Dear Partners,

I am pleased to share OpenBiome’s Biannual Quality and Safety Report for June through December 2018.

As of December 31, 2018, your practice and over 1,100 others have received more than 40,000 FMT preparations for the treatment of recurrent C. difficile infection (CDI) not responsive to antibiotics.

The information you share about each treatment and each patient’s response through the Material Tracking Logs and Follow-Up Forms provides invaluable data that we use to maintain the quality of our service and share best practices in patient care. As we continue to evaluate our program and continually improve it, we are thankful for your ongoing input and partnership.

This fall, we presented abstracts at Infectious Disease Week as well as conferences held by the American College of Gastroenterology (ACG) and The American Society of Tropical Medicine and Hygiene (ASTMH). We were excited to meet several of you during this time and discuss advances in FMT use, including expanding pediatric access to FMT and evaluating whether clinical factors could predict engraftment.

At ASTMH, Dr. Majdi Osman moderated a panel on global health where we discussed the widening disparity between microbiome research being conducted in North America and Europe compared to the rest of the world. To narrow this gap, we are applying knowledge we have gathered from working with you and treating C. difficile to address global health challenges that may present possibilities for treatment through the microbiome. With support from the Bill & Melinda Gates Foundation, Child Relief International, and the Thrasher Foundation, we have opened enrollment in our inaugural global health study – a pilot study taking place in South Africa evaluating FMT as a treatment for refractory pediatric severe acute malnutrition.

The growth of the microbiome field over the past five years has been remarkable. We look forward to sharing future findings and working with you to explore how engineering the microbiome can be used to improve patient care.

Sincerely,

Carolyn Edelstein
Executive Director
Dear Clinical Partners,

Thank you for your continued collaboration in enabling safe access to fecal microbiota transplantation (FMT) for patients. Because of your care and dedication, we were able to reach a significant milestone: the shipment of our 40,000th treatment.

FMT is regulated as an investigational treatment and your participation in the Material Tracking Log and Follow-Up Form Program provides invaluable information on patient safety. This data is compiled and shared with our network and with regulators. It informs our stool banking practice and helps us maintain the highest levels of safety across our network. Please continue to report any suspected adverse events to us at www.openbiome.org/adverse-events.

In the second half of 2018, 22 adverse events (AEs) were reported to OpenBiome: 18 were determined to be unrelated to FMT, and 4 were identified as possibly related to FMT. **No AEs were determined to be definitely related to FMT material.** More detailed information on these cases is located on page 9.

In addition to serving patients, OpenBiome is also committed to clinical education and promoting research seeking to better understand FMT and the human microbiome. We enjoyed seeing presentations and exchanging ideas with many of you at Infectious Disease Week this fall. We presented data on the determinants of microbial engraftment in patients receiving FMT for recurrent *C. difficile*. In collaboration with our colleagues at the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition FMT Special Interest Group we also presented an analysis of the expansion of pediatric facilities offering FMT over the past 5 years.

Working with and learning from a community of physicians and researchers has been an honor, and I look forward to meeting many of you at future conferences. Please do not hesitate to reach out to me with any questions or specific issues you would like to see addressed in future editions of this report. We greatly appreciate your feedback and your continued collaboration.

Dr. Majdi Osman, MD MPH
Clinical Program Director
BIANNUAL SAFETY DEBRIEF
JUNE-DECEMBER 2018

From June 15, 2018 through December 31, 2018, 22 adverse events (AEs) were reported to OpenBiome by members of our clinical network. During this window, OpenBiome shipped a total of 6,571 treatments to clinical partners. OpenBiome revised our pharmacovigilance program to recommend reporting of all deaths following FMT, regardless of relatedness; this has increased the overall number of AEs reported in this period compared to previous periods. Below, we have aggregated patient characteristics from reported adverse events and lessons learned from the subsequent investigations.

Patient characteristics in reported adverse events. Ten of the patients involved in adverse events were reported as having refractory CDI (45.5%, n=10). The treatment modalities included liquid preparations delivered via the lower gastrointestinal tract (40.9%, n=9) and upper gastrointestinal tract (31.8%, n=7), as well as oral capsules (27.3%, n=6). There were twelve deaths (54.5%, n=12) during the reporting period, all of which were determined to be unrelated to FMT. Reported adverse events are graded according to severity by NIH grading criteria (Figure 1).

Adverse Event (AE) NIH Relatedness. Based on information gathered through in-depth collaborative investigations with reporting partners, all cases were classified according to NIH Relatedness definitions. 18 of the reported AEs (81.8%) were determined to be not related to the FMT material and the remaining 4 AEs (18.2%) were identified as possibly related to the FMT material. No reported AEs were determined to be definitely related to FMT material.

1. Disease Adverse Event Grading Scale, National Institutes of Health
   Grade 1. Mild: Symptoms causing no or minimal interference with usual social & functional activities
   Grade 2. Moderate: Symptoms causing greater than minimal interference with usual social & functional activities
   Grade 3. Severe: Symptoms causing inability to perform usual social & functional activities
   Grade 4. Potentially Life Threatening: Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, or persistent disability
   Grade 5. Death

2. Definitions of Relatedness, National Institutes of Health
   Not Related: The adverse event is clearly not related to the investigational agent/procedure. - i.e. another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible.
   Possibly Related: An adverse event that follows a reasonable temporal sequence from administration of the study intervention follows a known or expected response pattern to the suspected intervention, but that could readily have been produced by a number of other factors.
   Definitely Related: The adverse event is clearly related to the investigational agent/procedure - i.e. an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject’s clinical state.
OpenBiome’s Clinical Outreach team supports physicians looking to perform FMT to treat recurrent *C. difficile*, and their patients. Representatives are available to share information and answer your questions by email at info@openbiome.org or phone (617-575-2201) from 9AM-5PM ET Monday-Friday. Below, we have answered some commonly asked questions.

