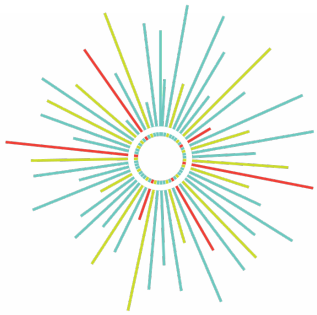

Tracking Patient Outcomes and Responding to Reports of Adverse Events

Considerations for Material Tracking and Pharmacovigilance

Justin Chen PhD, Director of External Affairs
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Abstract

Detection and response to reported safety events is one of a stool bank's most important roles. A robust material tracking and pharmacovigilance program enables timely responses to suspected adverse events including safety measures to mitigate risk to patients receiving FMT at centers being supplied by the stool bank. This paper presents OpenBiome's material tracking and pharmacovigilance program as an example for surveilling patient responses to FMT.

Table of Contents

Introduction

Tracking the safety and effectiveness of FMT material is a vital component of OpenBiome's Quality and Safety Program (Figure 1). All stool banks should ensure robust traceability of material and be able to quickly act on new safety information. The Pharmacovigilance (PVG) Department of a stool bank continuously monitors the efficacy and safety of FMT treatments on a per-unit basis and responds to suspected adverse events in a timely manner.

A list of personnel and communications involved in PVG is outlined below.

Personnel

Pharmacovigilance (PVG) Department

The size and organization of the Pharmacovigilance Department may vary depending on the scale and needs of the stool bank. At minimum, the department should comprise a physician whose responsibility is to review incoming safety and effectiveness data and communicate with regulatory authorities such as United States Food and Drug Administration (FDA). Larger stool banks, like OpenBiome, may use a third-party PVG vendor (e.g. a contract research organization) to support in case processing and responding to reports of adverse events.

OpenBiome's PVG Department interacts with the following organizations, teams, and individuals:

1. **Outreach Team:** Stool banking team responsible for registering healthcare facilities as clinical partners, collecting contact information of physicians and other healthcare facility staff and communicating with sites.

2. **Fulfillment Team:** Stool banking team responsible for shipping FMT units and associated documentation, including PVG forms, to partner physicians.

3. **Partner Physicians:** After treating a patient with FMT, PVG requires physicians to provide patient follow-up data and report adverse events.

4. **Patients:** Patients or patient family members may also report adverse events.

5. **Clinical Advisory Board (CAB):** An independent panel of medical and scientific experts who provide clinical advice on safety and best practices in FMT. Depending on the nature of the adverse event, the PVG department may rely on guidance from the CAB on how to conduct an investigation or follow-up actions including recalling affected material.

6. **United States Food and Drug Administration (FDA)**: Depending on the severity of reported adverse events, PVG notifies the FDA of such reports and regularly shares aggregate safety reports updating the Agency of the safety profile of FMT material.

Follow-up reporting and key documents

OpenBiome's PVG Department has three key responsibilities (Figure 2), each with of which is instrumental to patient safety and complying with FDA reporting requirement for investigational treatments.

1. **Establishing Points of Contact and Tracking Status of FMT Units**

   Before ordering an FMT preparation, OpenBiome requires partnering healthcare facilities to complete a **Clinical Registration Form** (Appendix 1). This form captures important points of contact from the registering site including:
   - One person who will manage the submission of subsequent paperwork including the Material Tracking Logs and Follow-Up Forms.
   - One person who will manage the reporting of any suspected adverse events following administration of FMT.
   - Any physician planning to administer FMT at the healthcare facility.

   After an FMT treatment unit is shipped to hospital, OpenBiome keeps track of the unit's status through a **Material Tracking Log (MTL).** This inventory log (Appendix 2) is included with every shipment to physicians and must be completed and submitted back to OpenBiome's Outreach team before their next order. Using this information, OpenBiome determines which units have been received by the partner healthcare facility, as well as whether the unit has been used, destroyed, or remains in storage for future use.

2. **Following up on Patient Response**

   OpenBiome monitors patient response to FMT treatment through an **FMT Follow-Up Form** (Appendix 3). This form is given to the administrating physician or their staff at the time of treatment and returned to OpenBiome after the patient's 8-week follow-up has been completed. The form requests de-identified patient information including delivery modality, disease severity, and treatment outcome. Patients are considered clinically cured of *C. difficile* if their chronic diarrhea has resolved after 8 weeks. Importantly, the FMT Follow-Up Form includes the FMT treatment unit ID so that the clinical outcomes can be traced to a treatment unit.

3. **Responding to Serious Adverse Events**
   OpenBiome requires physicians to report cases of a **Serious Adverse Event (SAE)**, **Suspected Adverse Reaction (SAR), or Adverse Event of Special Interest (AESI),** so that the stool bank's medical staff can determine whether the health condition may have been linked to FMT material and whether material manufactured from the same donor poses a health risk to patients. OpenBiome provides physicians with a **Reporting Adverse Event Checklist** (Appendix 4) with each FMT preparation.

   In the case of a reported SAE, SAR, or AESI, OpenBiome follows a decision algorithm (Figure 3) for timely and comprehensive investigations. This algorithm is discussed in more detail in subsequent sections of this white paper.

Key Takeaway
A stool bank's PVG Department works with other stool bank team members, physicians, and other hospital staff to collect information on the FMT units and patient response. These data are used to inform best practices of FMT as well as to identify and respond to potential health risks posed by FMT material. Communication between the PVG Department and hospital staff is initially mediated through paperwork that is included with FMT preparations.

Adverse Event Response Overview

Upon receiving a report of a **Serious Adverse Event (SAE)**, **Suspected Adverse Reaction (SAR), or Adverse Event of Special Interest (AESI)**, OpenBiome responds and opens an investigation following an **Adverse Event Reporting Algorithm** (Figure 4), discussed in a subsequent section. The goal of the investigation is to:

1. Determine whether FMT material in OpenBiome's inventory or in circulation at partner healthcare facilities poses a risk to patients.
   a. Part of this determination may include retrospectively testing safety aliquots—samples stool taken at the time of manufacturing—for infectious pathogens. Testing results will be used by the PVG to help determine whether an infectious agent could have been transmitted to the FMT recipient via FMT material.

2. Protect patients from potential risk posed by FMT material by placing a shipping hold on all FMT material associated with a donor under investigation, quarantining FMT material at partner sites, and/or issuing a notice to partner sites to destroy FMT material derived from a donor under investigation. These actions may be taken preemptively (before an investigation begins), during an investigation, or after an investigation concludes.

While instructing partner sites to report **adverse events** and responding to reports, the PVG team uses the following definitions.

Adverse Event: An adverse event is defined as any untoward medical occurrence in a patient or a clinical trial subject who is administered a drug/product which does not necessarily have a causal relationship with the product. An AE can be an unfavorable sign or unintended sign, a symptom, or a disease temporally associated with the use of a product, whether or not considered related to the product. An AE can arise from the use of the drug (or in combination with another product) and from any route of administration, formulation, dose including an overdose. An AE also includes, but is not limited to, any clinically significant worsening of a pre-existing condition.

Example of an Adverse Event include:

- Any sign, symptoms, physical finding.
- Laboratory result including those that has worsened in nature, severity or frequency compared to baseline.
- Concurrent illness that was not present or worsened in nature (e.g., recurrence of cancer), severity, or frequency compared to baseline
- Injury or accident (i.e., fall)
- Exacerbation or worsening of a pre- existing condition (e.g., worsening of pre- existing hypertension)
- Drug interactions
- Congenital anomalies
- Adverse events associated with Product Quality Complaints.
- Unexplained fatal outcome
- AEs documented in literature reports
- Suspected transmission of any infectious agent, which will also be classified as an **Adverse Event of Special Interest (AESI).**

Serious Adverse Event (SAE): An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the site or OpenBiome, it results in any of the following outcomes regardless of causality:

- Death
- Hospitalization, or prolongation of hospitalization
- A life-threatening event
- A persistent or incapacitating disability
- A congenital anomaly or birth defect
- An important medical event (i.e. the event may not result in death, be life-threatening or require hospitalization but may be considered a serious event based on upon medical judgement. It may jeopardize the patient and may

require medical attention or surgical intervention to avoid one of the outcomes listed above)

Suspected Adverse Reaction (SAR): Any adverse event, regardless of seriousness or severity, for which there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.

Adverse Event of Special Interest (AESI): An AESI is any adverse event that meets one of the two scenarios below

- **Suspected Transmission of an Infectious Agent:** Any adverse event where transmission of an infectious organism via the FMT may have occurred.
- **Suspected Transmission of a Multi-Drug Resistant Organism:** Any adverse event where transmission of a multi-drug resistant organism via the FMT may have occurred.

