OpenBiome is seeking input on a draft proposal we intend to submit to the FDA on the regulation of FMT

**KEY POINTS:**

- We are soliciting input on a policy proposal that we intend to submit for consideration to the FDA.
- The goal of the proposal is to maintain patient access to fecal microbiota transplantation (FMT) while also supporting enrollment into trials evaluating FMT or similar microbiome-based therapies for FDA approval.
- Please share comments and suggestions by November 16, 2018 to comments@openbiome.org, or you may reach out directly to our Executive Director, Carolyn Edelstein, at carolyn@openbiome.org to discuss the proposal.
- Please consider supporting this proposal by adding your name or a statement of support for us to include. To do so, please write to comments@openbiome.org by November 16, 2018. We will share a final draft based on comments received for your approval.

Over the past five years, alongside our clinical partners and our stool donors, we have seen an expansion in access to fecal microbiota transplantation (FMT) that seemed unthinkable just a few years ago – today, 98% of the U.S. population is within a 2-hour drive of one of over 1,000 hospitals or clinics offering FMT.

This geographic access, however, comes with important limitations:

1. **It’s temporary.** FMT is not approved by the FDA. Instead, patients have been able to access treatment due to a policy of “enforcement discretion.” This guidance allows use of FMT outside of clinical trials for recurrent *C. difficile* infection that is not responsive to standard therapy on an interim basis as the agency develops its policies on FMT.
2. **FMT is still a treatment of last resort.** Currently, the FDA’s enforcement discretion policy permits the use of FMT for *C. difficile* only after a patient has failed antibiotic alternatives. In practice, this means that patients are often ill for months before they receive FMT. An FDA-approved therapy is crucial to providing the safety and efficacy data needed to advance earlier and broader use of FMT, expanding patient access and improving the quality of life for those suffering from *C. difficile*.
3. **FMT is often not covered by insurance.** As an investigational treatment, FMT is often not covered by insurers, leaving the vast majority of patients to pay out-of-pocket.

With a dual mission of enabling safe access to FMT and catalyzing research into the microbiome, we began providing FMT preparations for *C. difficile* as a temporary solution – a way to enable access to FMT for patients who needed it before an FDA-approved treatment was developed. We have always believed that the best long-term solution for patients is a treatment that is supported by the FDA, that doctors can prescribe, insurance companies can cover, and most importantly, that patients can access more easily. However, that outcome is at risk:
Challenges with trial enrollment threaten both short-term and long-term access to microbiome-based therapies: Right now, there are at least three late-stage clinical trials assessing microbiome-based therapies, like FMT, for prevention of recurrence in recurrent C. difficile, but reports indicate that trial enrollment has been slowed by, among other factors, access to FMT under enforcement discretion. It is unlikely that this policy will remain as-is if it undermines the development of new therapies for approval.

Existing policy proposals would likely restrict access even for those who could not participate in trials: The FDA has already released two draft guidance documents intended to limit access to FMT for patients outside of clinical trials (a first draft in 2014 and a revised draft in 2016). These policies would require that any physician who obtains material from a stool bank do so as part of a clinical trial, a requirement that we are concerned would unduly limit patients’ access to FMT.

We are proposing an alternative policy under which eligible patients receive treatment through clinical trials and enforcement discretion persists for those patients who cannot access an enrolling trial. Our goal is to work with you – with patients, with clinicians, with industry, and with the FDA – to arrive at a solution that promotes enrollment into these important and necessary clinical trials, while still maintaining access to FMT for patients who cannot enroll in trials.

Our proposal, in brief, is:

- Clinicians using FMT preparations from stool banks (i.e. OpenBiome) would pre-screen patients for participation in trials evaluating microbiome-based therapies for FDA approval prior to FMT treatment.
  - Patients who cannot feasibly participate in one of these trials could receive FMT from a stool bank for C. difficile that is not responsive to standard therapy.
  - Patients who could feasibly participate in a trial would be referred to the trial.
- Hospital-level stool-banking programs or clinicians overseeing donor qualification and FMT material preparation themselves would not need to take this step.

Please review the proposed policy on page 3.

We hope to hear your feedback and ideas as we develop this proposal to submit to the FDA for consideration:

- Please share your comments with us at comments@openbiome.org by November 16, 2018. If you would like to speak with us about the proposal, we would be glad to arrange a call between you and a member of our leadership team.
- Please consider supporting this proposal by adding your name or a statement of support for us to include. To do so, please write to comments@openbiome.org by November 16, 2018. We will share a final draft based on comments received for your approval.

