OPENBIOME
Research Collaboration Guide
For Clinical Researchers

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INTRODUCTION

OpenBiome is a nonprofit stool bank that was founded in 2012 to expand safe access to fecal microbiota transplantation (FMT) and to catalyze research on the microbiome. In our first five years, we have provided more than 50,000 fecal microbiota preparations for treatment of *C. difficile* infections that failed to respond to antibiotic therapies, to over 1,200 hospitals and clinics across all 50 states and 7 countries.

We have also partnered with investigators to uncover the role of the gut microbiome in human health across a broad array of indications, and to discover how engineering the microbiome might drive better health outcomes. OpenBiome has partnered on over 30 clinical trials and translational research studies across a number of disease indications, including Crohn’s disease, ulcerative colitis, antibiotic-resistant infection prevention and resolution, and irritable bowel syndrome.

OpenBiome seeks to work with passionate clinical researchers to combine their disease-specific clinical expertise with our extensive knowledge of the microbiome and FMT to shape the future of microbial therapies. In the sections below, you can learn more about the process of working with OpenBiome and explore the services that we can offer to support your research goals.

We invite you to join us and other thought leaders in the field as part of our growing network of collaborators. Together, we can work to evaluate the potential of microbial therapies across a wide range of indications.
RESEARCH INTERESTS

OpenBiome supports investigator-led research exploring whether modulation of the human gut microbiome can treat or prevent disease. Our portfolio spans over 30 trials that are using an FMT intervention for indications that include:

- *Clostridioides difficile* Infection
- Irritable Bowel Syndrome
- Inflammatory Bowel Disease
  - Ulcerative Colitis
  - Crohn’s Disease
  - Pouchitis & others
- Antibiotic-Resistant Bacteria
- Hepatic Encephalopathy
- Severe Allergies
- Obesity
- Severe Acute Malnutrition

As researchers around the globe identify additional areas of human health that are in associated with the gut microbiome, we continue to expand the indications we explore through our research partnerships.
WORKING WITH OPENBIOME

This guide provides a comprehensive overview of our program so you can determine if a collaboration with OpenBiome would be beneficial to your FMT clinical trial.

OpenBiome supports research programs at leading medical research institutions around the world. Through our Research Services Program, OpenBiome offers clinical investigators a range of services to enable their interventional FMT trials, including rigorously screened FMT preparations in multiple formulations, regulatory support, and clinical and scientific expertise.

The Research Services Program at OpenBiome is overseen by our Research Review Panel and further supported by our Clinical Advisory Board, whose members are leading clinicians and scientists with expertise in gastroenterology, infectious disease, internal medicine, and microbiology.

Our Research Review Panel accepts study proposals from investigators looking to conduct research using FMT, and reviews proposals quarterly to evaluate safety, feasibility, and other criteria. You can find a detailed overview of the process of submitting a proposal and working with us in the following sections.

We look forward to working with you!
Is working with OpenBiome right for your trial?

OpenBiome works with investigators planning clinical research trials that:

- Would benefit from access to a high-quality supply of FMT material
- Follow a clinical protocol that requires Investigational New Drug (IND) authorization from the FDA as well as approval institutional review board (IRB) to use FMT in a new disease indication
- Are well-planned and independently staffed, and require minimal scientific and technical consultation from our experts
- Are or will be fully funded

If your proposed study is (1) funded or sponsored by commercial entities or (2) investigating Inflammatory Bowel Disease (IBD) or C. difficile Infection (CDI), there will be an additional review process. We have a collaboration with Finch Therapeutics, who holds intellectual property on some of the material that we provide (learn more here). Due to the terms of our agreement, research that meets the above criteria will need to be reviewed by Finch prior to our engagement with you.

Although most investigator-initiated trials must be self-funded by applicants, OpenBiome may be able to offer limited collaborative trial support to study proposals that are of deep relevance to our mission. In these instances, OpenBiome may offer a combination of protocol development/consultation, additional regulatory assistance, and subsidized rates for FMT preparations in exchange for deeper engagement on the design and execution of the trial and access to resulting trial data.

We are happy to answer any questions you may have about this process – please do not hesitate to reach out to us at science@openbiome.org.
What OpenBiome Can Provide to Investigators

OpenBiome possesses a wide variety of resources to support clinical research. These resources fall into two categories: **cGMP FMT Supply** and **Scientific & Technical Input**.

