Fecal Microbiota Transplant National Registry

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PROTOCOL SUMMARY

This document complies with requirements of the Declaration of Helsinki, International Harmonized Standards: EN ISO 14155-1 and ISO 14155-2:2003(E) and with 21 CFR Parts 50, 54, 56, and 812.

Title:	Fecal Microbiota Transplantation National Registry
Précis:	A national data registry of patients receiving fecal microbiota transplantation (FMT) or other gut-related-microbiota products designed to prospectively assess short and long-term safety and effectiveness
Mission:	To expand knowledge and optimize practice in the transplantation of fecal microbiota or other gut-related-microbiota products.
Goals:	To assess short-term and long-term safety To assess effectiveness To gather information on practice in North America. To promote scientific investigation To aid practitioners and sponsors in satisfying regulatory requirements
Population:	All patients receiving FMT or other gut-related-microbiota products and the donors providing specimens for the enrolled patients' FMT. Patients will be enrolled regardless of race, gender, ethnicity, or age.
Number of Sites:	75
Number of Patients	4,000
Subject Participation Duration:	10 years

STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the NIDCR Clinical Terms of Award. All personnel involved in the conduct of this study have completed human subjects' protection training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

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LIST OF ABBREVIATIONS

21 CFR 11	Food and Drug Administration's 21 Code of Federal Regulations Part 11, Electronic Records; Electronic Signatures
ADaM	Analysis Data Mode
AE	Adverse Event
AGA	American Gastroenterological Association
CCFA	Crohn's &Colitis Foundation of America
AHRQ	Agency for Healthcare Research and Quality
CDASH	Clinical Data Acquisition Standards Harmonization
CDC	United States Center for Disease Control and Prevention
CDI	Clostridium difficile infection
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
CRO	Contract research organization
CSUCI	Computerized Systems Used in Clinical Trials
DEFINE.Xml	metadata model of SDTM, ADaM in extensible markup language
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
ePRO	Electronic Patient Reported Outcomes
EU Annex 11	EudraLex Volume 4 Annex 11 Computerised Systems (European rules for electronic records in clinical research)
FDA	United States Food and Drug Administration
FMT	Fecal Microbiome Transplantation
GCP	Good Clinical Practices
HIPAA	Health Information Portability and Accountability Act
IBD	Inflammatory Bowel Disease
IBS	Irritable Bowel Syndrome
ICH	International Conference on Harmonization
IDSA	Infectious Disease Society of America
IND	Investigational New Drug Application
IRB	Institutional Review Board
NASPGHAN	North American Society for Pediatric Gastroenterology, Hepatology and Nutrition
PI	Principal Investigator
OSMB	Observational Study Monitoring Board
SAE	Serious Adverse Event
SDTM	Standard Data Tabulation Mode
SEND	Standard for Exchange of Nonclinical Data

1 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 Background Information

The gut microbiome functions in a symbiotic relationship with the human body at a level of complexity akin to an organ or tissue. Recent advancements in genome sequencing technology have been used to identify the tremendous diversity of these microorganisms and the ability to analyze metadata has opened a new frontier for research into the role of the gut microbiome in health and disease. It is now well appreciated that intestinal microbiota constitute a microbial organ that is integral to overall host physiology, including pivotal roles in metabolism and immune system function[1]. Initial investigations have demonstrated that alterations in the gut microbiome (dysbiosis) may play a role in a number of gastrointestinal and non-gastrointestinal disorders (e.g., *Clostridium difficile* infection (CDI), inflammatory bowel disease (IBD) , irritable bowel syndrome (IBS), nonalcoholic fatty liver disease, obesity, diabetes, metabolic syndrome, cardiovascular disease, cancer)[2].

The first clinical therapeutic application of this knowledge has been the use of fecal microbiota transplantation (FMT). FMT involves administration of fecal material (containing intestinal microbiota) from a healthy individual (donor) to treat dysbiosis and restore beneficial intestinal flora and phylogenic diversity. The transfer of these highly complex whole communities of microorganisms has been shown to result in durable changes in the recipient[3] and careful donor eligibility and screening protocols are recommended to minimize the risk of transmission of infectious disease or other conditions associated with dysbiosis. FMT has proven to be beneficial in the treatment of recurrent CDI in numerous case series[4] and a recently published randomized controlled trial[5]. Because of recent trends in the incidence and severity of CDI and the growing body of literature, including current treatment guidelines, which support FMT, the number of physicians who perform FMT in the United States is growing. There are ongoing efforts to refine the process of FMT, with stool banks to supply donor material and commercially available encapsulated formulations both in the immediate future. Furthermore, investigations of FMT for the treatment of other conditions, such as IBD, are underway.

