Dear Partners,

As we enter the second half of 2016, I am pleased to introduce our new Biannual Safety and Quality Report. Every six months, we will 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)
- A spotlighted clinical practice
- Research highlights from OpenBiome

This biannual report will replace our existing quarterly safety report, and we hope that it will provide a more consolidated and information-rich summary of updates from our program and partner network. If you have feedback on this or any other aspect of our program, please reach out to info@openbiome.org or to safety@openbiome.org.

Safety monitoring and reporting: As a reminder, in June, we announced changes to our monitoring and traceability requirements, in response to your requests that we disaggregate material tracking and patient outcome reporting. The Material Tracking Logs (MTLs) and new FMT Follow-up Forms are crucial to our quality assurance efforts and to the protection of patients throughout our network. The information your practice provides allows us to monitor the efficacy of our material, and proactively respond to any network-wide patterns that could be linked to one of our stool donors. We also streamlined our system for responding to adverse events, including with the creation of an online reporting form.

We were delighted to meet many of you in person at Digestive Disease Week in San Diego this past May. As always, your thoughtful feedback will help shape many of our next steps as we strive to make improvements that will promote patient safety and best practices in the field.

Thank you very much for your continued partnership and support.

Sincerely,

James Burgess
Executive Director
September 29, 2016

Fellow Physicians,

It has been an immense pleasure to work with you over the first half of 2016 on enhancing safety in fecal microbiota transplant. It was wonderful to meet so many of you at this year’s Digestive Diseases Week and I look forward to engaging in further insightful conversations with you in the future.

Based on the feedback of clinical partners across our network, we have made changes to facilitate adverse events reporting. You can now report adverse events to OpenBiome through openbiome.org/adverse-events and a member of our clinical team will follow up within 24 hours. We welcome feedback on how we can improve.

A total of 17 potential adverse events, involving 14 unique donors were reported to OpenBiome between January 2016 and June 2016. All such cases were reviewed in-depth by our Clinical Program Director and Chief Medical Officer following our predetermined safety protocol.

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. Four of the potential adverse events reported to OpenBiome were determined to be possibly related to FMT and 13 were determined to be not related to FMT. The possibly related adverse events are described in more detail in this report.

There are several key takeaways from the adverse events reported to OpenBiome in the first half of 2016, which we are pleased to share with you below as well.

We are grateful for your continued collaboration in setting the highest levels of safety for all patients receiving FMT.

Sincerely,

Majdi Osman, MD, MPH, MRCP, DTM&H
Clinical Program Director
From January through June, 17 adverse events were reported to OpenBiome by members of our clinical network. Below, we have aggregated patient characteristics in suspected adverse events and lessons learned from the subsequent investigations.

**Patient characteristics in suspected adverse events.** Patients involved in adverse events predominantly had a Modified Horn Index 3 or higher (59%, n=10). Additionally, 29% (n=5) of recipients were reported as having severe or severe-complicated CDI disease. Treatment modalities were via lower delivery (53%, n=9), upper delivery (29%, n=5) and capsules (18%, n=3).

On reporting to OpenBiome, all adverse events are graded according to severity by NIH grading criteria. The severity of reported adverse events (Figure 1) were evenly distributed across all grades of severity.

**Adverse Event NIH Relatedness.** Based on information gathered through in-depth collaborative investigations with reporting partners, all cases were classified according to NIH Relatedness definitions. 13 of the reported AEs (76%) were determined to be not related and the remaining 4 AEs (24%) were identified as possibly related to FMT. No reported AEs were determined to be definitely related to FMT material.

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**Fig. 1: Adverse Events by NIH Severity Grade**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild: Symptoms causing no or minimal interference with usual social &amp; functional activities</td>
</tr>
<tr>
<td>2</td>
<td>Moderate: Symptoms causing greater than minimal interference with usual social &amp; functional activities</td>
</tr>
<tr>
<td>3</td>
<td>Severe: Symptoms causing inability to perform usual social &amp; functional activities</td>
</tr>
<tr>
<td>4</td>
<td>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</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
</tr>
</tbody>
</table>

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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

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**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.
In May, we announced changes to our safety monitoring and material tracking system in response to feedback from members of our clinical network. Below are summaries of the changes that we announced, as well as links to resources with more information.