**cGMP FMT Supply**

OpenBiome provides FMT preparations that have been produced in accordance with appropriate [current Good Manufacturing Practices](https://www.openbiome.org/safety) (cGMP) for use in clinical trials.

- **FMT Preparations:**
  OpenBiome offers three FMT formulations:
  - **Lower GI delivery (FMP250)** – 250ml frozen liquid formulation for delivery via colonoscopy, sigmoidoscopy, or enema
  - **Upper GI delivery (FMP30)** – 30ml frozen liquid formulation for delivery via nasogastric/nasoenteric tube or EGD
  - **Oral delivery (FMT DE Capsules)** – dose of 30 double-encapsulated frozen capsules

- **Research Aliquots:**
  1ml aliquots of donor stool material used to produce specific FMT units used in clinical trials can be made available to research investigators to perform post-trial microbial sequencing and analyses.

- **Quality and Safety:**
  FMT preparations are produced following industry-leading quality and safety controls. Our donors undergo a rigorous screening process, including a 200-point clinical evaluation with an internal medicine specialist, and a battery of serological and stool-based assays to screen for infectious pathogens, including multi-drug resistant organisms.

  Fewer than 3% of applicants pass screening procedures to become active donors. Additional documentation on our donor screening and process controls is available at [openbiome.org/safety](https://openbiome.org/safety).
• **Regulatory Support:**
  Conducting a clinical trial with FMT requires that the Principal Investigator obtain (1) formal study approval via an [Investigational New Drug (IND) application](https://www.fda.gov) from the FDA and (2) approval from his/her local or institutional review board (IRB). OpenBiome maintains a Biologics Master File (BBMF) registered with the FDA that fully describes all FMT manufacturing and donor process controls.

  By working with OpenBiome, your study will be authorized to reference the OpenBiome BBMF, which will facilitate the IND submission process for your study.

**Scientific & Technical Input**

OpenBiome's research partners have access to our scientific and clinical experts for consultation and guidance on study design and operations. Our standard service for clinical trials includes four phone consultations during study development to ensure the highest safety standards are applied, and to ensure that operations run smoothly.

1. **Protocol:**
   Ahead of this consultation, our medical and scientific team will review your protocol summary. We will cover any safety-related concerns and questions and will also use this time to discuss topics including dosing & formulation considerations, FMT pre-treatment and engraftment considerations, and more. (Estimated time: one hour)

2. **Regulatory:**
   Consultation with our regulatory team to discuss plans for IND submission, Biologics Master File (BBMF) authorization, safety reporting, and other key regulatory topics related to FMT research and your study. (Estimated time: one hour)

3. **Operations & Logistics:**
   This time with our operations team will be used to discuss key operational considerations including shipping, storing, and handling of FMT material for clinical trials. We will also discuss fulfillment and enrollment timelines. (Estimated time: one hour)
4. **Study Close-Out:**
   Following study completion, our operations team will hold a consultation with you to debrief successes and challenges from the study to continue improving our processes and ability to support future research. (Estimated time: 30 minutes)

5. **Scientific Consultation (optional):**
   Our scientific team and advisors can advise on topics including specimen collection methodologies, molecular characterization & analysis, microbial engraftment, and more. (Estimated time: one hour)

Beyond these sessions, the OpenBiome team is available for additional, formal consultations on a fee-for-service basis.
What OpenBiome Requires from Investigators

To ensure that the clinical trials we support meet the highest safety standards and allow us to continue our mission of catalyzing research into the human gut microbiome, we look for the following requirements to be met by our research partners:

- **Regulatory**
  All studies conducted using OpenBiome material must comply with appropriate regulatory requirements.

Within the U.S., FMT trials must be conducted under an FDA-approved Investigational New Drug (IND) protocol and must be conducted under the review of a local investigational review board (IRB). Outside of the U.S., local regulatory requirements and guidelines for conducting clinical research will apply.

Prior to study activation and product shipment, the following documents must be on-file with OpenBiome:

1. IND “Safe to Proceed” letter from the FDA authorizing the FMT trial protocol to commence
2. Study approval from investigators’ IRB of record
3. Fully-executed clinical trial agreement (CTA) between OpenBiome and Investigators’ home institution

Should a study continue for more than one year, OpenBiome will require ongoing documentation demonstrating continued regulatory oversight and approval.

