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Dear Partners,

I am pleased to share OpenBiome’s Biannual Safety and Quality Report for January 2019 through June 2019.

As you may know, we provide these reports every six months to keep you informed of safety information related to our fecal microbiota preparations. Each report, aggregating experiences from across our clinical network, depends on data that you provide through OpenBiome’s Material Tracking Logs and Follow-Up Forms. We are grateful for your ongoing partnership in maintaining patient safety.

OpenBiome’s mission is to enable safe access to fecal microbiota transplantation (FMT), for treating recurrent Clostridioides difficile infections, in keeping with clinical guidelines such as those published by the American College of Gastroenterology and the Infectious Disease Society of America. As of June 30, 2019, we have shipped over 47,000 FMT preparations to more than 1,200 healthcare facilities across the country. During this time, there were no reported infections or deaths definitely related to OpenBiome FMT material. Thank you again for your participation in our continuous monitoring of safety and adverse events.

The importance of maintaining and consistently improving upon a robust safety and quality infrastructure for FMT was underscored by a safety alert released on June 13 by the FDA. The report describes the transmission, through FMT material, of Extended Spectrum Beta-Lactamase (ESBL)-producing Escherichia coli into two FMT recipients, resulting in one death.

The FMT material in these cases was not from OpenBiome, and was not screened for antibiotic-resistant organisms. Our routine donor assessments include screens for multidrug-resistant organisms and already meet the new safety requirements set forth by the FDA. We look forward to continuing our service to patients with C. difficile as well as the community of healthcare providers enabling access to FMT. Please do not hesitate to use us as a resource or offer feedback on our services. We are thankful for your ongoing input and partnership.

Sincerely,

Carolyn Edelstein
Executive Director
Dear Clinical Partners,

Thank you for working with us to provide patients with recurrent *Clostridioides difficile* access to fecal microbiota transplantation (FMT). Your participation in the Material Tracking Log and Follow-Up Form program has been essential to maintaining the highest levels of safety across our network. Please continue to report any suspected adverse events to us at www.openbiome.org/adverse-events.

From January 2019 to June 2019, we received reports of 17 serious adverse events (SAEs) to OpenBiome: 12 were determined to be unrelated to FMT, and 5 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.

On June 13, the FDA issued a safety alert regarding two FMT recipients who acquired Extended Spectrum Beta-Lactamase (ESBL)-producing *Escherichia coli* infections following FMT, resulting in one death. The material used in these cases was not from OpenBiome. In response, the FDA has released new screening requirements, all of which are met by OpenBiome. More detailed information on our safety and quality controls is located on page 6.

OpenBiome’s highest priority is vigilant management of safety in the treatment of C. difficile infection and for research into other indications. In addition to regular management and continuous improvement of our own safety programs, we present on our lessons learned to share information across the field. At Digestive Diseases Week this year, we presented a prospective evaluation on our donor screening protocol, looking at over 15,000 candidates that we have screened and the etiology of their exclusion, leading to a 2.5% qualification rate and the selection of healthy, robustly screened donors. Additionally, as FMT is used for research in other disease areas, we presented a systematic analysis of the global landscape of FMT clinical trials to identify disparities in microbiome research and patient access.

As the field of FMT and microbiome research continues to mature, I look forward to continuing our partnerships and maintaining the best possible care for patients. Please do not hesitate to reach out to me with any questions or specific issues that you would like to see addressed in future reports. We greatly appreciate your continued feedback and collaboration that enables our mission at OpenBiome.

Dr. Majdi Osman, MD MPH
Clinical Program Director
From January 1, 2019 through June 30, 2019, 17 adverse events were reported to OpenBiome by members of our clinical network. During this window, OpenBiome shipped a total of 5,824 treatments to clinical partners. Below, we have aggregated patient characteristics from reported adverse events and lessons learned from the subsequent investigations.