1.2 Prior Literature and Studies

The gut microbiota in health and disease: Human microbiomes are very distinctive amongst various body sites and are composed of bacteria and other microorganisms, including prokaryotic organisms such as Archaea, microeukaryotes such as fungi, and viruses (principally bacteriophages). In this protocol, the term “microbiota” will denote the compilation of bacterial microorganisms within a specific environment whereas the “microbiome” refers to the bacterial taxa and their collective genomes. The human gut microbiota is a densely populated bacterial community with approximately 10^{17} organisms per gram of fecal weight composed of over a 1000 species, most of which are obligate anaerobes[7,8], with a collective genome size 150-fold greater than that of its human host[7]. Although there are over 50 bacterial phyla on Earth, human-associated

bacteria largely belong to one of four phyla, *Actinobacteria*, *Firmicutes*, *Proteobacteria*, and *Bacteroidetes*. Mammalian hosts and their gut microbiota have coevolved to exist in a mutualistic relationship where the hosts provide a uniquely suited environment in return for physiological benefits provided by the gut microbiota[3]. Examples of the latter include the fermentation of indigestible carbohydrates to produce short chain fatty acids that are utilized by the host, biotransformation of conjugated bile acids, synthesis of certain vitamins, degradation of dietary oxalates, urease-mediated hydrolysis of urea that is important in host nitrogen balance, and education of the mucosal immune system[9].

Despite the importance of the gut microbiota in maintaining the health of the host, growing evidence suggests that it may also be an important factor in the pathogenesis of a variety of diseases, particularly those that have shown a rapid increase in incidence over the past few decades. These include type 1 and type 2 diabetes mellitus, atherosclerosis, asthma, colon cancer, inflammatory bowel disease (IBD), and autism[10]. Advances in genomic technology, principally DNA sequencing and SNP mapping used for genome-wide association studies, combined with biocomputational algorithms, have revealed the host genetic underpinnings of these complex disease processes. In most circumstances, the contribution of host genetics to disease development is well under 50%, implicating the importance of environmental influences[11]. The observation that these diseases have shown a steadily increasing incidence over the past several decades, the geographic distribution of disease clustering in industrialized nations, and immigration studies revealing the adoption of disease risk of the host country within 1 or 2 generations, emphasize the importance of environment in the pathogenesis of these diseases. The notion that an alteration in the composition of the gut microbiota as a possible etiologic factor in the predisposition to immunologically-mediated disease has been proposed as one of the environmental factors that may play a role in the increasing incidence of the diseases associated with the gut microbiota mentioned previously[12].

Dramatic advances in DNA sequencing technology as well as the development of ever more sophisticated biocomputational tools to analyze massive datasets continue to fuel research into the gut microbiome. The future challenge in this field of research will be to address a number of fundamental questions relevant to human health and disease including: 1) Is there a microbiome associated with human health—the "healthy gut microbiome"; 2) Are there causal relationships between the gut microbiome and human disease?; 3) Is there a role for non-bacterial gut microbes (i.e., microeukaryote (yeast), viruses, and Archaea) in human health and disease?; and 4) What is the optimal method to alter the gut microbiota in a way that is beneficial to humans with disease? The answers to these, and other fundamental questions in the field of gut microbial ecology await further studies in human subjects in whom clinical metadata is carefully collected together with continued investigation in animal models. Rapidly advancing broad-based technologies in addition to DNA sequencing, such as transcriptomics, proteomics, and metabolomics, will allow assessment not only of the structure but also the function of the gut microbiome. Ultimately, the answers to these questions could lead to a fundamental shift in the way that we treat many common diseases. The clinical data collected in the FMT registry and its association with data generated from the analysis of fecal samples stored in a biorepository will provide one of the first opportunities to address some of these questions in a robust and systematic way, using CDI as a paradigm.

