
Dear Commissioner Califf and Director Midthun:

We write today on behalf of the American Gastroenterological Association (AGA) to provide comments on the Food and Drug Administration’s (FDA) recent draft guidance for industry regarding the applicability of investigational new drug (IND) requirements to fecal microbiota transplantation (FMT). Founded in 1897, the AGA is the trusted voice of the gastroenterology community that has grown to include more than 16,000 members from around the globe who are involved in all aspects of the science, practice and advancement of gastroenterology. Given the enthusiasm and interest within the gastroenterology community in FMT, the AGA has worked diligently to educate the physician community about the potential benefits and underlying concerns associated with FMT. A key aspect of these efforts was the creation of the AGA Center for Gut Microbiome Research and Education (Center), which is guided by a panel of leading researchers and physicians with expertise in the complexities of the microbiome. We appreciate the opportunity to provide feedback on the current draft guidance and share your commitment to ensuring the quality and safety of healthcare in the United States.

1. Current Clinical and Regulatory Environment for FMT

The AGA’s physician members have dedicated countless hours of research to studying FMT and conditions for which it shows promise. We agree with the FDA that recurrent Clostridium difficile infection (CDI) is a major issue facing the patient population and believe that the draft guidance rightfully distinguishes it from other conditions for which FMT is being studied. The Centers for Disease Control and Prevention has estimated that CDI was responsible for approximately 453,000 infections and 29,000 deaths in 2011 alone, which was a substantial increase from previous years.1 Much of this burden was borne by individuals over 65 and nearby

one in four cases occurred in hospital settings, with estimates indicating recurrence in an average of 20 percent of all cases.\(^2\) Alarmingly, pediatric CDI-related hospitalizations also increased from a rate of 7.24 to 12.80 per 10,000 hospitalizations between 1997 and 2006.\(^3\) Today, clinical research has shown that FMT has an efficacy rate of 90 percent or more as a treatment for recurrent CDI, which has resulted in increasing levels of acceptance on the part of both practicing physicians and the affected patient population. Importantly, FMT has become the standard of care for recurrent CDI unresponsive to standard therapies and is recommended in clinical guidelines and other publications from leading U.S. medical associations and expert working groups.\(^5,6\)

We appreciate the complexity of balancing patient safety interests with a regulatory framework that facilitates the growth of FMT as a means to treat a variety of symptoms impacting patient mortality and quality of life. The AGA has had prior communications with the FDA on this issue dating back to the original enforcement discretion in 2013. Since then, physicians and organizations that develop and distribute FMT have existed in a state of ambiguous requirements. We are appreciative of the FDA’s decision to release new draft guidance that will hopefully address some of these issues. The AGA is in agreement that stool banks should operate under an IND and that “[their] compliance with the IND requirements will help to ensure that the stool donor and stool are appropriately qualified by screening and testing and that centralized processing of FMT adheres to appropriate current good manufacturing conditions.”

However, as detailed below, we are concerned by the potential impact of the draft guidance on health care providers who use FMT material provided by stool banks. Given the urgency facing patients with recurrent CDI, we hope that the FDA will take whatever steps possible to ensure that patients will continue to have access to this life-saving treatment.

2. Waivers of IND Regulations Related to Sub-Investigators

Since the FDA’s July 2013 guidance announcing enforcement discretion regarding IND requirements for FMT, the use of stool banks as a source of FMT material has increased among health care systems and providers. The current draft guidance states:

“Health care providers who receive FMT product from the stool bank may be sub-investigators...IND sponsors requesting a waiver of certain investigator responsibilities may also include a request for waiver of those regulations related to sub investigators.”

The AGA believes that all IND regulations be waived for health care providers using FMT product from stool banks (i.e., sub-investigators) except IND safety reporting of serious and unexpected suspected adverse reactions (21 CFR 312.32). Sub-investigators should only be required to report such reactions directly to the IND sponsor through a platform administered by the sponsor. CDI patients tend to be older in age, and often have multiple comorbidities or are at high risk for comorbidities unrelated to CDI. Without explicitly clarifying that health care providers are

\(^2\) Id. at Lessa
responsible for reporting serious and unexpected suspected adverse reactions, hundreds of reports would be filed for each case of stroke, pneumonia, or some other comorbidity unrelated to the FMT procedure. The sponsor should be obligated to provide sub-investigators with a system for tracking and collecting data on serious and unexpected suspected adverse reactions, and should ultimately be responsible for preparing and submitting comprehensive safety reports to the FDA.

2.1. Assurance of IRB Review

Under the July 2013 guidance, health care providers treating patients with FMT are required to operate under an IND, which includes assurance of Institutional Review Board (IRB) review. The AGA believes that the requirement for assurance of IRB review (21 CFR 312.66) should be waived for sub-investigators. Under enforcement discretion, the FDA has remained silent on this requirement and individual IRBs have been left to determine requirements for local health care providers performing FMT. With the increasing number of health care providers using the services of stool banks, it is imperative that FDA clarify its stance on the requirement of IRB review for sub-investigators.

