Quality & Safety Program

BIANNUAL REPORT
2016 | JULY – DECEMBER
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Dear Partners,

Welcome to OpenBiome’s Biannual Safety and Quality Report for June-December 2016. Every six months, we share an update on the following topics:
• Adverse Events reported to OpenBiome by members of our clinical network
• Key lessons learned and accomplishments from across the network
• Updates to our Quality and Safety Program (Q&SP)
• Research highlights from OpenBiome

As of January 2017, your facility, along with more than 800 other medical centers that have partnered with OpenBiome, have accepted more than 20,000 treatments. At this year’s American College of Gastroenterology conference we were proud to share that 97% of the US population is now within a 2-hour drive of a center providing fecal microbiota transplantation (FMT). At IDWeek, we shared clinical outcome data you provided for 2,050 patients, which showed that FMT had an 84% efficacy across delivery modalities and CDI types. Coming just three years since our public launch, these milestones represent a significant advancement in safe access to FMT.

**OpenBiome’s collaboration with Finch Therapeutics**

To sustain patient access to this treatment, we are excited to announce that as of March 1, 2017, OpenBiome will be partnering with Finch Therapeutics to seek FDA approval for an FMT product for recurrent *C. difficile* infection and to develop next-generation microbial therapies. OpenBiome will license its stool banking technology to Finch’s team of microbiologists, data scientists, and drug delivery experts, and Finch will become the contract manufacturer of the material that OpenBiome provides.

OpenBiome will continue to provide safe access to fecal microbiota transplantation (FMT) for patients with recurrent *C. difficile* today, and we will help Finch secure FDA approval for FMT treatment so that patients continue to have access to FMT in perpetuity. For a complete statement on why we feel this is the best option for ensuring patient safety and promoting vital research, please see our open letter to the clinicians and researchers we serve at [www.openbiome.org/letter-to-clinicians](http://www.openbiome.org/letter-to-clinicians).

Sincerely,

James Burgess
Executive Director
Dear Physicians and Allied Health Professionals,

We hope that you have had a wonderful start to 2017 and wish to thank you for your continued collaboration in maintaining the highest levels of safety across our network.

**Safety and efficacy:**
I’d like to thank you for your continued participation in the Material Tracking Log (MTL) and Follow-up Form program. The information you provide is crucial to our quality assurance and for the protection of patients throughout our network. This quality assurance data allows us to monitor our material’s efficacy and proactively respond to any network-wide patterns. Your work is directly supporting the safety of patients around the country.

In the second half of 2016, 29 serious adverse events were reported to OpenBiome. 28 were determined to be not related to FMT, and one was identified as possibly related to FMT. **No reported AEs were determined to be definitely related to FMT material.** You may read more about these reports on page 7.

At ID Week 2016, I shared results from 2,050 patients at 482 healthcare facilities in 50 U.S. states and six countries between January 16, 2014 and April 12, 2016. Reported efficacy was 84% and no adverse events were definitively related to FMT materials. Out of 42 reported adverse events (AEs), no AEs were determined to be definitely related to FMT, three were possibly related to FMT and 39 were not related based on NIH criteria.

The foundation underpinning all our work is patient safety. We are grateful to you all for reporting clinical outcomes and suspected adverse events in a timely manner. From June-December 2016, I am pleased to confirm that through in-depth, collaborative investigations with all reporting clinical partners, no adverse events reported to OpenBiome have been determined to be definitely related to FMT material. Based on these investigations, there are several key takeaways from the adverse events reported to OpenBiome in the second half of 2016, which we are pleased to share with you in this report.

**Clinical research:**
In the second half of 2016 we were also thrilled to announce that we have received two grants from the Centers for Disease Control and Prevention (CDC) totaling $1,050,000 to study FMT in treating vancomycin-resistant enterococcus (VRE) and to explore the use of autologous fecal transplants, in which a patient receives their own banked fecal material to prevent to prevent colonization by multi-drug resistant organisms following antibiotic therapy.
I had the pleasure of meeting many of you at ID Week this year, and much of our team also enjoyed interacting with you at the American College of Gastroenterology Annual Meeting. I very much look forward to engaging with all of you in the coming months. We greatly appreciate your continued feedback and insights that shape our work at OpenBiome.

Thank you again for your continued collaboration as we expand safe access for patients with C. difficile.

Sincerely,

Majdi Osman, MD, MPH, MRCP, DTM&H
Clinical Program Director
From July through December 2016, 29 suspected adverse events were reported to OpenBiome by members of our clinical network. Below, we have aggregated patient characteristics from these suspected adverse events and lessons learned from the subsequent investigations.

**Patient characteristics in suspected adverse events.** Patients involved in the 29 adverse events predominantly had a Modified Horn's Index 3 or higher (59%, n=17). Additionally, 55% (n=16) of this patient group was reported as having severe or severe-complicated CDI. Patients received FMT via lower gastrointestinal delivery (62%, n=18), upper gastrointestinal delivery (28%, n=8) and capsules (10%, n=3).

The severity of all adverse events reported to OpenBiome are graded according to standard NIH criteria. The majority of reported adverse events this quarter were Grades 4 and 5 (Figure 1).