It is ironic that, juxtaposed to these technological advances and our rapidly increased understanding of the gut microbiome, is the re-emergence[13] of FMT. FMT is the delivery of stool from a healthy pre-screened donor to an individual with disease with the goal of restoring a healthy gut microbiome and correcting the underlying dysbiosis[14-16]. This "shot-gun" approach has proven to be a highly effective therapeutic modality for recurrent CDI[17]. The use of FMT has highlighted a gap in our current knowledge base. The availability of the therapeutic substrate (feces), together with the ease of administration, has advanced the practice in the field of gut microbiota modulation much more rapidly than our scientific understanding in the field. In addition the early adoption and expansion of FMT in clinical practice has bypassed the standard investigatory pathway (e.g., large randomized trials) that typically contributes important short- and long-term safety data. From a scientific standpoint, the success of FMT in the treatment of CDI is an important proof-of-concept that dysbiosis can be modified to treat a human disease, a notion that might extend to other disease processes such as IBD[18] and metabolic syndrome[19]. On the other hand, associations between the gut microbiota and a number of human diseases with cause-and-effect relationships demonstrated in animal models raise legitimate safety concerns about the use of FMT that extend beyond pathogen transmission[20]. We believe that our proposed FMT registry and its associated biobank will be of significant value in enhancing the scientific value of FMT to the gut microbiome research field while also helping to address safety concerns. Indeed, two of the four goals of the registry are: 1) To assess short-term and long-term safety and 2) To promote scientific investigation.

FMT for the treatment of recurrent CDI*:* Since approximately 2000, there has been an alarming increase in the incidence and severity of CDI[21,22]. Cases of CDI nearly doubled from 98,000 in 1996 to 178,000 in 2003[23], and the unadjusted case-fatality rate increased from 1.2% in 2000 to 2.3% in 2004. It is estimated that 3 million cases of CDI occur each year, obligating annual excess hospital cost of 3.2 billion dollars[24]. Equally concerning has been the increased incidence of community-associated CDI which now is being reported in populations previously believed to be at low risk, including children[25-26], peripartum women, and healthy individuals without a history of antibiotic use[21]. *C. difficile* recurrence is a common management problem and occurs in up to 20% of patients after initial treatment[27,28] . Patients who experience one recurrence have a 40% risk of an additional recurrence and those with 2 or more episodes face a 60% risk of another episode[21,29]. While the first recurrence is generally treated with a second course of metronidazole or vancomycin, current guidelines[30] recommend a tapering course of oral vancomycin. Treatment options are limited for the significant number of patients who continue to experience additional CDI recurrences. Interventions that have been used, but with little or no data to support efficacy, include intravenous immunoglobulin, rifaximin, nitazoxanide, and probiotics[15]. FMT is performed to restore the phylogenetic diversity of normal stool and the associated "colonization resistance" that enables normal intestinal flora to resist overgrowth of *C. difficile*[31]. Numerous case reports and retrospective case series have demonstrated benefit of FMT in patients with severe or recurrent CDI with a mean cure rate of 89% for the approximately 300 cases reported in the world literature[14,32-41]. A randomized controlled trial published in 2013 confirmed the high efficacy of FMT[40]. Methods used to administer FMT include nasogastric and nasointestinal tubes, upper gastrointestinal (GI) tract endoscopy, retention enemas, sigmoidoscopy, and colonoscopy[34-37,43,44].

The proof of concept regarding the role of the gut microbiota in human disease provided by the success of FMT for refractory CDI[45] has catalyzed efforts to extend this approach to other conditions that appear to have strong microbial pathogenic mechanisms, including metabolic syndrome[19] and IBD[18]. For example, in a double-blind, controlled trial, males 21-65 years old with BMI >30kg/m^2 and fasting plasma glucose >5.6 mmol/liter were randomized to receive FMT from either lean male volunteers or from themselves. Fecal transplantation from the lean donors improved peripheral insulin sensitivity during the short period in which this parameter was followed[19]. Also, a recent randomized trial in 70 patients with ulcerative colitis showed a significant benefit of FMT in induction of remission[18]

Actual and theoretical risks of FMT and the need for regulation[46]: There has been mounting demand from clinicians and patients to use FMT for many applications, including conditions where the role of the microbiota in disease pathogenesis is unclear. In the face of this demand, and motivated by concerns about safety, the U.S. Food and Drug Administration (FDA) initially ruled that FMT is both a drug and a biologic that has not currently received approval for any clinical indications. As a result, the FDA required an investigational new drug (IND) application for FMT to be used for any medical indication. More recently, however, the FDA decided to exercise "enforcement discretion" regarding INDs for the use of FMT in adults with CDI that is not responsive to standard therapies[47]. Importantly, FMT may not be used for any indication other than unresponsive CDI without an IND.

