FMT Capsule DE is a unique approach to FMT and is used to treat Clostridium difficile infection not responsive to standard therapy, as well as for clinical research. This primer represents the best available evidence to inform clinical practice but is subject to change as the field evolves. Clinical decisions should be made by the treating physician. We will continue to update this document as new information becomes available from ongoing studies aimed at informing the dosing and administration for OpenBiome’s FMT Capsule DE.
FMT Capsule DE Clinician’s Checklist

Clinician’s checklist for the administration of 30 capsules of FMT Capsule DE (1 dose) orally for recurrent Clostridium difficile infection (rCDI)

Patient Preparation

☐ Review indications and contraindications

☐ Confirm that the indication to be treated by Fecal Microbiota Transplantation (FMT) is C. difficile infection (CDI) that is not responsive to standard therapy, and rule out alternative diagnosis (e.g. post-infectious IBS, inflammatory bowel disease, celiac disease)

- For severe or severe-complicated CDI: Current evidence suggests that the treatment of severe or severe-complicated CDI by FMT may require different protocols than those outlined in this document. We suggest that clinicians treating severe or severe-complicated CDI by FMT review protocols in Fischer et al. “Faecal microbiota transplantation plus selected use of vancomycin for severe-complicated Clostridium difficile infection: Description of a protocol with high success rate,” Aliment Pharmacol Ther. 2015;42(4):470-476.

☐ Review contraindications for FMT Capsule DE, including but not limited to:

- Dysphagia: oropharyngeal, esophageal, functional, neuromuscular (e.g. stroke, multiple sclerosis, ALS), or patient shows evidence of dysphagia when the ‘safety test’ capsule is administered
- Risk of aspiration
- History of gastroparesis
- History of intestinal obstruction
- Severe food allergy (e.g. anaphylaxis or anaphylactoid reaction)
- Adverse event attributable to a previous FMT
- Patients with allergies to sodium chloride, glycerol, theobroma oil, hide bovine gelatin, sodium lauryl sulfate, colorants FD&C, or titanium dioxide, all ingredients Generally Recognized As Safe (GRAS)
- History of ongoing antibiotic use (e.g. nitrofurantoin for UTI prophylaxis)
- Any condition for which the treating physician thinks the treatment may pose a health risk (e.g. severely immunocompromised)

Warnings: OpenBiome cannot guarantee the inclusion or exclusion of any food allergens (e.g. tree nuts, seafood) from a donor’s diet. This material has not been screened for CMV and EBV and should not be used for patients at risk for CMV- or EBV-associated diseases (e.g., severely immunocompromised patients such as seronegative transplant recipients). FMT carries the risk of known and unknown infectious disease transmission and potentially microbiome-mediated diseases. The risk of aspiration (via naso-enteric administration), bacteremia, and death have been reported in the literature.
☐ Obtain informed consent
  ☐ Inform patients of the risks, benefits, and treatment alternatives for FMT in general
  ☐ Inform patients of the risks, benefits, and treatment alternatives for FMT Capsule DE.
  ☐ Inform the patient that the use of FMT to treat recurrent Clostridium difficile infection (rCDI) is investigational.

☐ Administer safety test capsule
  ☐ Patients should ingest 1 placebo ‘safety test’ capsule (included with each treatment) under direct observation of a physician. Any clinical concerns suggesting an aspiration risk is an absolute contraindication to capsule administration.

☐ Review medications
  ☐ Discontinue anti-rCDI antibiotics (e.g. vancomycin, fidaxomicin) **48 hours** prior to FMT Capsule DE administration. Concomitant use of other antibiotics could reduce the procedure’s efficacy.
  ☐ Administer oral proton pump inhibitor once daily for 48 hours prior to FMT Capsule DE administration
  ☐ Antiemetic medications are not recommended for routine administration.