Key Takeaway

Safety monitoring of FMT, which remains and investigational drug in the US, is a crucial aspect of stool bank operations. Clinical partners are required to report any related serious adverse events to OpenBiome. By including FMT treatment unit IDs, all adverse events can be linked to a treatment unit. Safety testing of donor aliquots associated with each treatment unit allow a full investigation in the case of an a suspected infectious disease transmission.

Adverse Event Reporting Protocols

OpenBiome—through the **Reporting Adverse Event Checklist**, website text, and emails—instructs partner sites that become aware of an SAE, SAR, or AESI that occur following treatment with FMT material to follow these steps:

1. **Report to OpenBiome within 24 hours:** An adverse event contact or the treating physician must inform OpenBiome using an online reporting tool at www.openbiome.org/adverse-events(Appendix 5).
2. **Follow local procedures:** Their institution may have further measures and reporting requirements in the case of an adverse event. Sites should be advised to consult local guidelines.
3. **Investigation:** Upon receipt of an adverse event report, an OpenBiome drug safety professional may reach out to the reporting individual to gather more information on the case and determine next steps.
4. **FDA reporting:** An OpenBiome medical professional will use the details of the report and any ensuing investigation to determine if there are any additional reporting requirements, which may include submission of the event to the FDA via Form FDA 3500A.

Adverse Event Decision-Making Algorithm

OpenBiome has established the following series of actions (Figure 3) that are triggered upon receipt of an adverse event report. Establishing a response algorithm (Figure 3) is critical for pharmacovigilance and allows stool banks to coordinate responses in a timely comprehensive manner.

Adverse Event Decision-Making Algorithm Steps

Part 1

- **1a:** Suspected Adverse Event Occurs

- **1b:** Site clinician should follow local adverse event policies and protocols that have been established at their institution.

- **1c:** Site determines if the adverse event requires reporting to OpenBiome according to OpenBiome guidance
    - OpenBiome does not require that all Adverse Events be reported, only those that fall under the category of Serious Adverse Events, Suspected Adverse Reactions, and Adverse Events of Special Interest.

If on the initial assessment by the site clinician, the AE fulfills either SAE, SAR or AEOSI criteria for reporting to OpenBiome then proceed to **Step 1.D.**

If on the initial assessment by the site clinician, the AE does not fulfill the above criteria for reporting then the AE does not need to be reported to OpenBiome.

- **1d:** Site reports AE to OpenBiome within 24 hours through an online reporting form (Appendix 5)

- **1e:** Pharmacovigilance (PVG) team, or designated PVG vendor is notified that an SAE has occurred
    - On reporting the adverse event to OpenBiome through the online reporting form, OpenBiome PVG, or designated PVG vendor, will be notified electronically and will retrieve the form. This is considered Calendar Day 0.
    - On reporting the adverse event to OpenBiome through other means, including via telephone, the OpenBiome staff member who receives the AE will immediately submit AE information to OpenBiome PVG or designated PVG vendor.

- **1f:** PVG, or designated PVG vendor, triages SAE and initiates investigation
    - On reporting the adverse event to OpenBiome, OpenBiome PVG or designated PVG vendor will triage the case. OpenBiome PVG or designated PVG vendor will conduct follow up with site or non-clinical individuals, including patient and their family, to obtain necessary case information.
    - Triage will determine:
        - The initial assessment of **severity, seriousness**, **expectedness**, and **relatedness**.
        - If the AE is an **adverse event of special interest (AEOSI).**
        - If the AE is a **Serious Unexpected Suspected Adverse Reaction (SUSAR)** and **requires expedited reporting to the FDA.**
            - For more information on SUSAR see page 8 of this Guidance for Industry and Investigators.

IF the reported case is determined to be not related to FMT material, **proceed to Endpoint A.**

IF the reported case is a suspected AEOSI, **proceed to 2a**
IF the case is suspected but is not an AEOSI then **proceed to 3a**
IF there is disagreement or uncertainty regarding the attribution **proceed to 3b** to consult with the Clinical Advisory Board (CAB)

Additional note for 2a and 3a: If the AE is determined to be a SUSAR by PVG then it will require initial reporting to FDA. Non-life threatening SUSARs must be reported to FDA as soon as possible but no later than within **15 calendar days** following the sponsor's initial receipt of the information. Unexpected fatal or life-threatening SUSARs must be reported to FDA as soon as possible but no later than **7 calendar days** following the sponsor's initial receipt of the information.

Part 2

- **2a**: Inventory hold of donor material if AEOSI
    - OpenBiome will halt shipments of and quarantine all material made from the donor whose stool was used in the reported suspected AEOSI. This quarantine will continue until the investigation has been completed and one of the Endpoints is reached.

IF safety aliquot testing is indicated as part of the investigation, **proceed to step 2b**.

IF safety aliquot testing is not indicated as part of the investigation, **proceed to step 3a**.

- **2b**: Perform safety aliquot testing
    - OpenBiome stores safety aliquots of every fecal microbiota preparation for at least 24 months for any retesting or clinical follow-up needed for an AE. These safety aliquots, are stored at -80°C.
    - OpenBiome will retest the safety aliquot of the donor material under investigation for the existence of the infectious organism that was identified and/or contributed to the AE/SAE.

Part 3

- **3a**: Risk assessment
    - Following the investigation, PVG will determine the causality following the investigation based on the World Health Organization's (WHO) system for standardized case causality assessment
    - Causality will be classified a one of the followings:
        - **Definite:** The adverse event and administration of FMT are related in time, and a direct association can be demonstrated.
        - **Probable:** The adverse event and administration of FMT are reasonably related in time, and the adverse event is more likely explained by FMT than other causes.
        - **Possibly:** The adverse event and administration of FMT are reasonably related in time, and the adverse event can be explained equally well by FMT than by other causes.
        - **Unlikely:** A potential relationship between FMT and the adverse event could exist (i.e., the possibility cannot be excluded), but the adverse event is most likely explained by causes other than FMT.
        - **Unrelated:** The adverse event is clearly explained by another cause not related to FMT.
        - **Unassessable:** Report suggesting an adverse reaction however relationship cannot be judged because information is insufficient or contradictory and data cannot be supplemented or verified.

      IF an AE is determined to be definitely or probably related to FMT, PVG also determines if the AE is "donor dependent" or "patient dependent"
        - **Patient Dependent:** The AE is definitely or probably due to current or historical health factors and/or patient-specific variables that are predominantly unique to the patient experiencing the AE, and does not pose a broader possible risk (e.g. allergic reaction experienced in a patient with a known history of food allergies)
        - **Donor Dependent:** the AE is definitely or probably due to factors related to the donor used in the AE, irrespective of patient factors,

and could pose a broader possible risk. Any adverse event where there is a positive safety aliquot result is categorized as "donor dependent".

IF the risk type of AE is uncertain, **proceed to step 3b**.

Otherwise, **proceed to step 4b**.

- **3b**: Risk assessment
    - PVG consults with a Clinical Advisory Board (CAB), comprising qualified medical professionals. The CAB provides independent and case-appropriate expertise to help determine the type of threat and classification of the suspected AE.

Part 4

- **4a**: Review of report by Medical Reviewers
    - An Individual Case Safety Report (ICSR) will be completed by the PVG or designated PVG vendor and reviewed by the stool bank's PVG Medical Reviewers. The report will provide an in-depth review of the adverse event including
        - Unit ID(s)
        - Patient clinical course
        - Patient lab results
        - Donor effectiveness and safety record
        - Initial report from the clinical site
        - Investigation by OpenBiome
        - CAB review (if necessary)
        - Consensus-based final determination of:
        - NIH severity grade
        - WHO relatedness grade
        - Risk level

- **4b:** PVG Finalizes Report
    - The finalized Individual Case Safety Report (ICSR) will be submitted to the safety database stored by the stool bank's PVG or a designated PVG vendor.
    - All AEs will have determinations of reportability, seriousness, and relatedness stored. SAEs and AESIs will be maintained in a safety database irrespective of causality

IF the AE meet SUSAR criteria and require 7-day or 15-day expedited reporting to FDA, then **proceed to 4c**.

If the AE is no longer suspected to be related to FMT material procced to **Endpoint A.**

If the AE remains suspected to be FMT definitely or probably related and is patient dependent in proceed to **Endpoint B**

If the AE remains suspected to be FMT definitely or probably related and is donor dependent proceed to **Endpoint C**

- **4c**: Submit MedWatch to FDA, clinical partners covered under stool bank's Investigation New Drug (IND) application, and cross-referenced IND holders.

Adverse Event Decision-Making Algorithm Endpoints

Endpoint A

- No further action required: Stool bank has determined that the adverse event is not attributable to the FMT material. No further action is required on the part of the stool bank.

- Donor material shipping: The stool bank can remove donor material from quarantine and resume fulfillment for routine clinical use.

- Complete any institutional adverse event protocols if needed: Partner healthcare facilities should complete any applicable adverse event protocols that are required by the FDA or their institution due to the adverse event.

