of documents available in Epistemonikos Database.
2. Discussion of terms with content and methods experts to identify relevant, irrelevant and missing terms.
3. Creation of a sensitive boolean strategy encompassing all the relevant terms.

Boolean search strategy

Epistemonikos. (((((fecal* OR stool* OR microbi*) AND (transplant* OR bacteriotherapy*))))) AND (((ulcerative* AND colitis*)) AND (((inflammatory AND bowel) OR IBD OR IBDs) OR (crohn*) OR (ulcerative* AND colitis*))))

Medline. PUBMED. (((((fecal* OR stool* OR microbi*) AND (transplant* OR bacteriotherapy*))))) AND (((ulcerative* AND colitis*)) AND (((inflammatory AND bowel) OR IBD OR IBDs) OR (crohn*) OR (ulcerative* AND colitis*))))) AND ((randomi* OR RCT OR placebo* OR trial OR "controlled-trial" OR randomly*))

Other sources. In order to identify articles that might have been missed in the electronic searches, and to maintain monitoring for the new evidence that will arise, we will do a manual search of the reference lists of included studies and will run additional searches in WHO International Clinical Trials Registry Platform and clinicaltrials.gov.

Selection of studies

The results of the literature searches will be automatically incorporated into the L·OVE platform (automated retrieval) identified as "Fecal microbiota transplant in ulcerative colitis".

Firstly, titles and abstracts will be independently screened by at least two reviewers against the inclusion criteria. We will resolve disagreements by consensus or by discussion with a third review author. Secondly, we will obtain the full reports for all records that appear to meet the inclusion criteria (according to the Delphi results). We will record the reasons for excluding studies and show the study selection process in a Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram[18].

Data extraction and management

We will use an excel spreadsheet to extract information about studies characteristics (characteristics of participants; inclusion-exclusion criteria; intervention and comparison description, outcomes and results). Data extraction will be performed by two authors.

Data analysis

Assessment of risk of bias of included studies. We will evaluate the risk of bias of the included randomized trials using the ROB-2 tool[19]. Two independent review authors will do this assessment. Discrepancies will be resolved by consensus.

Measures of treatment effect. Study results will be reported as pooled relative risks (RR), odds ratios (OR) for categorical outcomes or mean differences (MD) (or standardized mean differences, (SMD)) for continuous outcomes with the corresponding 95% confidence intervals (95% CI).

Data synthesis. We will evaluate the heterogeneity of the included studies with I^2 as follows: I2 < 50% as low, heterogeneity, I2 > 50% and < 90% as high, and > 90% as very high. When heterogeneity is below 90%, we will perform a meta-analysis in RevMan 5.4.

Subgroup analysis. We will perform the following subgroup analyses if data is available:

- Moderate vs severe stage of the disease
- Previous surgical treatment versus non-surgical treatment

Sensitivity analysis. We will perform a sensitivity analysis excluding the studies with high risk of bias.

Certainty of evidence

We will assess the certainty of evidence using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach[20], both for the evidence found as part of the initial or baseline review, and for the updates resulting from the living evidence process.

Two reviewers will independently define the certainty of evidence and discuss any disagreement to reach consensus. We will present the results using summary of findings tables.

Evidence monitoring and surveillance plan

In order to maintain the living evidence process for this review, the Epistemonikos-L.OVE platform[15] will be used as a technological enabler to support the evidence identification, screening, and selection. We will maintain a living search in the L·OVE platform to detect systematic reviews and randomized controlled trials. Additionally, each three months, we will manually search for ongoing studies in the WHO International Clinical Trials Registry Platform and the clinicaltrials.gov.

One reviewer will be in charge of assessing the evidence that has entered the specific question in the L.OVE platform every month and apply the selection criteria presented above. If a potentially eligible study is found, a second reviewer will confirm its eligibility by reading the full text. Results of evidence surveillance will be collected and kept as part of the study records. Information for the PRISMA flow diagram will be updated accordingly. The PICO question and criteria for selecting studies will be revisited and changed if considered pertinent by the expert panel during the living evidence process every time new eligible evidence becomes available.