**Can I transfer FMT preparations between hospitals?**
We do not allow the transfer of FMT preparations between hospitals, even if they are in the same network. For safety and quality purposes, preparations need to be stored at -20 degrees Celsius or below. Transporting, thawing, or incorrectly storing materials will compromise the condition of the FMT preparation. To ensure optimal patient care, please order another FMT preparation to be shipped to the desired location.

**Can I use FMP30 for lower delivery or FMP250 for upper delivery?**
FMP30 is for administration only via upper delivery (i.e. nasoenteric/gastric tube, EGD). FMP250 is for administration only via lower delivery (i.e. colonoscopy, sigmoidoscopy, or enema). The FMP30 and FMP250 formulations have been designed to maximize the safety and efficacy of their respective modality. **Treating a patient with more than 30 ml of FMT at one time via upper delivery increases the risk of aspiration and other complications, and is strictly contraindicated per our guidelines.**

**Do I need to report a serious adverse event (SAE) even if I am sure that the event is unrelated to FMT?**
If you are concerned that or unsure if a serious adverse event could be related to an OpenBiome FMT treatment, please report it immediately. Further guidance is provided in the following pages. Our online adverse event form and more information can be found at [www.openbiome.org/adverse-events](http://www.openbiome.org/adverse-events).
Common, mild adverse reactions after FMT delivery:

Mild, self-limiting symptoms may occur after FMT and should be clearly discussed with patients during informed consent. Based on the peer-reviewed literature, potential expected non-serious adverse reactions that can be anticipated after FMT are:

- Transient diarrhea
- Transient abdominal cramps or discomfort
- Nausea
- Constipation
- Excess flatulence

In addition to the above, mild fever, bloating, vomiting, and borborygmus have been reported to occur after FMT. Expected mild adverse reactions do not require reporting to OpenBiome.

Managing treatment failure:

CDI recurrence or non-response has been known to occur in approximately 10-20% of patients post-FMT. In events where CDI recurrence or non-response is suspected (e.g. development of or continued diarrhea, abdominal pain, etc.), a full work-up should be conducted to rule out other infectious etiologies. Non-infectious etiologies should also be considered (e.g. post-infectious IBS). Cases where CDI recurrence or non-response has been confirmed do not require reporting to OpenBiome.

Serious adverse events that warrant reporting:

While there have not been any definitely related serious adverse events attributable to FMT material, should a serious adverse event (SAE) occur within a reasonable timeframe post-FMT where relatedness of the FMT material cannot be definitively ruled out, these SAEs should be reported to OpenBiome. Examples of such SAEs include:

- Post-FMT new onset of infectious diarrhea
- Post-FMT new onset of sepsis
- Allergy or anaphylaxis

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There is a theoretical risk of developing disease that may be related to donor gut microbiota. These include obesity, metabolic syndrome, cardiovascular disease, autoimmune conditions, allergic/atopic disorders, neurologic disorders, psychiatric conditions and malignancy. People with these and similar conditions are excluded from donating stool to OpenBiome. However, if an FMT recipient appears to be experiencing a new onset of any of these diseases and FMT is suspected, this should be reported.

In addition to the above, any SAEs, as defined by the FDA (21 CFR 312.32(c)(1)(i)) where there is uncertainty in the relationship between the event and the FMT, must be reported to OpenBiome.

Adverse events should be reported to OpenBiome through the online portal (www.openbiome.org/adverse-events). Clinicians may contact the Safety Team directly (617-575-2201 ext. 9) to discuss whether an SAE requires reporting.
All adverse events reported to OpenBiome that were possibly related to FMT and investigated between June and December 2018 are summarized in the table below. Clinicians who are interested in learning more about specific adverse events reported to OpenBiome are welcome to request a copy of the detailed case narratives by contacting safety@openbiome.org.

<table>
<thead>
<tr>
<th>Summary</th>
<th>CDI type</th>
<th>Severity (NIH grade)</th>
<th>Relatedness (NIH definition)</th>
<th>Background</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea, emesis</td>
<td>Recurrent CDI</td>
<td>Grade 1. Mild</td>
<td>Possibly related</td>
<td>38F</td>
</tr>
<tr>
<td>Dehydration, diarrhea, fever, abdominal pain</td>
<td>Recurrent CDI</td>
<td>Grade 4. Pot Life-Threatening</td>
<td>Possibly related</td>
<td>72M</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>Recurrent CDI</td>
<td>Grade 1. Mild</td>
<td>Possibly related</td>
<td>65F</td>
</tr>
<tr>
<td>Nausea, emesis</td>
<td>Recurrent CDI</td>
<td>Grade 1. Mild</td>
<td>Possibly related</td>
<td>58F</td>
</tr>
</tbody>
</table>