Endpoint B

- Donor material shipping: The stool bank can remove donor material from quarantine and resume fulfillment for routine clinical use.

- Update any clinician-facing documents: The stool bank will update any relevant documents pertaining to the patient dependent case and issue a notification to all sites using the stool bank's material should any new patient-related factors be taken into consideration that would inform the known risk-benefit ratio of using FMT in treatment (*e.g.* new relative or absolute contraindications to FMT).

- Review and implement updated FMT programs (*e.g.* new eligibility criteria for patients seeking an FMT to account for patient-specific risks): Partner healthcare facilities should factor in the patient's risk of experiencing an adverse event. An email will be sent to all site contacts to inform them of any new updates or

recommendations from OpenBiome. Sites will be expected review and implement any necessary recommendations.

Endpoint C

- Immediately report AE to all partners: Stool bank will notify all partner healthcare facilities that have received any material made from the same donor under investigation when a donor-dependent cause has been identified. This notification will be distributed via email to the Adverse Event (AE) contact provided as part of provider registration. This notification will include details on the AE and associated units under investigation, and any additional follow-up tasks that are required. In the notification, the stool bank will require that these partners halt the use of FMT material made from the same donor under investigation.

- Destroy all donor material and permanently exclude donor: The stool bank will immediately destroy all material associated with the donor related to the investigation. The stool bank will also permanently exclude the donor from providing any future material for clinical use.

- Update panel to include the diagnosis if a screen exists: In the case where a new pathogen or organism is determined to have been definitely transmitted to an FMT recipient, if there is a test available that can be performed in a CLIA-certified lab for the infectious disease, the stool bank will update its Clinical Screening Protocol to exclude donors containing this pathogen or organism during new donor enrollment. If an appropriate test does not exist, feasible and reasonable precautions and alternatives will be implemented to minimize the risk of the AE in the future. Specifically, the stool bank will consult its Clinical Advisory Board to debrief the situation and receive external guidance on appropriate prevention surveillance and risk management activities.

- Inform the FDA: The tool bank will update the FDA, seek guidance on appropriate prevention and response mechanisms, and ensure compliance with any applicable regulatory requirements as a result of the AE.

- Destroy all donor material: Partner healthcare facilities must immediately destroy all material associated with the donor under investigation. Manufactured FMT material contains human fecal material, therefore standard protocols for handling biohazardous material should be followed at all times.

- Assess all patients treated with donor material for any signs of the same adverse event: Partner healthcare facilities should perform proactive follow-up

assessments with all patients treated with material made from the donor under investigation to ensure there are no unreported adverse events that require escalation or signals of an adverse event that may require attention.

Key Takeaway

An Adverse Event Decision-Making Algorithm guides a stool bank's response to report of adverse events by:

1. Defining categories of adverse events that require responses.
2. Outlining the goals and outcomes of investigations.
3. Determining what responses are required to mitigate potential risk posed by the stool bank's FMT material

Additional Resources

In 2020 OpenBiome received reports of patients treated with investigational FMT who later tested positive for Shiga toxin-producing *E. coli* (STEC). Across more than 55,000 treatments shipped since 2013, this case was the first report of likely transmission of pathogens by FMT from OpenBiome. The case highlighted the importance of safety aliquot testing, network-wide traceability, utilized genomic sequencing to determine transmission of STEC and led to a change in donor screening practices. The safety event and associated investigation was described in a peer-reviewed manuscript published in *Clinical Infectious Disease*.

Figure 1

Overview of OpenBiome's Quality and Safety Program including its Pharmacovigilace process

Donor Assessment	Manufacturing	Quality Assurance	Pharmacovigilance
Clinical Assessment Prospective candidates undergo clinical evaluation that inlcudes medical histories, behavioral risks, and current health status **Laboratory Screening** Prospective candidates are screened for over 30 stool and serological tests. Less than 3% qualify to become donors.	**Standardized Stool Examinations** Lab technicians evaluate every stool sample based on Bristol type and stool pathology **Processing Controls** All stool processing occurs under a Class II biosafety cabinet that is UV-sterilized and cleaned with a sporicidal agent. All equipment is sterilized and/or disposable. **Storage and Shipping Controls** All samples are stored in a glycerol buffer at -80°C, sealed with tamper-evident bands, and transported on dry ice with temperature verification.	**Continuous Donor Requalification** Donors are under medical monitoring throughout the entire donation window and fully rescreened every 60 days. **Quarantine Procedure** Prior to release, donated material is quarantined for 60 days in between two full panel screens at a CLA-verified laboratory **Safety Aliquots** Multiple samples of all material are preserved for a minimum of 24 months, enabling retesting as needed.	**Material Tracking** Clinical partners complete Material Tracking Logs to evaluate unit-specific inventory regularly, enabling response coordination, and proactive system-wide recalls if necessary. **Efficacy Monitoring** Partners complete FMT Follow-Up Forms for each patient treated with OpenBiome material, reporting de-identified patient outcome data. **Adverse Event Reporting** All adverse events are reported to OpenBiome and evaluated using a standardized consensus-based decision-making algorithm.

Figure 2

Flow chart of Pharmacovigilance responsibilities

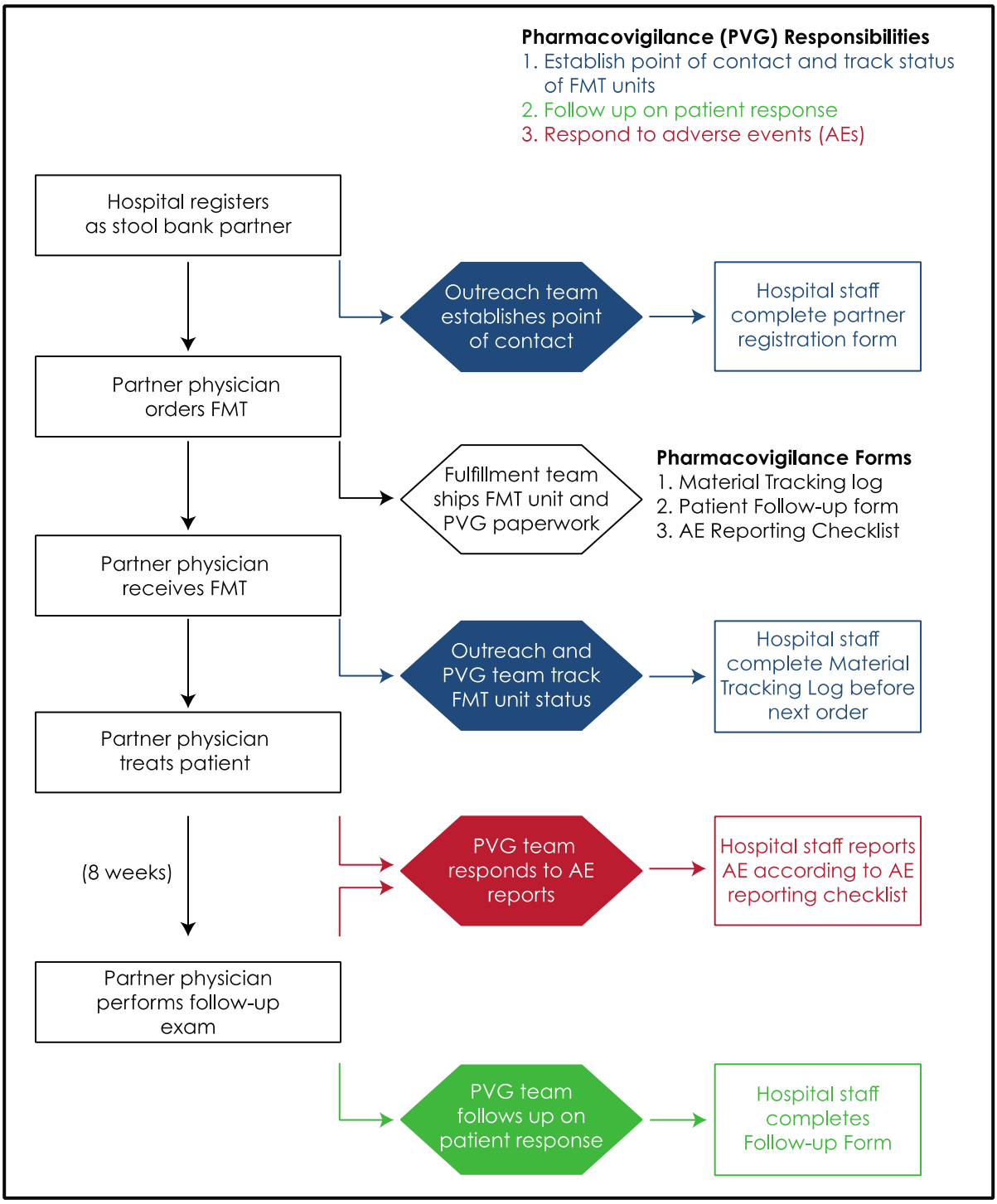
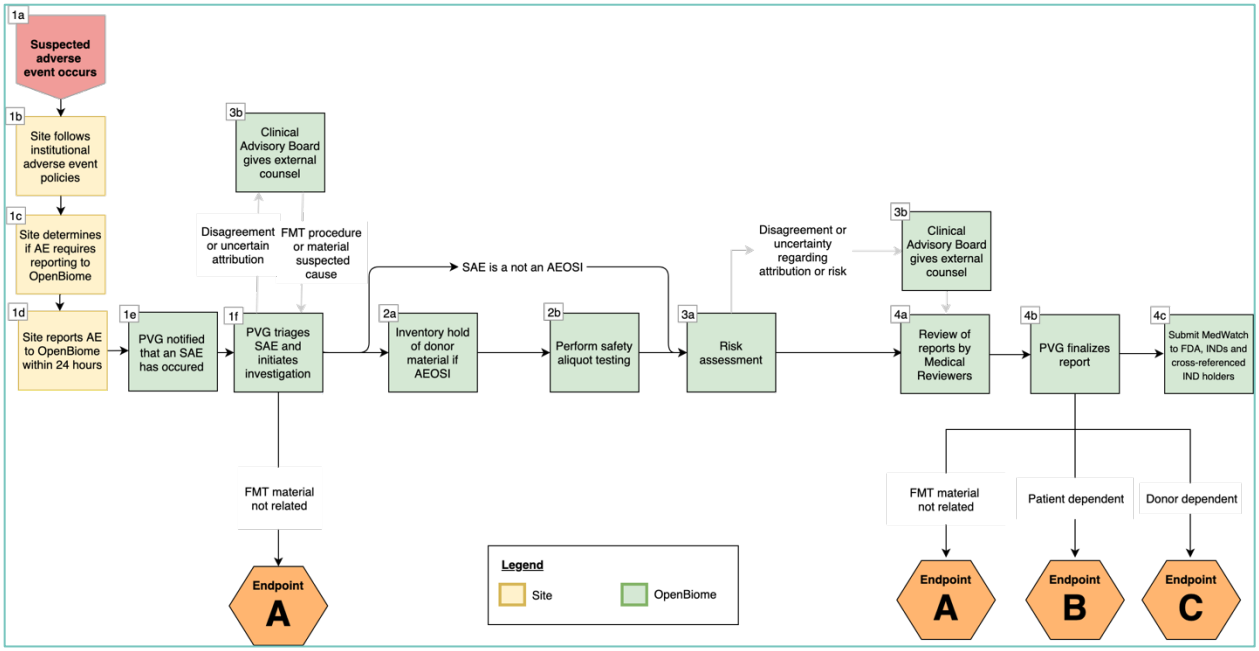