**Safety monitoring and tracking**
We collect data from clinical sites as part of the quality and safety monitoring we conduct. Through a review of the program, we learned that the data we request would be easier to collect and share if the tools were designed for different staff roles within a clinical practice. Guided by this feedback, we introduced the following reporting system:

1. **A revised Material Tracking Log**: This form asks for information about the receipt, storage, and use of the material we ship to you, and encourages healthcare staff to include the treatment ID in a patient’s records. Data from the Material Tracking Log would be used in facilitating a network-wide recall.

2. **A new FMT Follow-Up Form**: This new form replaces the information we removed from the Material Tracking Log, including de-identified patient specifics about disease severity, administration route, and the treatment outcome 8 weeks post-procedure. This form is designed for completion by the treating physician or medical staff at the time of treatment and returned to OpenBiome after the patient’s 8-week follow-up. It allows us to conduct network-wide surveillance for safety signals that should trigger further action.

As part of these changes, we no longer require submission of nonresponse forms.

**Adverse event reporting**
We introduced an online adverse event reporting tool to facilitate our coordinated response to suspected adverse events. The online tool may be found at [www.openbiome.org/adverse-events](http://www.openbiome.org/adverse-events). We ask that all clinical sites report suspected adverse events to OpenBiome within 24 hours. An OpenBiome clinician will be in touch within 24 hours of receiving a report to discuss next steps, including submission of Form FDA 3500 if necessary.

As always, our Clinical Assessment & Safety Team is available by phone at 617-575-2201, option 1 for a more timely response in the case of a serious adverse event.

For a more in-depth review of this new protocol, as well as examples of these new documents, please see the "Introduction to the OpenBiome Quality & Safety Program."
KEY LESSONS LEARNED
JAN-JUNE 2016

Reducing the risk of community acquired infectious gastroenteritis post-FMT
Adverse events where patients experience community acquired gastroenteritis after eating prepared meals from restaurants and fast food outlets immediately post-FMT, continue to be reported. FMT can have a transformative impact on CDI symptoms, with clinical cure in 82% of cases. Rapid improvement in symptoms and return of appetite can prompt patients to return to pre-CDI dietary habits. Patient education is crucial before and following FMT and can play a significant role in encouraging healthy eating and preservation of the transplanted microbiota. 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 presented with fever post-FMT, a full sepsis work-up with infectious diseases consult will assist in determining whether antibiotic therapy is indicated.

Use of FMT capsules in severely immunocompromised patients
Severe immunosuppression should be considered by the reporting clinician prior to FMT by capsule as a contraindication. There is limited data for FMT in recurrent CDI among the immunocompromised population. The most robust data come from a center retrospective review of 80 (75 adult and 5 pediatric) immunocompromised patients with CDI, predominantly outpatient, undergoing FMT (Kelly 2014). Broadly speaking, immunocompromised patients appear to have approximately the same rates of clinical cure; however, more data is needed given the limitations of retrospective case series data.

The need for proper assessment of patient allergies
Severe food allergy (e.g. anaphylaxis or anaphylactoid reaction) and allergies to ingredients “generally recognized as safe” (glycerol, sodium chloride, hypromellose, gellan gum, titanium dioxide, cocoa butter) are considered contraindications to FMT. A full allergy history should be taken prior to FMT to rule out these contraindications. In the consent process, patients should also be informed of the potential for allergic reaction to antigens in donor stool.
All adverse events reported to OpenBiome that were possibly related to FMT and investigated between January and June 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>CDI type and severity</th>
<th>Adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Summary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severity (NIH grade)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Relatedness (NIH definition)</td>
</tr>
<tr>
<td>64 y/o female</td>
<td>Recurrent Mild-Moderate</td>
<td>Urticaria</td>
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<tr>
<td>Penicillin allergy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>82 y/o male</td>
<td>Recurrent Mild-Moderate</td>
<td>Fever, leukocytosis</td>
</tr>
<tr>
<td>Ischemic bowel, coronary artery disease</td>
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<tr>
<td>36 y/o male</td>
<td>Recurrent Mild-Moderate</td>
<td>Crohn’s flare</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>86 y/o male</td>
<td>Recurrent Severe-Complicated</td>
<td>ESBL- Klebsiella pneumonia bacteremia</td>
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<tr>
<td>hx of atrial fibrillation, hypertension, glaucoma</td>
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</tbody>
</table>

Below, we have summarized these adverse events.