We are concerned that health care providers – particularly those outside of large, tertiary health care systems – will discontinue FMT due to the time-consuming administrative burden of obtaining and maintaining IRB approval. In turn, this may restrict FMT to a handful of health care providers at large health systems, thereby decreasing patient access to FMT and increasing the care burden on a limited number of clinicians. Further, it may inadvertently encourage patients to perform “do-it-yourself” FMT without medical supervision, using FMT material that has not been properly screened.

As the medical community increasingly acknowledges the value provided by FMT for treatment of recurrent CDI, it has also recognized the potential for manipulation of the microbiome to treat other disorders. This is a natural response to the proven effectiveness of FMT and we appreciate that the FDA makes this distinction in regard to IND waivers. We support the provision of waivers of certain IND requirements for sub-investigators and ask that it is administered in a way that provides the greatest access to treatment, while also recognizing that IRB approval is appropriate when FMT is being investigated in the research setting for CDI or for the treatment of disorders other than recurrent CDI.

2.2. Charging for Investigational Drugs under an IND

FMT material can be administered to a patient through a number of ways, and there is not yet consensus on the best method of delivery.7 However, all of these methods require the time and close supervision of a licensed health care provider, and delivery methods such as colonoscopy require additional technologies and materials adding to the total cost burden of an FMT procedure. All of these are direct costs incurred by the sub-investigator that cannot be charged under current IND regulations. The FDA’s guidance is silent on this issue, but our review of existing FDA standards for “investigational products” causes concern. Expanded access to FMT has been the result of a long campaign to inform practicing physicians and their patients about the value of FMT. If practices are no longer able to recover the cost of providing FMT, it would become infeasible to continue providing this service. The absence of willing practices will inevitably diminish access and harm patients. The AGA believes that the limitations for charging for investigational drugs under an IND (21 CFR 312.8) should be waived for sub-investigators. We ask that the FDA clarify that physicians using

7 Id. at Kelly
donor material from a stool bank are able to charge for services and materials without having to go through the process of “cost recovery” as stated in a previous FDA guidance.

Altogether, while we agree that enforcement discretion for the IND requirements for the use of FMT to treat recurrent CDI should not be extended to stool banks, the regulations should be appropriately waived as to not disrupt the practice of health care providers around the United States who use the services that stool banks provide.

3. Donor Tracking

The draft guidance clearly states the FDA’s concerns regarding donor populations, namely that the widespread dissemination of samples from small donor pools increases the potential for major safety occurrences and patient harms. We acknowledge the FDA’s concerns and believe the IND requirement for stool banks will ensure that the stool donor and FMT material are appropriately screened and tested, and that the processing facilities adhere to good manufacturing conditions. As part of the safety reporting requirement for IND sponsors, AGA underscores the importance of recording the source of donor stool administered to FMT recipients. This is particularly important when using FMT material from a stool bank, as an infectious agent in a single donor has the potential to be transmitted to many recipients. However, health care providers using “known” donors without the service of a stool bank should also be expected to maintain such records.

4. Long-Term Safety Monitoring and Reporting

The safety and progress reporting requirements under an IND provides a standard framework by which long-term data regarding safety and adverse events must be tracked and recorded. Stool banks in particular are often large, well-administered organizations that have fully refined processes for collection, treatment and distribution of samples. The AGA believes that these organizations, as IND sponsors, should be responsible for working with the FDA to develop a plan for safety monitoring, appropriate follow up, and reporting of adverse events.

Under enforcement discretion, health care providers performing FMT would not be required to report safety information to the FDA. Therefore, the AGA believes that a national FMT registry must be established as a reporting vehicle for clinicians who are not sub-investigators under an existing IND. We believe this registry will meet a significant need, as researchers and clinicians continue to explore the long-term safety and efficacy of FMT as a treatment for recurrent CDI and other disorders.

5. Conclusions

In summary, the AGA:

1. Agrees that stool banks should operate under an IND and that “[their] compliance with the IND requirements will help to ensure that the stool donor and stool are appropriately qualified by screening and testing and that centralized processing of FMT adheres to

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appropriate current good manufacturing conditions.” It will also mandate safety reporting of serious and unexpected suspected adverse reactions.

2. Believes that all IND regulations should be waived for health care providers using FMT product from stool banks (i.e., sub-investigators) except IND safety reporting of serious and unexpected suspected adverse reactions.

3. Believes that the requirement for assurance of IRB review (21 CFR 312.66) should be waived for sub-investigators.

4. Believes that the limitations for charging for investigational drugs under an IND (21 CFR 312.8) should be waived for sub-investigators.

5. Believes that all health care providers performing FMT should be required to record the donor stool used for each FMT recipient.

6. Believes that a national FMT registry must be established as a reporting vehicle for health care providers performing FMT.

The AGA, with the support of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), thanks the FDA for its interest in ensuring that FMT remains a safe therapeutic option for patients with recurrent CDI. We recognize that this guidance is an interim policy. Microbiome-based therapeutics are evolving rapidly, and the regulatory framework should accommodate the advent of new therapies and technologies. However, these emerging therapies are still years away from becoming available to patients in immediate need; we believe that the FDA should allow health care providers to continue current practice in using FMT as an effective treatment for recurrent CDI as we await the advent of new therapeutic options. We appreciate the opportunity to provide feedback on the draft guidance before it takes effect and look forward to future opportunities for comment relating to FMT and other microbiome-related therapies on behalf of the gastroenterology community.

Sincerely,

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