Figure 3

OpenBiome's Adverse Event Decision-Making Algorithm



Appendix 1: Clinical Partner Registration Form

OPENBIOME

Clinical Partner Registration Form

RETURN THIS FORM ALONG WITH ANY NEW VENDOR FORMS TO **INFO@OPENBIOME.ORG** OR BY FAX TO **617-575-2201.**

IF YOU ARE PART OF A LARGER HOSPITAL NETWORK AND WOULD LIKE TO INQUIRE IF YOUR NETWORK IS ON CONTRACT WITH US PRIOR TO FILLING OUT THIS FORM, PLEASE REACH OUT TO **INFO@OPENBIOME.ORG.**
NOTE: WE MUST RECEIVE THIS FORM COMPLETED IN FULL BEFORE YOUR FIRST ORDER. THIS IS NOT AN ORDER FORM.

Institution Information

A. HOSPITAL / CLINIC / PRACTICE INFORMATION		
Name of hospital, clinic, or practice		
Department(s) using material		
Has your facility previously performed a fecal transplant (FMT)? ☐ Yes ☐ No		
Type of hospital, clinic, or practice: ☐ Academic ☐ Community ☐ Government ☐ Private Practice ☐ Other:		
Health System or Network: ☐ Facility does not belong to a Health System or Network		

Shipping Information

Provide your facility's shipping address and a contact to be notified in the event of shipping disruptions.

B. SHIPPING INFORMATION		
ATTN:		
Address Line 1		
Address Line 2		
City	State	Zip
Shipping contact name	Shipping contact title	
Shipping contact phone	Shipping contact email	

Billing Information

Provide your billing address and an accounts payable (A/P) contact (an individual with whom we can discuss invoices and payment).

C. BILLING INFORMATION		
Please indicate your institution's tax status: ☐ Non-Exempt ☐ Exempt (Please submit certificate of exemption with your registration)		
ATTN:		
Address		
City	State	Zip
Email to receive PDF invoices		
☐ Check if your facility requires purchase order numbers to pay invoices	☐ Check if you can only receive invoices by mail (default is by email)	
A/P contact name	A/P contact title	
A/P contact phone	A/P contact email	

1

Rev. June 2020
www.openbiome.org

2067 Massachusetts Avenue
Cambridge, MA 02140

Phone/Fax: 617-575-2201
info@openbiome.org

Supervising Physician Information

Provide information for the licensed physician (MD/DO) who will be our primary clinical contact for the FMT program at your facility.

D. SUPERVISING PHYSICIAN INFORMATION	
Name	Specialty
Phone	Email

Administering Physician(s) Information

Provide information for all physicians who will be administering OpenBiome FMT at your facility in addition to the Supervising Physician (Section D). Supervising physicians will be added automatically.

E. SUPERVISING PHYSICIAN INFORMATION	
Administering Physician	
Name	Specialty
Phone	Email
Administering Physician	
Name	Specialty
Phone	Email
See Appendix A to list additional physicians.	

Adverse Event Contact

Provide information for the contact with a medical role (e.g. doctor, nurse) who is able to investigate and help resolve reported adverse events.

F. ADVERSE EVENT CONTACT	
Name	Title
Phone	Email

Patient Resource Contact

Provide information for the contact who will serve as a resource for patients reaching out to the facility. The contact's name and phone number will be shared externally on our online Find a Doctor tool. The email address is collected for our internal records only.

G. PATIENT RESOURCE CONTACT	
Name	Title
Phone	Email

Material Tracking Logs Contact

Provide the contact responsible for the submission of Material Tracking Logs; see Information & Policies section for guidance.

H. MATERIAL TRACKING LOGS CONTACT	
Name Phone	Title Email

Rev. June 2020
www.openbiome.org
2067 Massachusetts Avenue
Cambridge, MA 02140
Phone/Fax: 617-575-2201
info@openbiome.org

General Information & Policies – *Initial & Sign*

A. Terms and Conditions

Subject to the terms and conditions set forth in this Clinical Partner Registration Form ("CPRF"), OpenBiome will supply you with the type and quantity of Fecal Microbiota Preparations ("Product") requested on one or more Order Forms or Purchase Orders at the pricing described herein and solely to the extent that such Product is not available for purchase from a commercial seller. The term of this CPRF will begin on the date of your signature below, and continue for a period of two (2) years therefrom, at which time this CPRF will expire and you will be required to fill out and execute a new CPRF prior to purchasing additional Product. If you breach any provision of this CPRF and fail to cure such breach within thirty (30) days of OpenBiome's notice to you of such breach, OpenBiome may terminate this CPRF and your registration as a clinical partner of OpenBiome.

Initials _____

B. Price List

Any price adjustments to the below will be forwarded to your listed billing contact no later than 30 days prior to the effective date of the price adjustment. **These prices are effective as of March 10, 2019.**

Initials _____

ITEM	DESCRIPTION	UNIT PRICE
FMP250	FMT Lower Delivery (for colonoscopy, sigmoidoscopy, & enema)	$1695
FMP30	FMT Upper Delivery (for EGD & naso-enteric tube)	$6595
FMPCapDE	FMT Capsule DE (physician orientation required before first order)	$2050

C. Ordering

Submit OpenBiome Order Form or Purchase Order by email to orders@openbiome.org (*preferred*) or by fax to 617-575-2201. All Order Forms or Purchase Orders will be governed by the terms and conditions set forth in this CPRF.

Initials _____

D. U.S. Shipping

Standard S&H Flat $150 fee per shipment, waived on orders of 10 units or more. We strongly encourage partners to consolidate orders and store Product locally to reduce shipping fees and ensure reliable access.

Initials _____

- Orders placed Monday-Wednesday will be delivered in 2 business days.
- Orders placed on Thursday or Friday will be scheduled for delivery the following Tuesday.
- Product arrives on dry ice in a temperature-monitored container.
- Shipped using UPS Next Day Air (10:30AM delivery for most locations).

Optional Next-Day Delivery $50 additional fee

- Same-day shipping, for delivery the following morning.
- Order must be received before 3PM ET Monday-Thursday.
- Availability not guaranteed.
- Confirmation of additional fee must be included with order.

Optional UPS Early AM Delivery $100 additional fee

- Confirmation of additional fee must be included with order.