While the value of FMT in treating recurrent CDI is clear, its potential long-term detrimental consequences are not known. The gut microbiota is a complex consortium with many components that have never been characterized. *A priori* knowledge is not available regarding the impact of transferring these complex communities from one individual to another, although many studies in mice indicate that the composition of the gut microbiota can affect host susceptibility to diseases. Recall the unexpected consequence of the hepatitis C virus epidemic from the transfusion of contaminated blood before its presence was recognized. Similarly, the transmission of HIV to thousands of hemophiliacs by contamination of a biologic produced from human materials serves as another illustration of how the 'precautionary principle' needs to be applied to FMT[46]. Patients need to be informed of potential risks and consent to the procedure. Protocols need to be developed about donor sample preparation, characterization, archiving (so that follow-up analyses can be performed), and host preparation/administration/dosing. Registries need to be established for collection of data on donor and recipient characteristics, FMT techniques, and short-term and long-term outcomes. Best practices for FMT need to be established, and critically evaluated, clinically-relevant recipient responses to FMT, both beneficial and adverse, need to be defined and monitored.

Current state of knowledge in the U.S. on the practice of FMT: Despite the safety concerns about transferring a complex and undefined microbial living microbial community from one human to another, there is very little current information about practice of FMT in the U.S. Critical methodologic data such as donor/recipient screening, fecal preparation, modality of delivery, and patient consent practices are lacking. Information about the effectiveness of FMT as well as both short- and long-term safety data are not systematically collected with the only available

information being case reports published in the literature. The only currently available modality to capture adverse outcome data for FMT is through the FDA Medwatch portal, a mechanism constrained by reporting bias. Remarkably, the number of FMT practitioners as well as number of patients being treated in the US are also unknown. Based on self-reporting, there are at least 90 FMT sites but the number may be much greater. Based on this information void, national societies have attempted to provide guidance to practitioners through published guidelines and editorials[48-50] but the degree of adherence to these recommendations is unknown.

1.3 Rationale

FMT and future methods of providing gut-related microbiota for treatment of disease are in their infancy, and a great number of questions exist regarding technique, practice, safety, and efficacy. Currently, the FDA is exercising enforcement discretion for IND requirements for use of FMT to treat CDI not responding to standard therapies provided treating physicians obtain informed consent from the patient.

As the practice of FMT and related therapeutic methods rapidly expands in the U.S., it is crucial to assess short-term and long-term safety, to determine the effectiveness in "real-world" settings, and to identify the techniques being used by practitioners in an attempt to standardize and optimize practice in the future. Perhaps the greatest concern is to determine if there may be long-term safety consequences of FMT that are not currently recognized. For example, can transfer of fecal microbiota lead to chronic diseases such as diabetes, obesity, or cardiovascular disease? Animal models have suggested such a possibility, as transfer of specific phenotypes (e.g., obesity) have been demonstrated after fecal transplant in mice[52].

1.4 Potential Risks and Benefits

1.4.1 Potential Risks

There are no risks of physical harm associated with participation in the data registry. Participation in the registry does involve the potential risk of breach of confidentiality of medical information and associated privacy of the participants.

1.4.2 Potential Benefits

There is no expected direct health benefit immediately associated with a patient's participation in the registry. However, the use of the information from the registry may provide future benefit to healthcare providers and patients who require treatment for CDI and other conditions that may be associated with dysbiosis by expanding knowledge regarding FMT and other gut-related microbiota products with the goal of optimizing practice. The potential future benefits include determining if short-term and long-term safety issues exist, characterizing effectiveness, establishing best practices for FMT, providing a resource for investigators to conduct research related to FMT and the gut microbiome, and assisting practitioners and sponsors in satisfying regulatory requirements.