**Patient characteristics in suspected adverse events.** Nine of the patients involved in adverse events were reported as having severe or severe-complicated CDI (52.9%, n=9). The most common treatment modalities were liquid preparations delivered via the lower gastrointestinal tract (70.6%, n=12) and upper gastrointestinal tract (17.6%, n=3). There were nine deaths (52.9%, n=9) 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 investigations with reporting partners, all cases were classified according to NIH Relatedness definitions. 12 of the reported AEs (70.6%) were determined to be not related to the FMT material and the remaining five AEs (29.4%) 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, 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.
KEY LESSON LEARNED
Response to FDA Safety Alert

FDA Safety Alert: On June 13th, the FDA issued a safety alert regarding two FMT recipients who acquired Extended Spectrum Beta-Lactamase (ESBL)-producing Escherichia coli infections following FMT, resulting in one death.

- OpenBiome FMT material was not involved with the adverse events described in the FDA-issued safety alert.
- The FDA has confirmed that OpenBiome FMT material may continue to be used to treat patients with C. difficile, and for ongoing clinical trial collaborations.
- OpenBiome FMT donors are screened for multidrug-resistant organisms (MDROs) and MDRO risk factors, and meet all FDA screening requirements.

OpenBiome rigorously screens potential donors to identify infectious risk factors and potential microbiome-mediated conditions. To screen for multidrug-resistant organisms (MDROs), we use the following culture-based assays, which are performed by a third-party Clinical Laboratory Improvement Amendments (CLIA)-certified testing facility:

- **Stool Testing:** Vancomycin-Resistant Enterococcus (VRE); Extended spectrum beta-lactamase (ESBL); Carbapenemase producing gram-negative rods (CRE).
- **Nasal Swab:** Methicillin-resistant Staphylococcus aureus (MRSA).

OpenBiome also excludes donors over MDRO risk factors, which include working in a health care facility and engaging in medical tourism.

Less than 3% of potential donors pass our screening protocol. Those that do become eligible to donate stool for up to 60 days following the initial screening. During this collection period, material is placed in quarantine until the donor passes a second round of testing on Day 60. More information on our quality and safety program can be found on our website.

**Informed consent is a mandatory and crucial step in patient preparation:** Patients should have an informed discussion with their physicians in order to understand the risks associated with FMT and weigh them against other treatment options including no treatment and standard antibiotic regimens. In the informed consent discussion, patients should consider the risks associated with FMT, including the risk of infectious disease transmission, such as antibiotic resistant bacteria, and the potential of developing microbiome-mediated diseases. If needed, a template for obtaining informed consent can be requested at info@openbiome.org. You may also find our Pre-FMT Patient Guide a helpful educational resource.
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 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 January 1, 2019 and June 30, 2019 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, Mild-Moderate</td>
<td>Grade 3. Severe</td>
<td>Possibly related</td>
<td>57F with a history of Addison’s disease, chronic pain, and opioid dependence</td>
</tr>
<tr>
<td>Sepsis (source unknown)</td>
<td>Recurrent CDI, Mild-Moderate</td>
<td>Grade 4. Pot. Life-Threatening</td>
<td>Possibly related</td>
<td>70M with history of renal transplant, diverticulosis, and atrial flutter</td>
</tr>
<tr>
<td>Sepsis (source unknown)</td>
<td>Recurrent CDI, Severe-Complicated</td>
<td>Grade 5. Death</td>
<td>Possibly related</td>
<td>71F with history of obesity, acute renal failure, myocardial infarction, and chronic obstructive pulmonary disorder</td>
</tr>
<tr>
<td>Lymphocytic colitis</td>
<td>Recurrent CDI, Mild-Moderate</td>
<td>Grade 2. Moderate</td>
<td>Possibly related</td>
<td>62F with history of bipolar disease, thyroid disorder, and NSAID use</td>
</tr>
<tr>
<td>Infectious diarrhea (EPEC, ETEC, and Shiga producing E. coli 0157:H7)</td>
<td>Recurrent CDI, Severe</td>
<td>Grade 3. Severe</td>
<td>Possibly related</td>
<td>19M with history of Primary IgA deficiency.</td>
</tr>
</tbody>
</table>