Weather Notice

OpenBiome will make every effort to process and ship your order for delivery within the estimated delivery date. However, some events beyond OpenBiome's control can occasionally delay a shipment, even an expedited shipment. When forces of nature delay a carrier's delivery of an order, OpenBiome cannot guarantee the arrival date of your order. To reduce any issues caused by a late arrival of treatments, especially during the winter months where weather delays are more frequent, please place your order early to allow extra time for delivery.

E. Billing Policy

Initials

Electronic Invoicing: **All invoices will be sent via e-mail by default** to the e-invoice e-mail address provided in the Billing Information section above. Partners requiring mailed paper invoices must indicate this preference above.

Payment Terms: OpenBiome's payment terms are **Net 30**, and you agree that you shall pay all invoices for Product within thirty (30) days from receipt of such invoices.

Late Payment Penalties: OpenBiome reserves the right to assess late payment penalties for invoices not fully paid on-time, including but not limited to recouping the cost of any collection agencies employed.

Payment Options: OpenBiome accepts the following payment methods:

1. Electric Funds Transfer: Via "Pay Now" button on e-invoices or any other method of e-payment.
2. Checks: Made payable to Microbiome Health Research Institute. Our remit-to address is:
   ATTN: Accounts Receivable
   Microbiome Health Research Institute
   2067 Massachusetts Avenue, Cambridge, MA 02140
3. Credit card: Via phone by calling 617-575-2201 x5

If you require any registration or credentialing services, please contact info@openbiome.org.

F. Safety Policy

Initials

All clinicians using Product will review our introduction to the Quality and Safety Program available online at www.openbiome.org/safety. Should an adverse event occur, a clinician will notify OpenBiome within 24 hours using our online reporting tool at www.openbiome.org/adverse-events or by phone to 617-575-2201, option 1. You agree to complete a Material Tracking Log and FMT Follow-Up Form (provided) for all Product supplied, and to return these to OpenBiome. Information obtained from these Logs may be used for any purpose, which may include quality assurance and/or commercial purposes. These forms will not include any patient-identifiable information and OpenBiome may use the data on these forms for any purpose, which may include quality assurance and/or commercial purposes. For more on this requirement, read our primer found at www.openbiome.org/safety.

G. Usage Policy

Initials

The Product is intended for clinical use under medical supervision only. Fecal Microbiota Transplantation is an investigational therapy that is not approved by the FDA. Use of this Product is part of the practice of medicine as exercised by appropriately licensed individual practitioners. OpenBiome provides quality assurances that the Product meets the specifications and quality assurance guidelines outlined in the OpenBiome Quality Metrics found at https://www.openbiome.org/s/Quality-Metrics.pdf You understand and agree that there are considerable risks associated with use of the Product, including, but not limited to, the potential for the presence of infectious agents. Such agents could include both agents not included in OpenBiome's screening panel or agents that were not detected by the assays employed by OpenBiome. You acknowledge the inherent risks associated with the clinical use of the Product and accept these risks as a condition of use. OpenBiome provides a summary of its donor screening, and you may request raw results to review directly and make an informed medical decision about the use of the Product. Responsibility for medical interpretation of these results lies with the medical practitioner and not with OpenBiome. Furthermore, you accept the ethical and legal responsibility to inform patients of the risks associated with this procedure and provide treatment under informed consent. You agree that you will maintain true and accurate records regarding the handling, storage, and use of the Product, and will provide such records OpenBiome upon request. In handling, storing, utilizing, and disposing of Product, you shall at all times comply with all applicable laws, regulations and generally accepted industry practices, and will follow all instructions provided by OpenBiome. You further agree that your purchase of the Product is for the treatment of your own patients only, and that you will not transfer, distribute or release the Product to any other person or entity.

H. No Warranty

Initials

Products are understood to be experimental in nature and may have hazardous properties that are not known or fully appreciated. THE PRODUCT IS PROVIDED WITHOUT ANY WARRANTY, EITHER EXPRESS OR IMPLIED, AS TO ITS SAFETY OR FITNESS FOR ANY PARTICULAR PURPOSE OR USE. Acceptance by you of the Product will constitute your acceptance of liability for any damages or injuries resulting from your possession, use, or disposal of the Product. OpenBiome makes no representation that the use of the Product will not infringe on any patent or other proprietary rights of third parties.

I. Intellectual Property and Confidentiality

Initials

Nothing in this CPRF shall grant or may be construed as granting to you any rights in or to any intellectual property rights of OpenBiome, whether by implication, estoppel or otherwise. For purposes of this CPRF, "Confidential Information" means any and all information of a confidential, secret, and/or proprietary nature provided by or on behalf of Supplier or its agents to Customer in connection with this Agreement. Confidential Information includes, but is not limited to, the Product specifications and quality assurance information provided at the link in Section F above. You agree that you will maintain OpenBiome's Confidential Information in strict confidence and shall disclose OpenBiome's Confidential Information only to those of your employees, officers, and agents who have a need to know and who are obligated to keep such information confidential. The obligations of this section do not apply to information that you can demonstrate: (a) was generally known to the public prior to disclosure or being generated under CPRF or later becomes generally known to the public through no fault of yours; (b) was already known to you prior to disclosure or generation under this CPRF; (c) was obtained by you from a third party in lawful possession of such information and with the right to disclose the same; and (d) was independently developed by you without reference to OpenBiome's Confidential Information. This section shall survive the termination or expiration of this CPRF or any Order Forms or Purchase Orders hereunder.

J. Insurance

Initials

You agree that you shall, for as long as you possess or make use of Product under any Purchase Order or Order Form issued hereunder, at your own cost and expense, obtain and maintain in force: (1) general liability insurance with minimum limits of $1 million per occurrence or claim, $2 million annual aggregate, and (2) worker's compensation insurance that meets statutory requirements in the state in which you are located. You shall provide a certificate of insurance verifying such coverage upon request by OpenBiome. If the form of insurance is claims made, you agree to maintain appropriate tail coverage for claims, demands, or actions reported in future years for acts or omissions during the term of your use or possession of Product. Your failure to maintain coverage according to this paragraph shall be grounds for termination of your registration as a Clinical Partner of OpenBiome.

K. Indemnification

Initials

You hereby agree to indemnify, protect, and save harmless OpenBiome and its agents, officers, and employees, from and against that portion of any and all losses, claims, demands, actions, or judgments, joint or several, for which OpenBiome may become liable arising out of or in connection with this CPRF or the Product that result from the negligence, willful misconduct or wrongful acts or omissions of you or any of your agents, officers, or employees, or from any medical services provided by you or any of your agents, officers, or employees, whether utilizing the Product or otherwise. The provisions of this paragraph shall survive the expiration or termination of this CPRF or any Order Forms or Purchase Orders hereunder.

L. Miscellaneous

Initials

This CPRF contains the entire agreement between you and OpenBiome regarding the subject matter hereof, and there are no other promises or conditions in any other agreement whether oral or written. This CPRF supersedes any prior written or oral agreements between you and OpenBiome. This CPRF may be modified or amended only if the amendment is made in writing and agreed by both you and OpenBiome. If any provision of this CPRF shall be held to be invalid or unenforceable for any reason, the remaining provisions shall continue to be valid and enforceable. If a court finds that any provision of this CPRF is invalid or unenforceable, but that by limiting such provision it would become valid and enforceable, then such provision shall be deemed to be written, construed, and enforced as so limited. The failure of OpenBiome to enforce any provision of this CPRF shall not be construed as a waiver or limitation of OpenBiome's right to subsequently enforce and compel strict compliance with every provision of this CPRF. You may not assign this CPRF or any Order Form or Purchase Order without the prior written consent of OpenBiome. This CPRF will be governed by the laws of the Commonwealth of Massachusetts, without giving effect to its conflicts of laws principles. You represent and warrant that your signatory to this CPRF is duly authorized to execute this CPRF on your behalf, and that no consents (which have not already been obtained) are required in order for this CPRF to be effective and enforceable against you in accordance with its terms. OpenBiome shall not be liable in damages for failure to comply with its obligations to the extent that its performance is prevented by causes beyond its reasonable control including acts of God or of the public enemy, acts of any governmental authority, fires, war, riots, terrorist acts, unavailability or shortages of electricity or other utilities, floods, unusually severe weather, epidemics, quarantine restrictions, strikes, labor disputes or shortages of labor, freight embargoes, or inability to secure necessary parts and materials.

By your signature below, you agree to purchase Product subject to, and abide by, the terms and conditions contained in this CPRF, and that the terms and conditions hereof will be binding on you, your successors and permitted assigns.

CLINICAL PARTNER

Signature of authorized hospital / clinic / practice representative	Date
Printed name	Title

Rev. June 2020
www.openbiome.org
2067 Massachusetts Avenue
Cambridge, MA 02140
Phone/Fax: 617-575-2201
info@openbiome.org

Appendix A

Additional Administering Physician(s)

Provide information for all physicians who will be administering OpenBiome FMT at your facility in addition to the Supervising Physician (Section D). Supervising physicians will be added automatically. Leave blank if not needed.