☐ Day of FMT Capsule DE administration
  ☐ Patients should maintain a clear liquid diet the day of FMT Capsule DE administration
  ☐ Patients should fast (NPO) for 2 hours prior to the FMT Capsule DE administration

Administration
  ☐ Capsules must be administered under direct observation by a physician
  ☐ Capsules must be kept frozen at a minimum of -20 degrees Celsius until ready for administration
  ☐ When ready for administration, remove capsules from freezer, confirm that the capsules are not expired, and note the time that they are removed
  ☐ Open bottle and remove cotton immediately
  ☐ Empty capsules from bottle into a sterile container. A clean K-basin or equivalent container should be used.
  ☐ Provide the patient with plenty of clear liquid to drink during administration
  ☐ All 30 FMT Capsule DE pills should be ingested within 90 minutes after extraction from the freezer

Post Administration
  ☐ Patients should fast (NPO) for 1 hour after the administration of FMT Capsule DE
  ☐ Patients may return to a full diet following post-administration fasting

Rev. March 2019
Adverse Reactions

This is a summary of adverse reactions reported in peer-reviewed literature; however, may not be a comprehensive list. Please consult the primary sources listed in the references section of the OpenBiome Clinical Primer for more detailed information. Procedure-related adverse events (e.g. perforation, aspiration) are beyond the scope of this document.

- **Common, mild adverse events**: transient diarrhea (70%), transient abdominal cramps/discomfort (20%) and nausea (<5%) in the 24 hours post FMT. Transient fever, bloating, belching, vomiting, borborygmus have also been reported. Constipation (20%) and excess flatulence (25%) have been reported in follow-up. There is also a theoretical risk of small intestinal bacterial overgrowth.

- **Rare, serious adverse events**: There have not been any definitely related serious adverse events attributable to FMT material. However, the following risks should be considered:
  - Infection: Although this material has been screened for bacteria, viruses, fungi and parasites there is a risk of transmission of known and unknown infectious organisms contained in the donor stool. Post-FMT bacteremia (e.g. E. coli), sepsis and fatal events may rarely occur.
  - Inflammatory bowel disease (IBD) flare in those with underlying IBD;
  - Allergy/Anaphylaxis to antigens in donor stool;
  - Non-infectious disease transmission: There is a theoretical risk of developing disease that may be related to donor gut microbiota. These include obesity, metabolic syndrome, cardiovascular disease, autoimmune conditions, allergic/atopic disorders, neurologic disorders, psychiatric conditions and malignancy. Persons with these known conditions are excluded from donating stool.
  - Aspiration: Capsule administration carries a risk of aspiration (see "Indications & contraindications")

**Mandatory Clinical Follow-Up**

- Assess patients 8 weeks after FMT Capsule DE administration (phone/clinic visit) for clinical cure (e.g. absence of 3 or more liquid bowel movements a day)
- Complete mandatory Material Tracking Log and FMT Follow-Up form included with your shipment
- Send Material Tracking Log and FMT Follow-Up Form by email to info@openbiome.org or by fax to (617) 575-2201, reporting de-identified patient outcomes.

This quality assurance data is critical to our efforts to guard against potential threats to the safety and efficacy of FMT, and your participation is a strict condition for receiving future supplies of FMT Capsule DE.
**Post-FMT Patient Counseling**

- Advise patient to thoroughly clean their home to avoid reinfection after FMT. When cleaning, the patient should:
  - Use an Environmental Protection Agency (EPA)-registered disinfectant with a *C. difficile*-sporicidal label claim, such as household bleach
  - Scrub high-touch surface areas such as toilets, faucets, and showers
  - Wear disposable gloves when cleaning; wash hands with soap and water thoroughly afterwards
  - Consult OpenBiome’s Patient Education materials, which can be found on our website: www.openbiome.org/patient-support

**Important Reminders**

- FMT Capsule DE must be stored in a medical-grade freezer at -20°C or colder at all times, and should **never be refrozen**
- FMT Capsule DE that has been removed from the freezer for administration to a patient should be disposed of if not consumed within 90 minutes

**INGREDIENTS**

Frozen human fecal microbiota filtered to 330 microns, theobroma oil, glycerol, hide bovine gelatin, sodium lauryl sulfate, colorants FD&C, titanium dioxide, interior gelatin capsule, exterior acid-resistant capsule.