**Adverse Event NIH Relatedness.** All cases were classified according to NIH Relatedness definitions based on information gathered through in-depth collaborative investigations with reporting partners. 28 of the reported AEs (97%) were determined to be not related and the remaining 1 AE (3%) was identified as possibly related to FMT. **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.
Below are summaries of the changes that OpenBiome has initiated over the past 6 months to improve safety and efficacy, as well as links to resources with more information.

**Donor Screening Program**

OpenBiome continuously works to improve the safety of the FMT preparations that we provide. To this end, in August 2016, we added several new screens for multi-drug resistant organisms (MDROs) to our regular donor screening program including:

- Extended Spectrum Beta-Lactamases (ESBL)
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Methicillin-resistant Staphylococcus aureus (MRSA)

**Adverse event reporting**

As of March 1, 2017, OpenBiome will be contracting Finch Therapeutics to conduct the biomanufacturing of FMT preparations. A synopsis of the agreement is available in our letter to the clinicians and researchers we serve at [www.openbiome.org/letter-to-clinicians](http://www.openbiome.org/letter-to-clinicians).

Reports of adverse events (AE) will be relayed directly to our manufacturer to enable rapid, coordinated responses to suspected adverse events. You may continue to report adverse events through any of the following channels:

- Online: [www.openbiome.org/adverse-events](http://www.openbiome.org/adverse-events)
- Email: safety@openbiome.org
- Phone: (617) 575-2201 option 9 to contact Finch’s Clinical Safety Team

We ask that all clinical sites report serious adverse events within 24 hours. A clinician from Finch Therapeutics will be in touch upon receiving the report to initiate an investigation and discuss any next steps, including submission of Form FDA 3500 if necessary.

For a more in-depth review of this new protocol, as well as examples of these new documents, please see the [OpenBiome Quality & Safety Program](#).
Reducing the risk of community-acquired infectious gastroenteritis post-FMT
Adverse events where patients experience community acquired gastroenteritis after eating prepared meals from fast food outlets immediately post-FMT continue to be reported. As we presented this past fall at ACG Week, rapid improvement in symptoms and return of appetite can prompt patients to return to pre-CDI dietary habits (Osman et al. 2016). Patient education is crucial before and following FMT and can play a significant role in encouraging healthy eating and mitigating the risk of food-borne illnesses. Patients should be counseled on healthy eating behaviors, hand washing and ensuring that food is prepared in hygienic conditions.

Fever of unknown origin post-FMT
Transient, self-limiting, pan-culture negative fevers have been reported shortly after FMT in several adverse events. When a patient presents with fever post-FMT, a full sepsis work-up with infectious diseases consult will assist in determining whether antibiotic therapy is indicated.

Clinical response in recurrent CDI patients with inflammatory bowel disease (IBD)
IBD flares have been reported in the literature as a possible adverse event following FMT (Kunde et al. 2013; De Leon, Watson, and Kelly 2013; Khoruts et al. 2016). As such, we list this risk among potential adverse events in the inserts that accompany each treatment. However, although IBD flare is a potential complication of FMT, there is also a growing body of evidence suggesting that FMT may ameliorate the symptoms of IBD and reduce the frequency of flares (Colman and Rubin 2014; Moayyedi et al. 2015; Paramsothy et al. 2016). We advise our clinical partners that all patients with IBD should be counselled on the potential risks, benefits, and alternatives to FMT through appropriate informed consent process.

Evaluate for potential food allergies prior to FMT
Considering the risk of inadvertent allergen consumption among donors, to mitigate the risk of allergen exposure among FMT recipients clinicians should assume that any potential food allergen is present in fecal microbiota preparations. The responsible and administering physicians should screen recipients for food allergies and consider any serious food allergy as exclusion criteria for treatment with our fecal microbiota preparations.
SUMMARY OF ADVERSE EVENTS
JUNE-DEC 2016

All serious adverse events reported to OpenBiome that were possibly related to FMT and investigated between July and December 2016 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>Background</th>
<th>Adverse event</th>
<th>Summary</th>
<th>Severity (NIH grade)</th>
<th>Relatedness (NIH definition)</th>
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<tr>
<td>17 y/o male Ulcerative colitis</td>
<td>Fever, hypersensitivity</td>
<td>3</td>
<td>Possibly Related</td>
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Below, we have summarized this suspected adverse event.

Background: 17 y/o male Ulcerative colitis
Adverse event: Fever, hypersensitivity
Severity: 3
Relatedness: Possibly related

Summary: This suspected adverse reaction occurred in a patient with known poorly controlled ulcerative colitis. The hypersensitivity reaction occurred immediately after FMT. Hypersensitivity reactions have been known to occur in the context of enemas. Allergy and anaphylaxis is explicitly stated as a potential side effect on the product insert and materials. On further investigation, no clear cause for the self-limiting hypersensitivity reaction was identified. FMT could not be ruled out as a contributing factor to this patient’s symptoms and therefore this adverse event could possibly be related to FMT. Given the patient’s known history of poorly controlled ulcerative colitis and hypersensitivity reactions this adverse reaction was likely patient-dependent.