All new eligible studies will undergo the data extraction process. The data synthesis will be updated immediately after taking into account the predefined subgroups of interest, and the body of evidence for the outcomes of interest will be assessed following the GRADE approach accordingly looking for changes on the certainty assessment results.

The living process for this question will end when the certainty of the evidence on the updated estimates for the desirable and undesirable effects becomes high or after 12 months of surveillance foreseen in the Living Evidence to Inform Health Decisions project whatever is reached first.

Statistical considerations for the living evidence synthesis

The inclusion of new studies identified as part of evidence surveillance and reporting on the outcomes of interest will follow this approach: We will perform a meta-analysis for each of the outcomes of interest reported by the new studies using a fixed-effect model in order to evaluate the statistical heterogeneity among included studies by using I^2 statistics. If new heterogeneity is detected (i.e. compared to the previous metaanalysis, new heterogeneity appears or increases), we will explore its potential sources by reviewing the new studies against previously included studies in order to identify reasons that may explain inconsistent results among studies. "In the presence of unexplained heterogeneity ($I^2 \geq 70\%$), we will consider not to meta-analyze them and explain the evidence synthesis narratively. If the I^2 is below 70%, we will perform a meta-analysis by using the fixed effects of the random effects model, whichever is pertinent.

Dissemination plan

If during the living process, new relevant results that imply changes in the current clinical practice are identified, we will update the report of this review and disseminate the update among potential users.

We plan to communicate our review results as a publication in a scientific journal. We will also share technical reports to the hospital Health Assessment Committee. We will share the results through our social media channels. All periodical updates will be available in the LE_IHD project website (https://livingevidenceframework.com/en/).

Study status

The searching and screening phases have been completed at the time of this submission.

Data availability

Underlying data

No data are associated with this article.

Extended data

Open Science Framework: Fecal microbiota transplantation for treatment of moderate to severe ulcerative colitis: living systematic review (Protocol). https://doi.org/10.17605/OSF.IO/NRZF6[13].

This project contains the following extended data:

- Appendix1_Delphi questionaire.pdf

Reporting guidelines

Open Science Framework: PRISMA-P checklist for "Fecal microbiota transplantation for treatment of moderate to severe ulcerative colitis: living systematic review (Protocol)". https://doi.org/10.17605/OSF.IO/NRZF6[13].

Data are available under the terms of the Creative Commons Zero "No rights reserved" data waiver (CC0 1.0 Public domain dedication).

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Current Peer Review Status: ✔ ?

Version 2

Reviewer Report 11 May 2022

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Hector Pardo-Hernandez
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The authors have addressed several of the comments raised during the review process. As a result, the manuscript has improved substantially. Only a few minor concerns remain, as detailed below.

Authors should specify the eligibility criteria of the national experts in the field of gastroenterology and colorectal surgery who will participate in the consultation-Delphi process. In addition, how will potential conflicts of interest be addressed?

Authors mention that “The PICO question and criteria for selecting studies will be revised and changed accordingly during the Living Evidence process every time new eligible evidence becomes available”. Authors should clarify whether, at that later stage, they plan to consult the national experts eligible for the consultation-Delphi process.

In this new version, authors mention that “The living process for this question will end when the certainty of the evidence on the updated estimates for the desirable and undesirable effects becomes high or after 12 months of surveillance foreseen in the Living Evidence to Inform Health Decisions project whatever is reached first”. Authors should better explain their rationale for this cut-off point, e.g., why this number of months is used in the Living Evidence to Inform Health Decisions project.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Public health, research methods.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Version 1

Reviewer Report 02 March 2022

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The authors present the protocol for a systematic review on the efficacy and safety of fecal microbiota transplantation for adult patients with moderate or severe ulcerative colitis. The work is methodologically sound and the manuscript is well-structured. There are some aspects that would need to be addressed before this manuscript is ready for publication.

The abstract would better reflect the objective of the proposed living review if the following sentence from the introduction is used “a living systematic review with the aim of updating the estimates of the effect of the FMT on ulcerative colitis patients once new evidence emerges.”.