**CAUTION**

New Drug—Limited by Federal (or United States) law to investigational use. Immediately report any adverse events to safety@openbiome.org.
Clinical Context

Formulation | Clinical Evidence | Dosing and Delivery | Material Handling

The standardization of FMT through the universal stool donor model has transformed the therapy from an irregular procedure developed by a handful of bold pioneers to a widely practiced treatment for recurrent *Clostridium difficile* infection (rCDI). Standardized, safe access to FMT has helped thousands of rCDI patients benefit from dramatically lower morbidity, mortality, and costs of care.

Yet, despite the improvements in donor screening, material processing, and clinical availability enabled by the OpenBiome universal donor model, the methods of administering fecal microbiota have not been significantly refined since their early development. Currently, clinical practice includes infusing microbiota preparations into the colon via a lower delivery route (i.e. colonoscopy, sigmoidoscopy, and enema) or an upper delivery route (i.e. naso-enteric tube or esophagogastroduodenoscopy). All of these routes of delivery are moderately invasive and carry procedure-related costs and risks. Delivery by pill can reduce the costs and risks of delivery, and is strongly preferred in a survey of patients preferences.¹ FMT capsules provide a valuable addition to available delivery options.

A stable oral formulation of FMT

We developed FMT capsules in response to demand from our partner physicians and from patients, recognizing that there are circumstances when it may be inappropriate, contraindicated or simply contrary to patient preferences to deliver material via traditional routes of administration for FMT. Dissolution assays have been performed comparing the degradation of DE capsules and our previous G3 capsule formulation. These assays aimed to evaluate the breakdown of these capsules on exposure to stomach contents. DE capsules significantly outperformed the G3 capsules. These results suggest that DE capsules will remain intact through the stomach, preserving the bacteria contained in the capsules for effective post-pyloric delivery. In comparison, G3 capsules are less likely to remain intact in the stomach.
FMT Capsule DE contains the identical cryoprotectant used for traditional frozen FMT preparations. As with these treatments, to preserve microbial viability, providers should strictly maintain the cold chain without allowing freeze-thaw cycles. Material should be delivered within 90 minutes of removal from frozen storage.

Clinical Evidence

Broadly, the use of FMT capsules for the treatment of rCDI builds on the extensive literature established through traditional delivery modalities. There are four small published case series utilizing FMT capsules and a randomized dose-finding study, detailed below. More recently, a randomized controlled trial found double-encapsulated FMT to be non-inferior to FMT by colonoscopy. Of note, this study was not performed using OpenBiome material. Those that used OpenBiome material are indicated with a ★. Overall, the clinical experience with FMT capsules suggests that this delivery modality has lower efficacy than traditional delivery modalities, but clinical efficacy may be improved with repeat treatment of non-responsive patients.

Efficacy

Preliminary evidence for FMT via capsules suggests a 70% clinical cure rate with a single administered dose of 30 capsules, and a cumulative clinical cure rate of 94% if non-responders are retreated with an extended dose of 30 capsules on 2 consecutive days.\(^2\) These results are in keeping with other studies that suggest between a 68-70% clinical cure rate with a single administration of FMT capsules.\(^3,4\) Reported efficacy rates for traditional modalities are higher: 82% for upper delivery (naso-enteric or esophagogastroduodenoscopy tube), and 91% for lower delivery (colonoscopy, sigmoidoscopy, enema).\(^5\)

Safety

Each delivery route carries its own set of potential procedure-related adverse events. No serious adverse events have been reported in the studies using FMT capsules. Please review the list of absolute contraindications for the use of FMT Capsule DE on page 1 of this guide. The majority of contraindications can be categorized as conditions that would prevent swallowing and moving the capsules through the gastrointestinal tract. Patient candidacy for FMT in general should also be assessed (you may refer to general clinical primer as necessary).