E. SUPERVISING PHYSICIAN INFORMATION	
Administering Physician	
Name	Specialty
Phone	Email
Administering Physician	
Name	Specialty
Phone	Email
Administering Physician	
Name	Specialty
Phone	Email
Administering Physician	
Name	Specialty
Phone	Email
Administering Physician	
Name	Specialty
Phone	Email
Administering Physician	
Name	Specialty
Phone	Email
Administering Physician	
Name	Specialty
Phone	Email
Administering Physician	
Name	Specialty
Phone	Email
Administering Physician	
Name	Specialty
Phone	Email

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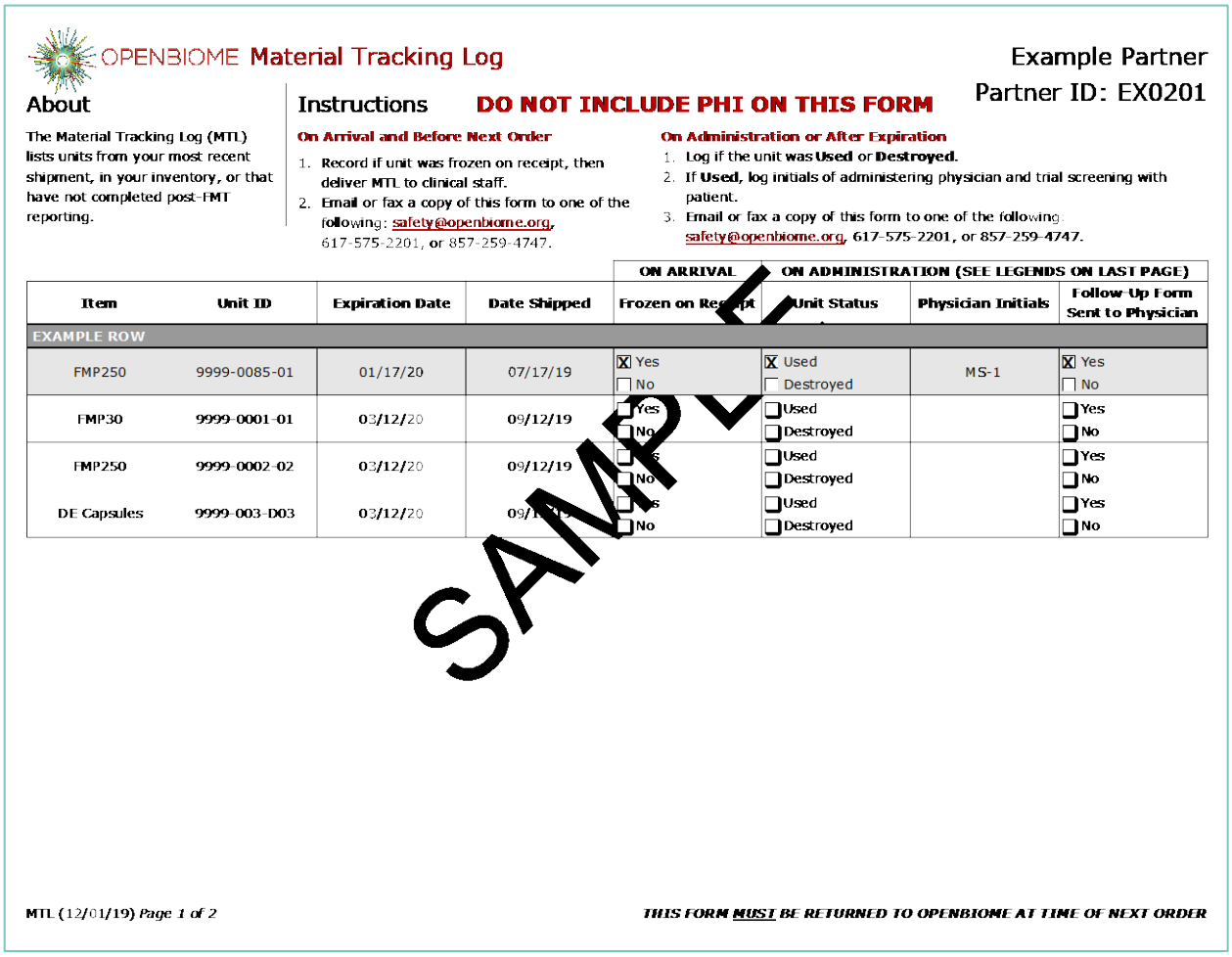
www.openbiome.org
2067 Massachusetts Avenue
Cambridge, MA 02140
Phone/Fax: 617-575-2201
info@openbiome.org

Appendix 2: Sample Material Tracking Log



OPENBIOME Material Tracking Log

Example Partner
Partner ID: EX0201

About

The Material Tracking Log (MTL) lists units from your most recent shipment, in your inventory, or that have not completed post-FMT reporting.

Instructions **DO NOT INCLUDE PHI ON THIS FORM**

On Arrival and Before Next Order

1. Record if unit was frozen on receipt, then deliver MTL to clinical staff.
2. Email or fax a copy of this form to one of the following: safety@openbiome.org, 617-575-2201, or 857-259-4747.

On Administration or After Expiration

1. Log if the unit was **Used** or **Destroyed**.
2. If **Used**, log initials of administering physician and trial screening with patient.
3. Email or fax a copy of this form to one of the following: safety@openbiome.org, 617-575-2201, or 857-259-4747.

				ON ARRIVAL	ON ADMINISTRATION (SEE LEGENDS ON LAST PAGE)		
Item	Unit ID	Expiration Date	Date Shipped	Frozen on Receipt	Unit Status	Physician Initials	Follow-Up Form Sent to Physician
EXAMPLE ROW							
FMP250	9999-0085-01	01/17/20	07/17/19	☒ Yes ☐ No	☒ Used ☐ Destroyed	MS-1	☒ Yes ☐ No
FMP30	9999-0001-01	03/12/20	09/12/19	☐ Yes ☐ No	☐ Used ☐ Destroyed		☐ Yes ☐ No
FMP250	9999-0002-02	03/12/20	09/12/19	☐ Yes ☐ No	☐ Used ☐ Destroyed		☐ Yes ☐ No
DE Capsules	9999-003-D03	03/12/20	09/12/19	☐ Yes ☐ No	☐ Used ☐ Destroyed		☐ Yes ☐ No

SAMPLE

MTL (12/01/19) *Page 1 of 2*

THIS FORM MUST BE RETURNED TO OPENBIOME AT TIME OF NEXT ORDER

OPENBIOME **Material Tracking Log - Physician Initials**

Example Partner
Partner ID: EX0201

Only physicians registered with OpenBiome can be entered on the MTL. If the physician using the material is not listed here, please contact the Outreach Team via phone at 617-575-2201 or email at info@openbiome.org.

Name	Initials
Kathleen Rodgers	KR-1
Manuel Santos	MS-1
Charles Paulsen	CP-1
Christine Parnes	CP-2

THIS FORM MUST BE RETURNED TO OPENBIOME AT TIME OF NEXT ORDER

Appendix 3: FMT Follow-Up Form

FMT Follow-Up Form

OPENBIOME
2067 Massachusetts Avenue, Cambridge, MA
p. 617-575-2201

Your participation in our Quality & Safety Program is invaluable and allows us to monitor the outcomes of FMTs on a per-donor basis across our network. We appreciate yourcontribution to patient safety and the field of FMT. Only submit this form once the patient has been assessed for clinical cure and all sections are complete.

FMT Unit ID:_____ **Partner ID:** _____

Patient Information

Patient Initials: _____ **Patient Age:** _____

Case Information

Delivery method: Lower Delivery (250mL): Sigmoidoscopy; Colonoscopy; Enema
Upper Delivery (30mL): Upper endoscopy; Nasogastric delivery; Nasoduodenal delivery
Oral: Capsule
Other: _____

Recurrent CDI: Yes No **If recurrent, number of confirmed episodes pre-FMT:**

Refractory CDI: Yes / No

CDI Severity: Mild-to-moderate / Severe / Severe-complicated

8 Week Clinical Follow-Up

Clinical Cure: Yes / No

Adverse Event: Yes / No

If **adverse event** is **Yes,** select one of the following:
A Non-Serious Adverse Event (AE)
A Serious Adverse Event (SAE)
An Adverse Event of Special Interest (AESI)

If **adverse event** is **Yes**, complete form at http://www.openbiome.org/adverse-events. This information will be passed on to Finch Therapeutics, OpenBiome's licensed manufacturer. A member of the Finch safety team will contact you to follow up on this report.

Please return this form to safety@openbiome.org or fax to 617-575-2201.

