Dear Partners,

I am pleased to share OpenBiome’s Biannual Safety and Quality Report for December 2017 through June 2018.

OpenBiome’s nonprofit mission is to enable safe access to fecal microbiota transplantation (FMT) for patients with recurrent C. difficile infection. Through our partnership with practices like yours, thousands of patients have received life-saving treatment.

To date, we have shipped over 36,000 FMT preparations to more than 1,100 healthcare facilities across the country.

We enjoyed seeing many of you again at Digestive Disease Week in June 2018. To share some of the data from our programs, Dr. Pratik Panchal and colleagues mapped patient access to FMT in the United States from 2013-2017, demonstrating that 98% of Americans now live within a two-hour drive from one of our clinical partners.

We continued our collaborations with academic investigators to explore FMT as a treatment in other indications including food allergies, cirrhosis, and depression. Our research portfolio represents 36% of all active FMT trials in the United States.

This year, we also launched OpenBiome’s Global Health Initiative to evaluate whether FMT can combat diseases that primarily affect low- and middle-income countries. Our inaugural global health study, THRIVE, will evaluate microbial therapy as a new treatment for pediatric severe acute malnutrition (SAM), a life-threatening condition affecting 20 million children. The study was recently approved by SAPHRA, the governmental body regulating clinical trials in South Africa.

We are excited to continue working with you to explore the promise and scope of FMT. Please let us know if you have feedback on the contents of this report.

Sincerely,

Carolyn Edelstein
Executive Director
Dear Clinical Partners,

Thank you for your continued collaboration and assistance in providing safe, accountable, high-quality fecal microbiota transplantation (FMT) for patients.

At OpenBiome, we rely on your feedback—through the Material Tracking Log and Follow-up program—to ensure the highest possible level of safety across our network. Because of your participation, we are able to monitor treatments of individual donors and quickly respond to any suspected adverse events.

From December 2017 to June 2018, we received reports of 35 serious adverse events (AEs) to OpenBiome: 29 were determined to be unrelated to FMT, and 6 were identified as possibly related to FMT. You can read about these cases in more detail on page 8. No reported AEs were determined to be definitely related to FMT material.

Please continue to document any suspected adverse events (AEs) at: https://www.openbiome.org/adverse-events

It was wonderful to see many of you at Digestive Disease Week in June. I was inspired to see such a large body of work ranging from using machine learning to predict whether a C. difficile patient would experience recurrence to demonstrating efficacy of FMT in solid organ transplant recipients with C. difficile infections. Several presenters also shared study results exploring the potential of FMT to treat other illnesses such as irritable bowel syndrome, hepatic encephalopathy, and ulcerative colitis.

As the progress of microbiome-based therapies continues to accelerate, I look forward to continuing our partnerships and bringing the best possible care to patients. Thank you again for all your hard work. We appreciate your continued feedback and engagement that guides our mission at OpenBiome.

Dr. Majdi Osman, MD MPH
Clinical Program Director
From December 15, 2017 through June 15, 2018, 35 adverse events were reported to OpenBiome by members of our clinical network. During this window, OpenBiome shipped a total of 6,266 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 suspected adverse events.** Eighteen of the patients involved in adverse events were reported as having severe or severe-complicated CDI (51.4%, n=18). The most common treatment modalities were liquid preparations delivered via the lower gastrointestinal tract (62.9%, n=22) and upper gastrointestinal tract (28.5%, n=10). Three patients involved in adverse events were treated with capsules (8.6%, n=3). There were fifteen deaths (42.8%, n=15) 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. 29 of the reported AEs (82.9%) were determined to be not related to the FMT material and the remaining 6 AEs (17.1%) were identified as possibly related to the FMT material. **No reported AEs were determined to be definitely related to FMT material.**

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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, that is confirmed by improvement or 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.
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 have 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

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

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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 December 15, 2017 and June 15, 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>Fever</td>
<td>Recurrent CDI</td>
<td>Grade 2. Moderate</td>
<td>Possibly related</td>
<td>80M</td>
</tr>
<tr>
<td>Fever, septic shock</td>
<td>Recurrent CDI, Severe</td>
<td>Grade 4. Pot Life-Threatening</td>
<td>Possibly related</td>
<td>4F with history of heart transplant</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Recurrent CDI, Severe</td>
<td>Grade 4. Pot Life-Threatening</td>
<td>Possibly related</td>
<td>51M with history of acute kidney injury on hemodialysis, positive blood culture, alcohol abuse (ETOH)</td>
</tr>
<tr>
<td>IBD flare</td>
<td>Recurrent CDI, Mild-Moderate</td>
<td>Grade 3. Severe</td>
<td>Possibly related</td>
<td>29M with history of Ulcerative colitis, primary sclerosing cholangitis</td>
</tr>
<tr>
<td>Microscopic colitis</td>
<td>Recurrent CDI, Mild-Moderate</td>
<td>Grade 1. Mild</td>
<td>Possibly related</td>
<td>34F with history of Pseudotumor cerebri, anxiety, obesity, nonalcoholic steatohepatitis</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa bacteremia</td>
<td>Recurrent &amp; Refractory CDI, Severe</td>
<td>Grade 4. Pot Life-Threatening</td>
<td>Possibly related</td>
<td>5M with history of DiGeorge syndrome, complex congenital heart disease, intestinal failure requiring TPN, respiratory failure, recurrent central line infections</td>
</tr>
</tbody>
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