Upper gastrointestinal delivery (naso-enteric or oral) administration carries a risk of aspiration. Additionally, anecdotal observations suggest that upper gastrointestinal delivery may carry a risk of small bowel bacterial overgrowth, although this is not well described. Broadly, upper gastrointestinal delivery should be avoided if there is evidence of an ileus, which may be part of the severe-complicated CDI spectrum.
(Section 10), or if patients are experiencing nausea/vomiting, as the risk of aspiration is likely elevated.

Colonoscopy has rare but recognized procedure-related adverse events including perforation, bleeding, sedation-related aspiration or cardiopulmonary events. However, colonoscopy also has added utility in its diagnostic value. There are anecdotal reports of previously undiagnosed inflammatory bowel disease and colon cancer detected at the time of FMT by colonoscopy. It is worth noting that a full colonoscopy in some CDI patient populations (e.g., toxic megacolon, severe pancolitis) may carry increased risk of perforation, and a flexible sigmoidoscopy or an alternate less invasive delivery modality is likely preferable, although there is limited data.

Lastly, retention enema is likely low-risk but may be less effective in some patients with poor sphincter tone. Regardless, in patients with advanced age, multiple comorbidities or limited life expectancy, this less invasive mode may be preferable. Overall, clinicians should use their clinical judgment on the ideal delivery modality based on the risks, benefits and alternatives directly related to an individual patient’s clinical situation.

Kao et al., JAMA 2017: In this noninferiority randomized clinical trial that included 116 adults with CDI, Kao and colleagues compared FMT delivered by capsules to colonoscopy. The proportion without recurrence over 12 weeks was 96.2% after a single treatment in a group treated with oral capsules and in a group treated via colonoscopy, meeting the noninferiority margin of 15%. Rates of minor adverse events were 5.4% for the capsule group vs 12.5% for the colonoscopy group.

★ Fischer M*, Allegretti M* et al., UEGJ 2015: In a cluster randomized dose finding study presented as a late breaking abstract at United European Gastroenterology Week, researchers from Brigham Women’s Hospital-Harvard-Medical School and Indiana University demonstrated that patients in receiving a high dose (30 capsules on 2 consecutive days) of FMT capsules achieved clinical resolution at 8-week follow-up in 5/7 (71%) compared to 7/10 (70%) patients receiving a low dose (30 capsules once). Non-responders in both arms were treated with 30 capsules for 2 consecutive days, and aggregate clinical cure rate was achieved in 16/17 (94%) without any reported adverse events. It should be noted that patients with IBD and IBS were excluded, and a lower rate of efficacy would be expected among these groups.

★ Stollman et al., JAMA 2015: Dr. Neil Stollman and OpenBiome researchers reported on their use of standardized encapsulated stool among 4 elderly FMT non-responders with rCDI in whom colonoscopic delivery was not optimal. Overall, 2 of 4 patients achieved clinical resolution with no adverse events 162 and 81 days after follow-up, respectively. Additionally, 2 of 4 had recurring symptoms 21 and 13 days after follow-up,
and underwent colonoscopic FMT with clinical cures and no adverse events 21 and 38 days after follow-up.\textsuperscript{6}

\textit{Hirsch et al., BMC Infect Dis 2015}: Dr. Bruce Hirsch and colleagues present results from the treatment of 19 rCDI patients treated with frozen FMT capsules. Overall, 13 patients (68\%) experienced resolution of symptoms lasting at least 90 days. Of the 6 patients that failed initial therapy, 4 responded after a second dose, for a cumulative efficacy of 89\%.

\textit{Youngster et al., JAMA 2014}: Researchers at Massachusetts General Hospital and Boston Children’s Hospital reported the results of an open-label, single-group feasibility study in which 20 patients received 15 capsules per day for 2 consecutive days. Of the group, 14 patients (70\%; 95\% CI, 47\%-85\%) experienced a resolution of diarrhea with no adverse events. All 6 non-responders were re-treated; 4 had resolution of diarrhea, resulting in an overall 90\% (95\% CI, 68\%-98\%) rate of clinical resolution of diarrhea.