- **Safety**
  All studies conducted in partnership with OpenBiome are subject to a mandatory safety review by our research team and require timely safety reporting by the investigator’s study team.

We retain the right to withhold access to FMT material if a protocol does not address FMT-specific clinical safety concerns, or if adverse events are not reported to us in a timely manner.
• **Financial**  
As a small non-profit research institution, OpenBiome is generally unable to subsidize or discount FMT units needed for clinical trials. **Investigators or their institutions are responsible for covering all costs associated with FMT material supplies, including a project support fee to enable our services.** A final budget must be formally and contractually agreed upon to prior to the start of any trial.

• **Operational**  
We will work with investigators to develop an operational plan for each trial. Investigators are responsible for providing timelines for initiation and enrollment of the study, and OpenBiome will provide fulfillment and product delivery timelines. FMT production involves human donors, so unexpected delays may occur from time to time. We understand that these delays can present challenges for clinical trials, and we are committed to working closely with you to ensure that any potential delays or changes in timelines are communicated rapidly. We will work with you to troubleshoot potential supply-related delays.

• **Legal**  
For each trial partnership, OpenBiome must execute a Clinical Trials Agreement (CTA) with your institution. FMT is an investigational procedure, and all liability associated with the procedure and outcomes must be held by the investigator and the investigator’s institution.

• **Publications & Data**  
We ask for a courtesy copy of manuscripts related to the study prior to journal submission, and we request formal acknowledgment in any publications sharing results from studies conducted using OpenBiome material.
How to Begin Working with OpenBiome

Step 1: Submit a Letter of Interest (LOI)

If you are interested in working with OpenBiome on your clinical trial, please submit a Letter of Interest (LOI) submission package to initiate a discussion about your study proposal. The submission package consists of:

- Completed Letter of Interest (LOI) Form
- Completed OpenBiome Project Budget Estimate
- A recent NIH biosketch for Key Personnel (or CV documents that include a list of research support)
- Any other supplementary proposal-related documents
- Accepted Research Agreement Form (if necessary)*

All LOI packages are reviewed quarterly by OpenBiome’s Research Review Panel. Proposed studies will undergo a comprehensive safety evaluation and will be assessed on study safety profile, research focus, clinical research experience of the study team, and supply, logistical, and financial considerations.

Following each quarterly review, OpenBiome will communicate project decisions, outstanding questions, or next steps to applicants.

*Accepted Research Agreement Form:

Is your trial: (1) funded or sponsored by commercial entities or (2) investigating Inflammatory Bowel Disease (IBD) or C. difficile Infection (CDI)?

We have a collaboration with Finch Therapeutics, who holds intellectual property on some of the material that we provide (learn more here). Due to the terms of our agreement, research that meets the above criteria will need to be reviewed by Finch prior to our engagement with you. We are happy to answer any questions you may have about this process – please do not hesitate to reach out to us at science@openbiome.org.
Step 2: Planning & Review

The OpenBiome research team will conduct all required consultations with your study team during this step.

OpenBiome and investigators will also agree upon a finalized operational plan/budget and negotiate and execute a Clinical Trial Agreement. Regulatory applications and approvals from the FDA and IRB, or other relevant regulatory agencies, should be completed during this step.

Step 3: Study Activation

OpenBiome’s Clinical Research team will approve the release of FMT preparations and activate your study. OpenBiome and the investigator will execute agreed-upon study tasks along the finalized operational timeline, and our teams will work together to navigate any potential delays and challenges that may emerge.

Step 4: Study Close-Out

When the study is complete, our Clinical Research team will conduct a study close-out call with your study team to debrief successes and challenges. If requested, 1ml aliquots of donor stool material used to produce specific FMT units used in your clinical trials can be shipped to your site to perform post-trial microbial sequencing/analyses. Courtesy copies of related manuscripts will be shared with OpenBiome, and if applicable, relevant data will be shared.