**Summary:** A 64-year-old female with known history of penicillin allergy and recurrent *C. difficile* infection was treated with fecal microbiota preparation via capsules and developed urticaria approximately 4-5 hours post treatment. Her symptoms were mild with urticaria across trunk and arms. There was no pruritus, mucosal involvement or respiratory distress. Given the temporality of symptoms, it is not possible to definitively rule out capsules or material as factors in the development of urticaria within 24 hours post FMT. Based on this collaborative investigation, we concluded that this adverse event was possibly related to capsule FMT. The urticaria resolved with use of over the counter antihistamines.
Background: 82 y/o male
Ischemic bowel, coronary artery disease

Summary: 82-year-old male with multiple co-morbidities experienced a transient fever immediately post-FMT which resolved spontaneously with no intervention. Whilst no clear etiology was identified, this adverse event was deemed possibly related to FMT. Infectious disease work-up was unremarkable and a watch and wait approach was suggested. There was no noted change to consistency or frequency of bowel pattern with patient maintaining approximately 3 semi-formed stools per day post-FMT.

CDI type and severity: Recurrent
Adverse event: Fever, leukocytosis
Severity: 1
Relatedness: Possibly

Background: 36 y/o male
Crohn’s disease

Summary: 36-year-old male with a history of colectomy and ileal pouch since age 9 was diagnosed with mild to moderate recurrent C. difficile infection (Modified Horn Index 2) and underwent an FMT via pouchoscopy. The patient presented 4 weeks post FMT with low-grade fever and symptoms consistent with an IBD flare. Pouchoscopy was notable for inflammation and ulcerations in the pouch and in the terminal ileum. Infectious disease work-up was negative, including C. difficile by qPCR. It is unlikely that the IBD flare was related to FMT given the patient’s underlying pattern of frequent IBD flares on the background of active disease, suggesting disease progression. Additionally, the temporality of the symptoms (4 weeks) post-FMT are not supportive of causality given the nature of frequent flares in this IBD patient, and the patient’s symptoms resolved post-FMT. However, it is not possible to fully confirm that FMT did not contribute to this patient’s IBD flare and therefore this adverse event could possibly be related to FMT.

CDI type and severity: Recurrent
Adverse event: Crohn’s flare
Severity: 3
Relatedness: Possibly

Background: 86 y/o male
hx of atrial fibrillation, hypertension

Summary: 86-year-old male with a background of rCDI (Modified Horn Index 4) was admitted to with severe-complicated CDI. Despite maximal antimicrobial management, he continued to decline clinically with pseudomembranes noted on colonoscopy. The patient received a FMP 250 via sigmoidoscopy. Following FMT, the patient’s condition deteriorated rapidly with pneumonia precipitating septic shock. Blood cultures returned positive for Klebsiella pneumonia. Chest radiograph revealed pulmonary edema and retrocardiac density suggestive of pneumonia as the likely source for Klebsiella spp. The patient was intubated and placed on vasopressors but continued to deteriorate with worsening hypoxia and hypotension. CT abdominal exam showed no significant findings. Patient was started on broad spectrum antibiotics for septic shock. The most likely differential diagnosis for the source of the Klebsiella pneumonia bacteremia is pneumonia as evidence by notable chest radiograph and profound hypoxia. However, as there was no microbiological confirmation to definitely determine the source, this adverse event was classified as possibly related.

CDI type and severity: Recurrent
Adverse event: Klebsiella pneumonia bacteremia
Severity: 5
Relatedness: Possibly