Glossary

Recurrent CDI: Recurrence of CDI symptoms for 48 hours or longer within 8 weeks after the completion of at least 10 days of CDI treatment.

Refractory CDI: Persistent or worsening of diarrhea characteristic of CDI and 1 of the following:

Ongoing abdominal pain, fever (temperature ≥ 38.0°C)

Peripheral white blood cell (WBC) counts greater than 15.0 × 109/L despite treatment with oral vancomycin at a dose of 500mg 4 times daily for at least 5 days

Mild-to-moderate CDI: Diarrhea plus any additional signs or symptoms not meeting severe or complicated criteria

Severe CDI: Hypoalbuminemia (albumin < 3 g/dl) and WBC count ≥ 15,000 cells/mm^3 or abdominal tenderness

Severe-complicated CDI: Any of the following attributable to CDI:

- Admission to ICU for CDI
- Hypotension with or without required use of vasopressors
- Serum lactate levels > 2.2 mmol/l
- End organ failure (mechanical ventilation, renal failure, etc.)
- Mental status changes
- WBC ≥ 35,000 cells/mm^3 or < 2,000 cells/mm
- Fever ≥ 38.5 °C
- Ileus or significant abdominal distention

Clinical Cure: The absence of treatment failure.

Treatment Failure: Any of the following from 0- to 8-weeks of FMT:

- Persistence of diarrhea (> 3 unformed stool for 48 hours) with either a positive C. difficile toxin assay (EIA) or toxin B polymerase chain reaction (PCR) assay
- The need for additional therapy for CDI
- The need for colectomy for CDI
- Death directly attributable to CDI

Non-Serious Adverse Event (AE): (An event that does not meet the criteria of a Serious adverse event as described below.) An adverse event is defined as any untoward medical occurrence in a patient or a clinical trial subject who is administered a drug/product which does not necessarily have a causal relationship with the product. An AE can be an unfavorable sign or unintended sign, a symptom, or a disease temporally associated with the use of a product, whether or not considered related to the product. An AE can arise from the use of the drug (or in combination with another product) and from any route of administration, formulation, dose including an overdose. An AE also includes, but is not limited to, any clinically significant worsening of a pre-existing condition

Serious Adverse Event (SAE): Any of the following outcomes:

- Death,
- Life-threatening health events,
- Hospitalization (initial or prolonged),
- Disability or permanent damage,
- Congenital anomaly/birth defect,
- or other serious important medical event(s)

Adverse event of special interest (AESI):

- Suspected Transmission of an Infectious Agent: Any adverse event where transmission of an infectious organism via the FMT may have occurred
- Suspected Transmission of a Multi-Drug Resistant Organism: Any adverse event where transmission of a multi-drug resistant organism via the FMT may have occurred.

Appendix 4: Reporting Adverse Events

Reporting Adverse Events

As with any medical intervention, Fecal Microbiota Transplantation (FMT) carries certain risks. Risks include possible transmission of infectious pathogens, including multi-drug resistant organisms (MDRO), and a potential risk of causing microbiome-mediated diseases. The procedure of FMT administration (e.g., colonoscopy, upper endoscopy) poses risks that vary by delivery modality. These risks should be clearly communicated to your patient during the informed consent process prior to the FMT procedure.

Purpose of reporting adverse events

Clinicians should notify us of serious adverse events suspected to be related to FMT material within 24 hours of knowledge so we can effectively respond in a timely manner for the protection of all patients being treated in the OpenBiome network.

Because the FDA regulates the stool used in FMT as an investigational new drug, our clinical partners are required to report any related serious adverse events to OpenBiome. The adverse events contacts for your FMT program should be familiar with these risks, and should communicate the following Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESIs) reporting protocol to all physicians before performing FMT at your institution.

What is an Adverse Event (AE)?

An adverse event is defined as *any untoward medical occurrence* in a patient or a clinical trial subject who is administered a drug/product which does not necessarily have a causal relationship with the product. An AE can be an unfavorable sign or unintended sign, a symptom, or a disease temporally associated with the use of a product, whether or not considered related to the product. An AE can arise from the use of the drug (or in combination with another product) and from any route of administration, formulation, dose including an overdose. An AE also includes, but is not limited to, any clinically significant worsening of a pre-existing condition.

Examples include:

- Any sign (e.g., elevated temperature or blood pressure), Symptoms (e.g., headache, infection), physical finding (e.g., rash, tender abdomen)
- Laboratory result (e.g., elevated glucose, elevated liver function tests), including those that has worsened in nature, severity or frequency compared to baseline
- Concurrent illness that was not present or worsened in nature (e.g., recurrence of cancer), severity, or frequency compared to baseline
- Injury or accident (i.e., fall)
- Exacerbation or worsening of a pre-existing condition (e.g., worsening of pre-existing hypertension)
- Drug interactions
- Congenital anomalies
- Adverse events associated with Product Quality Complaints.
- Unexplained fatal outcome
- AEs documented in literature reports
- Suspected transmission of any infectious agent, which will be classified as an Adverse Event of Special Interest

What is a Serious Adverse Event (SAE)?

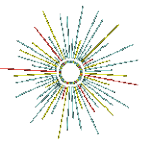
An SAE is any adverse event that results in any of the following:

- Death
- Hospitalization, or prolongation of hospitalization
- A life-threatening event
- A persistent or incapacitating disability
- A congenital anomaly or birth defect
- An important medical event (i.e. the event may not result in death, be life-threatening or require hospitalization but may be considered a serious event based on upon medical judgement. It may jeopardize the patient and may require medical attention or surgical intervention to avoid one of the outcomes listed above)

What is an Adverse Event of Special Interest (AESI)?

AESIs are adverse events that we are particularly interested in to ensure that they are promptly reported to OpenBiome. Any of the below AESIs suspected to be related to FMT material should be reported within 24 hours of knowledge:

- **Suspected Transmission of an Infectious Agent:** Any adverse event where transmission of an infectious organism via the FMT may have occurred.
- **Suspected Transmission of a Multi-Drug Resistant Organism:** Any adverse event where transmission of a multi-drug resistant organism via the FMT may have occurred.

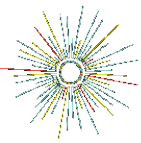


How are SAEs or AESIs reported?

If the treating physician or a member of the FMT program staff become aware of an **SAE or AESI that occurs following treatment with OpenBiome FMT treatment**, please follow these steps:

1. **Report to OpenBiome within 24 hours:** An adverse event contact or the treating physician must inform OpenBiome using our online reporting tool at www.openbiome.org/adverse-events. Consult the checklist on the next page for the information needed to submit this report.
2. **Follow local procedures:** Your institution may have further measures and reporting requirements in the case of an adverse event. Please consult your local guidelines.
3. **Investigation:** Upon receipt of an adverse event report, an OpenBiome drug safety professional may reach out to the reporting individual to gather more information on the case and determine next steps.
4. **FDA reporting:** An OpenBiome medical professional will use the details of your report and any ensuing investigation to determine if there are any additional reporting requirements, which may include submission of the event to the Food and Drug Administration via Form FDA 3500A.

If you have any questions regarding an adverse event please contact our Clinical Safety team at safety@openbiome.org or call (617) 575-2201, option 1.



OPENBIOME

Clinician Checklist for Reporting Adverse Events to OpenBiome

To report an adverse event to OpenBiome, please collect the following information, and submit your report through the online form at www.openbiome.org/adverse-events.

	Case Information
	Patient demographics: Initials, DOB sex, weight, race, and ethnicity
	Preexisting medical condition(s)/History
	Medication(s) taken prior to FMT and any known allergies
	Comprehensive *Clostridioides difficile* infection (CDI) history • Initial diagnosis technique (e.g. toxin EIA, qPCR, anaerobic culture) • Modified Horn Index • Recurrent or refractory disease • Number of recurrences • Anti-CDI therapy • Previous FMT history
	Information about the FMT procedure including the following **key pieces of information**: • The **Unit ID(s)** of the OpenBiome treatment(s) used • Route of administration • Pre-procedural preparation by the patient • Site of material delivery and how verified, if applicable (e.g., fluoroscopic verification of nasogastric tube placement) • Any documented difficulty during the procedure • Any significant findings documented during the procedure • Current patient disposition and discharge date, if applicable
	Detailed description of adverse event, including tests performed (with both dates and results), new medical conditions, new medications, etc.

Version 22-Mar-2021
www.openbiome.org

2067 Massachusetts Avenue
Cambridge, MA 01240

Phone/Fax: 617-575-2201
info@openbiome.org

Appendix 5: Adverse Event Online Reporting Form

As part of our commitment to enable safe access to accountable, high-quality FMT treatments and ensure compliance with FDA safety reporting regulations, all clinical partners and investigators that utilize OpenBiome FMT material are required to report adverse events (AEs) to OpenBiome and possibly to the FDA.