We will post an updated draft based on feedback and leave it open for comment for one week before circulating the draft for signatories’ sign-off and submitting it to the FDA.

Thank you for working alongside us to ensure safe access to FMT for patients today and in the future.

Carolyn Edelstein
Executive Director
OpenBiome
carolyn@openbiome.org
PROPOSAL FOR NEW DRAFT GUIDANCE

Enforcement Discretion will apply for the use of fecal microbiota for transplantation (FMT) to treat *Clostridium difficile* (*C. difficile*) infection not responding to standard therapies, provided that:

1. The treating physician obtains adequate informed consent from the patient or his or her legally authorized representative for the use of FMT products. Informed consent should include, at a minimum, a statement that the use of FMT products to treat *C. difficile* is investigational and a discussion of its reasonably foreseeable risks; AND

2. The stool donor and stool are qualified by screening and testing performed under the direction of the licensed health care provider for the purpose of providing the FMT product for treatment of the patient; OR

3. The FMT product is obtained from a stool bank for a patient who cannot practically participate in a Covered Trial of an investigational microbiome-based therapy for the treatment or prevention of *C. difficile* infection conducted under an Investigational New Drug (IND) application. For the purposes of this proposal:
   a. An investigational microbiome-based therapy refers to an unapproved microbial therapy delivered to the gastrointestinal tract.
   b. A Covered Trial is a randomized placebo-controlled trial with an open-label extension that is open for enrollment.
   c. A patient cannot practically participate in a trial if:
      i. The patient has fulminant *C. difficile* infection or the patient and treating physician determine that the patient’s medical condition requires immediate treatment OR
      ii. There are no trial sites that are within a reasonable distance for the patient to travel (i.e., 50 miles or one hour of travel from the patient’s primary residence) based on publicly available information (i.e., trial sites listed on clinicaltrials.gov) OR
      iii. The patient fails to meet clinical criteria for trial participation based on publicly available information (i.e., inclusion/exclusion criteria listed on clinicaltrials.gov) OR
      iv. The patient presents written documentation from an investigator of a trial that the patient has failed to meet the trial inclusion/exclusion criteria.
   d. The treating physician is responsible for documenting informed consent and the criteria that exclude each patient from trial participation in order for enforcement discretion to apply.
PROPOSAL DETAILS

We hope to receive feedback on all aspects of the proposal, but, in particular, we are seeking feedback on the following issues:

1. It only includes randomized, placebo-controlled trials with open-label extensions:
   a. Randomized, placebo-controlled trials are needed to ensure adequate, well-controlled studies of microbiome-based therapies that can be ultimately submitted for approval by the FDA.
   b. Open-label extension: patients who experience a recurrence of *C. difficile* infection during the trial will be offered the study drug, regardless of whether they initially received the study drug or a placebo. Given clinical guidelines and experience with FMT, we feel that it would be unethical for some patients to receive a placebo with no opportunity to receive a potentially efficacious microbiome-based therapy if they experience a recurrence.
   c. There are currently at least three industry groups with active studies that meet these guidelines. You may learn more here:
      i. ECOSPOR III – clinicaltrials.gov or sponsor’s website
      ii. PRISM 3 – clinicaltrials.gov or sponsor’s website
      iii. PUNCH CD 3 – clinicaltrials.gov or sponsor’s website

2. It ensures that patients who need urgent treatment will receive FMT from stool banks as easily as they do today:
   a. Patients who present with severe or severe-complicated cases of *C. difficile* or *C. difficile* that is refractory to antibiotics, and others who need to be treated immediately should experience no change to their ability to get treatment.

3. It recognizes that geography is a constraint on patients’ feasible participation in trials:
   a. If a patient’s primary residence is over 50 miles away or more than an hour’s travel time from the nearest eligible study site, or the patient faces a comparably challenging barrier to reaching the nearest site, patients will continue to have FMT available as it is today.

4. It provides that any patient who does not meet the inclusion and exclusion criteria for a trial will be able to access FMT as they would today. This includes any trial participants who experience a recurrence but do not meet the inclusion and exclusion criteria for participation in the open-label extension (should such a case occur).