\textit{Louie et al., IDWeek 2013}: Researchers from the University of Calgary, Canada presented an abstract at IDWeek 2013 in which they described their experience using oral capsules to administer FMT to patients who could not tolerate a jejunal catheter (esophageal varices) and/or were unable to retain fecal enemas due to anal incontinence and failed treatment for rCDI. They reported that 27 of 27 patients achieved clinical resolution of rCDI after a single administered dose.\textsuperscript{7}

\textbf{Dosing and Delivery}

We suggest the following 6 steps for the administration of FMT capsules, noting that preliminary data indicates that a single treatment with FMT capsules has a lower efficacy rate than that for FMT by colonoscopic administration. Colonoscopy remains the most effective mode of delivery for FMT according to the current body of evidence.

1. \textbf{Assess contraindications} specific to capsule administration. To prioritize safety, patients with a history of the following conditions should \textbf{not} undergo capsule administration:
   a. Severe or severe-complicated \textit{Clostridium difficile} infection
   b. Dysphagia: oropharyngeal, esophageal, functional, neuromuscular (e.g. stroke, multiple sclerosis, ALS) or patients who show evidence of dysphagia when the ‘test’ capsule is administered
   c. Risk of aspiration
   d. History of intestinal obstruction
   e. History of ongoing antibiotic use (e.g. nitrofurantoin for UTI prophylaxis)
f. Patients with allergies to ingredients Generally Recognized As Safe (glycerol, sodium chloride, hypromellose, gellan gum, Theobroma oil, titanium dioxide)
g. Adverse event attributable to a previous fecal microbiota transplantation (FMT)
h. Any condition for which the treating physician thinks the treatment may pose a health risk (e.g. severely immunocompromised)

2. **Obtain informed consent:** Patients should be informed of the risks and benefits of FMT and treatment alternatives, both in general and with respect to FMT capsules, in accordance with FDA guidelines and protocols from healthcare facilities and medical professional societies. This discussion should also include, at a minimum, a statement that the use of FMT products to treat rCDI is investigational.

3. **Direct-observed capsule test:** Capsules are size 00, approximately the size of a large multivitamin. Patients should be asked to ingest 1 placebo 'safety test' capsule under direct observation of a physician. Any clinical concerns suggesting an aspiration risk is an absolute contraindication to capsule administration.

4. **Pre-treatment:**
   a. Oral vancomycin or fidaxomycin should be discontinued 48 hours prior to clinical visit for capsule administration
   b. Oral proton pump inhibitor should be administered once daily for 48 hours prior to capsule administration

5. **Dietary instructions:** Patients should maintain a clear liquid diet the day of visit and should fast (NPO) for 2 hours prior to the visit

6. **Capsule administration:**
   a. Patient should ingest 30 capsules under the direct observation of a physician
   b. Patient should ingest capsules after extraction from freezer, and no longer than 90 minutes after removal
   c. Patients should remain fasting (NPO) for 1 hour following ingestion but may then return to a full diet

**Vomiting**

There have been no reported cases of vomiting in the literature, nor have there been any cases of nausea or vomiting using OpenBiome’s capsules. If the patient vomits, the procedure should be aborted. Standard of care management should be employed in the case of an aspiration at the discretion of the treating physician.
Special populations

Pediatrics
Given the large size of the capsules and the recommended dose of 30 capsules ingested within 90 minutes, exercise caution when considering the use of FMT Capsule DE in this patient population. Although teenagers may be good candidates, young children and infants are not ideal candidates for this delivery modality.

Pregnant
FMT, including FMT Capsule DE, is not recommended for patients who are pregnant.

Material Handling
The recommended dose of 30 capsules arrives in a tamper-evident plastic bottle inside packaging on dry ice, and should remain frozen until consumed by the patient. To maintain viability, capsules should not remain at room temperature for more than 90 minutes before they are ingested. To mitigate the risks of aspiration and to avoid the diversion of capsules for unsanctioned use, we require physicians directly observe the administration of the complete dose.
Quality Assurance and Safety Reporting

REPORTING ADVERSE EVENTS

As with any medical intervention, FMT carries certain risks. In addition to the possible transmission of infectious pathogens and a theoretical risk of causing microbiome-mediated diseases, the procedure itself poses risks that will vary by delivery modality. The risk of such events should be clearly discussed with your patient during the informed consent process prior to the FMT procedure.