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If you have any outstanding questions, please contact us at science@openbiome.org, and we’d be happy to help!
ADDITIONAL RESOURCES

i. Clinical Research Website
ii. Clinical Research Letter of Interest Form
iii. Current Studies
iv. Publications
v. Research Partners
FREQUENTLY ASKED QUESTIONS

1. **How is the use of fecal microbiota transplantation in clinical research regulated?**
   The U.S. Food and Drug Administration (FDA) regards stool for fecal microbiota transplantation (FMT) as an Investigational New Drug (IND). Although the FDA is currently exercising enforcement discretion for the use of FMT in treating recurrent *Clostridioides difficile* infections, provided that informed patient consent is acquired, the use of FMT in clinical research on *C. difficile* and other indications requires submission of an IND application. OpenBiome has Biologics Master Files with the FDA that may be referenced to facilitate the IND application process for approved study partners.

2. **How are OpenBiome stool donors screened?**
   To qualify, a prospective donor must pass an in-depth, 200-point clinical assessment conducted by a nurse and overseen by a physician over a 45-minute visit. Donors also pass a panel of over 30 stool and serological tests. Risk factors for infectious diseases and potential microbiome-mediated conditions are excluded. Active donors are rescreened every 60 days.

3. **How are laboratory assays of donor health and product safety performed?**
   Stool-based and serological assays are conducted by third party Clinical Laboratory Improvement Amendments (CLIA)-certified testing facilities to assess for infectious pathogens and general health metrics. For stool preparations, these tests include a combination of microbiological culturing, enzyme immunoassays and PCR technologies to detect potential infectious agents. These diagnostics were developed through the review of best clinical practices\(^2\)\(^,\)\(^8\)\(^,\)\(^9\) coupled with consensus guidance from our clinical advisory board and reviewed by the U.S. FDA upon submission of each Investigational New Drug (IND) application. Please see our for more information.

4. **Are placebo versions of liquid and capsule FMT units available?**
   Yes.
5. **What measures are taken to ensure that placebos cannot be differentiated from treatment material?**

   Placebo versions of both liquid and capsule FMT are tinted to be visually comparable to their respective stool preparations. Capsules are tasteless and odorless.

6. **What is the safest or most effective FMT dosage and mode of delivery?**

   For recurrent CDI, please refer to the [OpenBiome Clinical Primer](https://www.openbiome.org). Development of evidence-based recommendations for other indications poses a challenge, as the role of gut microbiota in the etiology and pathogenesis of many disorders is still an area of active research. Therefore, careful consideration of patient risks and potential therapeutic mechanisms specific to each indication is necessary to design a study that is both safe and informative.

7. **Once I receive FMT doses for my trial, am I allowed to remove material from the units in order to allow for patient/donor microbiome sequencing comparisons at the end of enrollment?**

   Investigators are not authorized to remove FMT material from units meant for treating patients enrolled in clinical trials. However, OpenBiome can provide 1ml aliquots of the same donor stool used to create the FMT units used in a trial (regardless of the FMT product). More details about this process will be communicated to investigators after proposals are reviewed and trial planning begins.

8. **Is funding support for research available from OpenBiome?**

   As a small non-profit organization, OpenBiome is not typically able to fund LOI applicants’ clinical trial proposals, although we are eager to support clinical research and actively seek opportunities for collaboration. We encourage all prospective collaborators to seek external funding. Please contact us at science@openbiome.org with any questions or concerns, or to discuss the possibility of letters of support for external funding opportunities. On occasion, OpenBiome may reach out to offer financial or in-kind support to a study that is exceptionally well-aligned with our mission and own research objectives.
9. **What is OpenBiome’s relationship with Finch Therapeutics Group?**

OpenBiome collaborated with Finch to develop CP101, a freeze-dried oral FMT capsule, for treatment of recurrent *C. difficile*. Finch is running a clinical trial to test CP101, and trial sites around the U.S. and Canada are now enrolling patients. Learn more about participating in the trial at [prism3trial.com](http://prism3trial.com). You can read more about the relationship between OpenBiome and Finch, and our commitment to integrity [here](#).

10. **Was OpenBiome impacted by the safety alert from FDA in June 2019? Does OpenBiome screen for multi-drug resistant organisms (MDROs) and meet the updated screening guidelines from FDA?**

OpenBiome material was not involved with, nor impacted by, FDA's safety alert from June 2019. We have been screening for MDROs, including Extended-Spectrum Beta Lactamase (ESBL) since 2016, and meet all updated guidelines from FDA. Trials using OpenBiome material were not halted, and OpenBiome material may continue to be used under FDA’s latest guidance.
REFERENCES