If you suspect that one of your patients or study subjects experienced a serious adverse event following their FMT, **please complete the following online AE report in its entirety**. Upon submission, your report will go to the Patient Safety Team at OpenBiome and MMS, a contract research organization that provides support as our pharmacovigilance contractor. We will then work with you to determine any actionable steps required.

If you have any additional questions, please also contact us at **safety@openbiome.org** or call 617-575-2201, option 9. We are more than willing to discuss the specifics of your case in more detail.

Name of Reporting Individual*
First Name:
Last Name:
Institution*
Name:
Institutional Address *
Address 1:
Address 2:
City:
State/Province:
Zip/Postal Code:
Country:

Phone *
Please provide a phone number where you can be easily reached by a member of the Clinical Assessment and Safety team to conduct an investigation of this adverse event.
Phone Number:
Alternate Phone Number:
Email Address:
Alternate Email:

Occupation *
Select one of the following:
- Administrator/Supervisor
- Nurse
- Nurse Practitioner
- Pharmacist

- Physician
- Physician Assistant
- Risk Manager
- Other Healthcare Professional
- Non-Healthcare Professional

Patient/Participant Information

Patient/Participant Identifier *:
Please do not use PHI (e.g., patient/participant's name, medical record number, social security number)

Age:

Sex *

Male
Female

Weight:
Unit of weight:

- lbs
- kgs

Ethnicity (Select One):

- Hispanic/Latino
- Not Hispanic/Latino

Race
Check any that apply.

- Asian
- American Indian or Alaskan Native
- Black or African American
- Native Hawaiian or Other Pacific Islander
- White

Pre-Existing Medical Conditions:
Please list all comorbidities. If none, write n/a

List of Medications Prior to FMT (including Anti-CDI medications):
Please list names of all medications. If none, write n/a

Drug Allergies:
Please list all known drug allergies. If none, write n/a.

Clostridium difficile infection (CDI) History

CDI Diagnosis
Check any that apply and describe below

- Toxin EIA
- qPCR
- Anaerobic culture
- Clinical symptoms
- Other
- Not applicable

Date of most recent CDI diagnosis and result (if available):

CDI Severity (Select one):
Please scroll down to the bottom of the page for detailed descriptions of CDI severity.

- Mild
- Moderate
- Severe
- Severe-Complicated

Disease Type
Check all that apply

- Recurrent (3 episodes of CDI and failure of 6-8 week standard of care antibiotics or >= 2 episodes of CDI resulting in hospitalization)
- Refractory (Moderate CDI not responding to vancomycin for >= 1 week)
- Fulminant (C. difficile colitis with significant systemic toxic effects and shock, resulting in need for colectomy, or death)
- Other

FMT History

Was an FMT performed?

- Yes
- No

FMT Procedure Date (MM/DD/YYYY):

Was the FMT performed under an IND?

- Yes
- No

If yes, please provide the IND number and study name:

Treating MD (if different from individual completing this survey):
Treating MD's Phone Number:
Treating MD's Email Address:

FMP Unit ID Number (e.g., ID# XXXX-XXXX-XX OR XXXXX-XX):

Route of FMT Administration (Select one):

- Colonoscopy
- Sigmoidoscopy
- Nasoenteric Delivery
- Upper Endoscopy
- Capsule
- Enema
- Other

If other, please describe here:

Delivery Location (specific segment: e.g., post-pylorus):

Any problems with the procedure or patient during FMT?

- No
- Yes

If yes, please describe:

Was the patient discharged post-FMT?

- No
- Yes

If yes, please list discharge date, patient disposition at discharge, and location where discharged to:

Adverse Event Information

Start Date of Adverse Event (MM/DD/YYYY):

End Date of Adverse Event (MM/DD/YYYY):

If ongoing, leave blank and check box below

- Ongoing

Please provide the adverse event terms *:

Please describe the adverse event in detail *:

Please describe the clinical course and any new medical conditions, procedures, or medications for each event. Please include dates

Please list any pertinent tests, their dates, and their results:

E.g. stool, urinalysis, pathology, autopsy, laboratory, diagnostic imaging, etc.

Please describe the patient's current disposition: *

In your opinion, was the adverse event attributable to the FMT material? (Select one) *:

- Definitely Related
- Probably Related
- Possibly Related
- Unlikely to be Related
- Not Related

Please explain the rationale for this opinion *:

Severity (Select One)*:

- Grade 1 (Mild)
- Grade 2 (Moderate)
- Grade 3 (Severe)
- Grade 4 (Life-Threatening)
- Grade 5 (Death due to event)

Outcome (Select One)*:

- Not Recovered/Not Resolved
- Recovering/Resolving
- Recovered/Resolved
- Fatal
- Unknown
- Recovered/Resolved with sequelae*

***Specify sequelae, if applicable:**

Was the adverse event unexpected? (Select one)*:

- No
- Yes

Was the adverse event serious? (Select one) *

- Not serious
- Death (Please report if you suspect that the death was an outcome of the adverse event)
- Life-threatening (Please report if you suspect that the patient was at substantial risk of dying at the time of the adverse event, or use or continued use of the device or other medical product might have resulted in the death of the patient)
- Hospitalization, initial or prolonged (Please report if admission to the hospital or prolongation of hospitalization was a result of the adverse event)
- Disability or Permanent Damage (Please report if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life)
- Required Intervention to Prevent Permanent Impairment or Damage (Please report if you believe that medical or surgical intervention was necessary to preclude permanent impairment of a body function, or prevent permanent

damage to a body structure, either situation suspected to be due to the use of a medical product)
- Congenital Anomaly/Birth Defect (Please report if you suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child)
- Adverse Event of Special Interest
- Other Serious - Important Medical Events (Please report when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes)

If you selected "Other Serious", please provide more details to describe why the event was considered serious.:

Was the MedWatch 3500 Report sent to the FDA? * (Select One):
- No
- Yes

If yes, what date was it sent (MM/DD/YYYY)?:

Thank you for taking the time to complete this form. Your information will be sent directly to the Pharmacovigilance and Safety Team. A representative from this team will contact you within 24 hours to follow up during weekdays, and within 24-48 hours during the weekend.

If your situation is urgent and you need to speak with a clinician immediately, *please call (617) 575-2201, Option 9*.

Glossary

Recurrent CDI: Recurrence of CDI symptoms for 48 hours or longer within 8 weeks after the completion of at least 10 days of CDI treatment.

Refractory CDI: Persistent or worsening of diarrhea characteristic of CDI and 1 of the following:

- Ongoing abdominal pain, fever (temperature ≥ 38.0°C)
- Peripheral white blood cell (WBC) counts greater than 15.0 × 109/L despite treatment with oral vancomycin at a dose of 500mg 4 times daily for at least 5 days

Mild-to-moderate CDI: Diarrhea plus any additional signs or symptoms not meeting severe or complicated criteria

Severe CDI: Hypoalbuminemia (albumin < 3 g/dl) and WBC count ≥ 15,000 cells/mm3 or abdominal tenderness

Severe-complicated/fulminant CDI: Any of the following attributable to CDI:

- Admission to ICU for CDI
- Hypotension with or without required use of vasopressors
- Serum lactate levels > 2.2 mmol/l
- End organ failure (mechanical ventilation, renal failure, etc.)
- Mental status changes
- WBC ≥ 35,000 cells/mm3 or < 2,000 cells/mm
- Fever ≥ 38.5 °C
- Ileus or significant abdominal distention

Clinical Cure: The absence of treatment failure.

Treatment Failure: Any of the following from 0- to 8-weeks of FMT:

- Persistence of diarrhea (> 3 unformed stool for 48 hours) with either a positive *C. difficile* toxin assay (EIA) or tcdB polymerase chain reaction (PCR) assay
- The need for additional therapy for CDI
- Colectomy
- Death directly attributable to CDI

Non-Serious Adverse Event: (An event that does not meet the criteria of a Serious adverse event as described below.) An adverse event is defined as any untoward medical occurrence in a patient or a clinical trial subject who is administered a drug/product which does not necessarily have a causal relationship with the product. An AE can be an unfavorable sign or unintended sign, a symptom, or a disease temporally associated with the use of a product, whether or not considered related to the product. An AE can arise from the use of the drug (or in combination with another product) and from any route of administration, formulation, dose including an overdose. An AE also includes, but is not limited to, any clinically significant worsening of a pre-existing condition.

Serious Adverse Event (SAE): Any of the following outcomes:

- Death,
- Life-threatening health events,
- Hospitalization (initial or prolonged),
- Disability or permanent damage,
- Congenital anomaly/birth defect,

- or other serious important medical event(s).

Adverse event of special interest (AESI):

- Suspected Transmission of an Infectious Agent: Any adverse event where transmission of an infectious organism via the FMT may have occurred.
- Suspected Transmission of a Multi-Drug Resistant Organism: Any adverse event where transmission of a multi-drug resistant organism via the FMT may have occurred.

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