The adverse events contacts for your FMT program should be familiar with these risks, and should communicate the following SUSAR (Suspected Unexpected Serious Adverse Reaction)* reporting protocol to all physicians performing FMT at your institution. If the treating physician or a member of the FMT program staff become aware of a SUSAR that could be related to an 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. Triage call: Upon receipt of an adverse event report, an OpenBiome medical professional will reach out to the report’s author to triage the case according to FDA guidelines and determine next steps in the investigation.

3. FDA reporting: An OpenBiome medical professional will use the details of your report and any ensuing investigation to advise you and your program of any additional reporting requirements, which may include submission of Form FDA 3500. Please consult with us before filing Form FDA 3500, as over-reporting can create inefficient delays.

*An OpenBiome clinician will assist you in determining if the adverse event meets the criteria for reporting to the FDA. Adverse events should only be reported to the FDA if it meets ALL three of the following criteria as outlined in (21 CFR 312.32(c)(1)(i)):

1. **Suspected**: Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the FMT material caused the adverse event. For the purposes of FDA safety reporting, ‘reasonable possibility’ means there is evidence to suggest a causal relationship between FMT and the adverse event.

2. **Unexpected**: An adverse event or suspected adverse reaction is considered “unexpected” if it is inconsistent with the risk information described in the FMT packaging inserts.

3. **Serious**: An adverse event or suspected adverse reaction is considered “serious” if it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to
conduct normal life functions, a congenital anomaly/birth defect, or other serious medical events (Report when the event does not fit the other outcomes, but may jeopardize the patient and may require medical/surgical intervention to prevent one of the other outcomes. Examples include allergic bronchospasm, requiring treatment in an emergency room, serious autoimmune disease (Sjogren’s syndrome, rheumatoid arthritis) or seizures/convulsions that do not result in hospitalization.)

**Clinician Checklist for Reporting Adverse Events to OpenBiome**

To report an adverse event to OpenBiome, please submit your report at [www.openbiome.org/adverse-events](http://www.openbiome.org/adverse-events). If you have any questions, please contact our Clinical Safety team at safety@openbiome.org or call (617) 575-2201, option 1.

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

The administering physician should schedule a phone call or office visit with the patient to assess for clinical cure 8 weeks after the FMT procedure, following standard of care. Clinical guidelines define clinical cure of CDI as the absence of diarrhea. Although there is no test of cure, patients with active diarrhea should be tested for C. difficile. Patients that are negative for C. difficile but have ongoing diarrhea likely have an alternative etiology (e.g. post-infectious IBS) and can be deemed a clinical cure for CDI.

An FMT Follow-Up Form must be completed for each patient that receives an FMT from OpenBiome. It asks for de-identified case specifics, including delivery modality, disease phenotype, treatment outcome, and incidence of any adverse events. The form should be provided to the administering physician or his or her staff and returned to OpenBiome after the patient’s 8-week follow-up.

Non-Response: In keeping with clinical guidelines, an FMT treatment response is defined as when either stool frequency decreases or stool consistency improves and parameters of disease severity (clinical, laboratory, radiological) improve with no new signs of severe disease. In all other cases, treatment is considered a non-response, being either:

- Recurrence: Clostridium difficile infection re-occurs within 8 weeks after the onset of a previous Clostridium difficile infection episode, provided the symptoms from the previous episode resolved after completion of treatment. This should be clinically distinguished from re-infection, commonly associated with repeat antibiotic exposure.
- Refractory: Ongoing or worsening Clostridium difficile infection symptoms despite treatment.

Available evidence suggests that FMT capsules may yield a lower cure rate than traditional FMT delivery modalities. Clinicians should counsel patients appropriately and discuss their treatment options in the event of a non-response.