5. It only applies to material obtained from stool banks.
   a. We recommend using the definition of stool bank from the FDA’s draft guidance from March 2016, where a stool bank is defined as “an establishment that collects, prepares, and stores FMT product for distribution to other establishments, health care providers, or other entities for use in patient therapy or clinical research. An establishment that collects or prepares FMT products solely under the direction of licensed health care providers for the purpose of treating their patients (e.g., a hospital laboratory) is not considered to be a stool bank under this guidance.”
   b. OpenBiome would qualify as a stool bank under this guidance. Physicians who oversee the qualification of a donor and stool to use in FMT for the patients they treat would not need to pre-screen their patients. FMT at this scale, it is argued, is
most appropriately considered practice of medicine and as such, it is not regulated by the FDA.¹

To support the smooth implementation of this alternative policy and ensure that patients maintain safe access to FMT, OpenBiome would:

- Create a user-friendly guide for physicians that enables them to easily review trial information with their patients, conduct pre-screening, and refer patients into appropriate trials.
- Provide information on our website with publicly available details about trials, including inclusion/exclusion criteria and trial site locations.
- Update our existing order logs to track trial pre-screening.

OpenBiome commits to:

- Standing with patients and patient advocates to maintain access to FMT for those who cannot participate in trials.
- Standing with clinicians to provide the information they need to have important and ongoing discussions with their patients about care options.
- Standing with industry to ensure that information about their trials is shared widely among FMT providers.
- Standing with the FDA to support enrollment in rigorous, controlled studies so that patients are getting the best and safest treatment in the long term.

FREQUENTLY ASKED QUESTIONS

What would this policy change mean for patients?
- If you are a patient with recurrent *C. difficile*, when you visit your doctor to discuss FMT treatment, your doctor will likely also review your condition to see if you meet the basic criteria to enroll in an ongoing clinical trial assessing similar treatments for FDA approval.
- If you meet the eligibility criteria:
  - Your doctor may help you connect with another doctor serving as an investigator in a relevant study. This investigator and other clinical trial staff will fully screen you for the trial, and if you meet the full criteria, you can enroll in the study. Your decision to participate in any clinical trial is voluntary and the trial staff will discuss the risks and benefits of participating with you and will give you the opportunity to ask questions.
  - The study will be a randomized, placebo-controlled trial that includes an open-label extension. This means that if you get sick again during the trial, regardless of whether you received the study drug or a placebo, you could be eligible to receive an active treatment.
  - You may return to your doctor for follow-up care.
- If you do not meet the eligibility criteria for a study or cannot otherwise participate in a trial:
  - You will be able to receive an FMT from your doctor in the same way you would today.

What would this policy change mean for doctors?
- If you obtain material from a stool bank, before treating your patients with an FMT, you would be required to pre-screen their eligibility for participation in applicable clinical

trials. OpenBiome will provide a summary checklist outlining the publicly available pre-screen criteria for enrolling trials, trial site locations, and links to more information.

- In addition to documenting your discussion of informed consent with your patients regarding their treatment options, you would document the patient’s eligibility or ineligibility for trial participation based on this pre-screen at that time.
- If your patient is eligible for a trial within 50 miles or one hour’s travel of their primary residence:
  - You would connect them with enrollment personnel for the trial.
  - If the trial site does not enroll the patient into the trial, or the patient participates in a trial and experiences a recurrence for which they do not receive the open-label extension, the patient may return to you for a standard FMT.
- If your patient is not eligible for a trial within 50 miles or one hour’s travel of his or her primary residence:
  - He or she may receive an FMT from you as you would provide it today.
- For OpenBiome users, we will require your attestation on our Material Tracking Logs that each patient who received an FMT preparation from us was pre-screened for participation in applicable trials and was found to be eligible for enforcement discretion.

What would this policy change mean for industry?

- OpenBiome would provide your publicly available pre-screen criteria, contact information, and listings of your trial site locations to FMT providers using our material. While OpenBiome has an ongoing collaboration with Finch Therapeutics (read more [here](#)), we are committed to providing public information about all applicable trials.
- All clinicians using OpenBiome FMT material would be required to pre-screen their patients for applicable active trials prior to providing an FMT and will be able to use FMT only if the patient is not eligible or able to enroll in an ongoing trial.
- You would be expected to manage the influx of potential study subjects from treating physicians and ensure that individuals are screened – and if eligible, enrolled – in a timely manner.

What would this policy change mean for OpenBiome?

- OpenBiome would provide publicly available pre-screen criteria, contact information, and listings of trial site locations on our website and in our guides to clinicians who use our FMT preparations. While OpenBiome has an ongoing collaboration with Finch Therapeutics (read more [here](#)), we are committed to providing public information about all applicable trials in these materials.
- OpenBiome would require that all of the FMT providers we serve confirm that they have pre-screened their patients for applicable trials prior to providing an FMT and that he or she qualified under enforcement discretion.

Please share your comments with us at comments@openbiome.org by November 16, 2018.