In the abstract, adding the list of PICO components is confusing. If prioritization will take place, it would be expected that the different PICO components will be sorted out later on and not at this early stage. Authors should reword this section in a fashion similar to the methods, e.g., “the comparator selected by the panel”. Authors should also add this section to the plain language summary.

Authors should specify the eligibility criteria of the national experts in the field of gastroenterology and colorectal surgery who will participate in the consultation-Delphi process. In addition, how will potential conflicts of interest be addressed?

Authors should provide an explanation of how the search strategy will be modified, if needed, depending on the results of the Delphi process.

Authors mention that “The PICO question and criteria for selecting studies will be revised and changed accordingly during the Living Evidence process every time new eligible evidence becomes available”. Authors should clarify whether, at that later stage, they plan to consult the national experts eligible for the consultation-Delphi process.

The choice of 12 months for evidence surveillance seems arbitrary. Authors should better explain their rationale for this cut-off point.

In order to improve readability, authors should limit the use of acronyms, e.g., it would be helpful to spell out SR, FMT, UC throughout the document.

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Public health, research methods.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 25 Apr 2022

Maria Ximena Rojas Reyes

Comment 1. The abstract would better reflect the objective of the proposed living review if the following sentence from the introduction is used “a living systematic review with the aim of updating the estimates of the effect of the FMT on ulcerative colitis patients once new evidence emerges.”. Response to comment 1: Thank you for the comments. We have modified the text to address all sugestions. The text now reads: “Primary studies and systematic reviews assessing the safety and effectiveness of fecal microbiota transplantation as a treatment for ulcerative colitis are being continuously published. The objective of this review is to synthesize and keep updated the evidence about the efficacy and safety of fecal microbiota transplantation for adult patients with moderate or severe ulcerative colitis through a living systematic review”...

Comment 2. In the abstract, adding the list of PICO components is confusing. If prioritization will take place, it would be expected that the different PICO components will be sorted out later on and not at this early stage. Authors should reword this section in a fashion similar to the methods, e.g., “the comparator selected by the panel”. Response to comment 2: **"**To prioritize the fecal microbiota transplantation administration route, comparators and outcomes more relevant for supporting the clinical decisions in the treatment of ulcerative colitis patients, we will perform a Delphi process conducted by an expert panel in the field of gastroenterology and colorectal surgery”

Comment 3. Authors should also add this section to the plain language summary. Response to comment 3: Thanks. We have also added this section in the plain language summary.

Comment 4. In order to improve readability, authors should limit the use of acronyms, e.g.,

it would be helpful to spell out SR, FMT, UC throughout the document. Response to comment 4: Thanks, we have revised and changed the use of acronyms for FMT and UC. We consider SR is largely known and accepted by the scientific community for "systematic review".

Comment 5. Authors should specify the eligibility criteria of the national experts in the field of gastroenterology and colorectal surgery who will participate in the consultation-Delphi process. Response to comment 5: Thank you for the comment. We will select a convenience sample of national experts in the field of gastroenterology and colorectal surgery. We have included this clarification in the text: “To define the research question most relevant to support the clinical decisions in patients with UC, we will ask a convenience sample group of national experts in the field of gastroenterology and colorectal surgery to compose a panel to select the population, intervention, comparators, and outcomes”

Comment 6. In addition, how will potential conflicts of interest be addressed Response to comment 6. Thank you for your suggestion. We will ask the experts participating to complete a Conflict of Interest statement.

Comment 7. Authors should provide an explanation of how the search strategy will be modified, if needed, depending on the results of the Delphi process. Response to comment 7: Thank you for your comment. However, we anticipate the search will be sensitive enough to get all relevant RCTs independently of the results retrieved by the panel.

Comment 8. Authors mention that “The PICO question and criteria for selecting studies will be revised and changed accordingly during the Living Evidence process every time new eligible evidence becomes available”. Authors should clarify whether, at that later stage, they plan to consult the national experts eligible for the consultation-Delphi process. Response to comment 8. Thank you for your suggestion. We will consult the expert panel in that case and we have modified the sentence accordingly: “The PICO question and criteria for selecting studies will be revisited and changed if considered pertinent by the expert panel during the Living Evidence process every time new eligible evidence becomes available.”