At the discretion of the treating physician, there are two options in FMT non-response:

- **Standard FMT**: At the discretion of the treating physician, a second FMT may be administered using a conventional delivery modality (e.g. colonoscopy, enema, naso-enteric delivery). All else being equal, FMT by colonoscopy may be preferable according to the current body of evidence; however, physicians should evaluate the patient’s individual risks, benefits and alternatives (Kassam et al. Am J Gastro 2013).

- **FMT Capsule DE Rescue Dose**: Based on the current body of evidence, an extended dose of FMT capsules may increase the clinical efficacy rate. Our preliminary data is consistent with this finding, and we suggest administering 30 capsules daily on 2
consecutive days, if the treating physician concludes it to be the safest approach for a particular patient.

**Use of OpenBiome material:** It is mandatory to complete the Material Tracking Log that accompanies each shipment. This quality assurance tool informs OpenBiome of the status of treatments across its network of FMT providers and of de-identified patient outcomes. It helps OpenBiome track the performance of treatments across our clinical network and is critical for coordinating a network-wide response to a material-associated serious adverse event.

Please use the Material Tracking Log provided with your order to update OpenBiome on the status of material that has been sent to your facility. When you administer a treatment, make note of the treatment Unit ID in the patient’s records (Note: no patient information should be shared with OpenBiome, nor will OpenBiome ever request patient information). Following your first order from OpenBiome, each new order must be accompanied by a Material Tracking Log or it will not be processed.
Ordering Information

Clinical Care | Research Use | Contact Information

We offer FMT Capsule DE for clinical management of rCDI and for clinical research. Below are the practical steps for ordering capsules in each case:

Clinical Care
In accordance with FDA regulation, FMT Capsule DE is available for the treatment of Clostridium difficile infection that is not responsive to standard antibiotic therapy. For the use of FMT Capsule DE to treat other indications, please see “Research” below.

Ordering
Hospitals and clinics in OpenBiome’s clinical network may order FMT Capsule DE for clinical use using the OpenBiome order form or through their own purchase order system. On a facility’s first order, our Clinical Outreach team will schedule a call with the treating physician to review key clinical information about FMT Capsule DE use, and to complete a Physician’s Acknowledgment form confirming their understanding of the key clinical information.

Pricing
The cost of OpenBiome’s FMT capsules is $1950, which covers production costs. This treatment cost will include 30 capsules and 2 placebo “safety test” capsules, as described in the recommended dosing & delivery protocols above. Additional shipping & handling charges may also apply.

Pro-bono availability
As always, OpenBiome is committed to facilitating universal access to FMT, and with the generous support of the Anna-Maria and Stephen Kellen Foundation, we can support a number of pro-bono treatments for patients who are unable to cover the costs of material. If any of your patients would be a candidate for support under this pro-bono fund, please contact us at capsules@openbiome.org.

For more information, please inquire at info@openbiome.org.

Research Use
OpenBiome is happy to make capsules available for clinical research using a unique acid-resistant formulation that enables patients to forgo the need for PPI therapy prior to FMT. We are actively focused on dose finding and molecular evaluation of
engraftment in rCDI patients. We also offer FMT capsules for clinical trials conducted under FDA supervision via IND for other diseases associated with dysbiosis of the microbiome. We can provide placebo controls as needed and have our encapsulation protocol registered with the FDA through our biologics master file (BB-MF). Interested clinicians can contact us at science@openbiome.org to discuss research opportunities in more detail.

Contact Information

- General and clinical use questions: capsules@openbiome.org or (617) 575-2201
- Research: science@openbiome.org or (617) 575-2201
- Quality Assurance & Safety reporting: safety@openbiome.org or (617) 575-2201
- Submission of Adverse Event Reports: www.openbiome.org/adverse-events
- Submission of FMT Follow Up Forms or Material Tracking Logs: Email forms to safety@openbiome.org or fax forms to 617-575-2201 (please note OpenBiome’s phone and fax numbers are the same)
- FDA Adverse Event reporting: Fax FDA MedWatch Form 3500 to 800-FDA-0178 or mail form to The FDA Safety Information and Adverse Event Reporting Program, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852-9787.
References