Comment 9. The choice of 12 months for evidence surveillance seems arbitrary. Authors should better explain their rationale for this cut-off point. Response to comment 9: Thanks, a year is the maximum time with available resources to maintain the process of evidence surveillance. We have included a sentence in the text: “The living process for this question will end when the certainty of the evidence on the updated estimates for the desirable and undesirable effects becomes high or after 12 months of surveillance foreseen in the Living Evidence to Inform Health Decisions project whatever is reached first.”

Competing Interests: No competing interests were disclosed.

Reviewer Report 21 February 2022

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I read the protocol for a living systematic review on Fecal microbiota transplantation for treatment of moderate to severe ulcerative colitis.

In my opinion, the protocol is quite innovative, in addition to fulfilling the methodological standards to reduce the risk of bias in systematic reviews. The subject is relevant for clinical practice, and the rationale and methods are detailed but remain brief and clear, which is laudable.

There are some writing/grammar mistakes that must be corrected, and some sentences that need revision. Those are:

Abstract:

- Acronym for fecal microbiota transplantation (*FTM*) appears also as “TFM” in the abstract. Should be the same acronym throughout the abstract and manuscript.

Plain language summary:

- The sentence: "*To meet our objective, we will search for all studies that answer our research question which have a design of a randomized controlled trials*" can be better written. "I suggest changing to *To meet our objective, we will search for all studies that answer our research question, but we will only consider those with a randomized controlled trial design."*

Introduction:

"The etiology of the UC is still unclear."

- Remove the word "the". And instead of "Etiology is unclear" I suggest using "etiology and pathogenesis are incompletely understood", as several processes are described in the literature and guide current therapies.

"The peak incidence is in the 15–25-year age group, and there is another peak between 55 and 65 years of age."

- Correct to "UC has two incidence peaks; between 15 and 25 years of age, and between 55 and 65 years of age"

"Approximately 15% patients may experience an aggressive course, and 20% of these patients may require hospitalization for severe disease activity"

- *15% *if* patients may experience an aggressive course, and 20% of these patients may require hospitalization <u>*because of*</u> severe disease activity>*
  Implement changes highlighted and in **.

"We identified 16 SRs conducted during 2014 and 2021, to assess the effect of FMT in inflammatory bowel diseases including ulcerative colitis."

- "To assess" must be changed to "that assessed".

"When reviewing the primary studies, we found that there is great variability in FMT delivery methods, type and dose of microbiota, target population and outcomes of interest."

- What is to be made of this sentence? Why mention it at the end of a paragraph without any follow-up on that finding? Add an explanation of why you find it relevant to describe these findings or how does it guide the methods described.

Methods:

- *"Living Evidence to Inform Health Decisions project"*, Is written differently throughout the manuscript, sometimes with all capitals, then just initial words with capitals, and sometimes in italic but other times not. Correct to make homogeneous.

"We will keep a living search in the L·OVE platform to detect systematic reviews and randomized controlled trials. "

- I believe that "maintain" is a better choice of words instead of "keep" in this sentence.

"The PICO question and criteria for selecting studies will be revised and changed accordingly during the Living Evidence process every time new eligible evidence becomes available"

- I do not think the PICO and criteria will change with each new study. They might be "revisited" and changed IF considered pertinent. Rewrite accordingly.

"In the presence of unexplained heterogeneity (I2> 70%), we will consider not to meta-analyze them and explain the evidence synthesis narratively. If the I2 is below 90%, we will perform a meta-analysis by using the fixed effects of the random effects model, whichever pertinent."

- *70%), we will consider not to meta-analyze them and explain the evidence synthesis narratively. If the I2 is below 90%, we will perform a meta-analysis by using the fixed effects of the random effects model, whichever *is* pertinent*>
  This segment is contradictory regarding the heterogeneity cut-offs mentioned (70% vs 90%). As it is written, a higher heterogeneity (up to 90%) would lead to random effects MA but I2 >70% would lead to no MA and narrative summary (clearly contradictory) Must be revised and corrected."

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Evidence-based medicine, evidence synthesis, clinical research methodology.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.