2 OBJECTIVES

2.1 Study Objectives

The overarching goal of the FMT registry is to expand knowledge and optimize practice in the transplantation of fecal microbiota or other gut-related-microbiota products.

Primary Objective: To assess short-term and long-term safety of FMT and other gut-related-microbiota products.

Secondary Objectives:

- To characterize effectiveness of FMT and other gut-related-microbiota products.
- To gather information on FMT practice in North America
- To promote scientific investigation.
- To aid practitioners and sponsors in satisfying regulatory requirements.

2.2 Rationale for Study Objectives Measures

2.2.1 To assess short-term and long-term safety

The safety of FMT is currently the greatest concern related to its use, and characterizing the safety of FMT and subsequent gut-related-microbiota products is the primary goal of the Registry. Short-term adverse events (AEs) relate primarily to the method of delivery (e.g., colonoscopy) and to acute infections or other adverse events from the donor fecal material and should be readily definable and quantifiable. Of greater concern and uncertainty is the possibility of long-term AEs. The human-to-human transfer of feces may be associated with long-term health risks to the recipient because the gut microbiota is composed of many components that have not been characterized and can change over time in ways that cannot be currently predicted. It is imperative to determine if FMT leads to unintended development of serious conditions due to the transfer of gut microbiota. In addition to infections, the possibility that gut microbiota associated with a disease phenotype (e.g., obesity, diabetes, cardiovascular disease) will be transplanted and result in chronic disease in recipients must be assessed. A prospective registry in a large sample of patients with long-term follow-up is the only practical method to achieve this aim at present.

2.2.2 To characterize effectiveness of FMT and other gut related microbiota products

Current information on the efficacy of FMT in treating clinical disease is restricted to case reports, case series, and one randomized trial in recurrent CDI. Furthermore, only short-term follow-up is generally provided in these reports. Determining the short-term and long-term effectiveness in real-world practice is crucial and assessing variations in efficacy outcomes related to methodology will enable standardization and optimization of FMT practice.

2.2.3 To gather information on practice in North America

FMT and future methods of providing gut-related microbiota for treatment of disease are in their infancy. Currently there is a lack of standardization in all aspects of FMT, and given a lack of current regulatory requirements for reporting, the methodology being employed (e.g., screening, preparation, delivery, indications, follow-up) is unclear. Obtaining information on current FMT methods in North America is an important first step in characterizing FMT practice with the future goal of standardizing and optimizing FMT.

2.2.4 To promote scientific investigation

A large FMT registry will provide an unprecedented and rich resource for investigators to advance the science of the gut microbiome in health and disease. The registry database will be available to investigators, with study proposals submitted for review by a Data Access and Publications Committee. Furthermore, this registry data will link to a biobank of fecal samples from the donor (one time) as well as recipient (before and after FMT). Together with the clinical metadata collected within the registry, information from analysis of specimens in the biobank will enhance short- and long-term safety surveillance as well as be a rich source of data to investigate modulation of the human gut microbiome.

2.2.5 To aid practitioners and sponsors in satisfying regulatory requirements

The FDA is currently determining the appropriate regulatory requirements for physicians performing FMT, exercising enforcement discretion regarding an IND requirements for use of FMT in treatment of CDI unresponsive to standard therapies. Participation in the FMT Registry provides an excellent method of oversight, helping to prevent marked departures in methodology from recommended practices, improve safety for patients, and gather data for quality improvement and future regulatory requirements. In addition, gut-related-microbiota products, from processed stool to defined microbiota consortia, require submission for regulatory approval. The Registry may function as an important vehicle for sponsors of gut-related microbiota products to satisfy pre-approval and post-approval assessment of product safety and efficacy.

3 STUDY DESIGN

3.1 Overview Study Design Summery

This registry will prospectively enroll 4,000 patients who undergo FMT at 75 sites throughout North America. Information on FMT methodology employed (e.g., screening of donor and recipient, preparation, FMT delivery) will be collected from each site. The indication for FMT as well as baseline information on recipient will also be collected. Following FMT, patients will be followed at regular intervals up to 10 years post FMT. This will include follow-up information from the patient's healthcare provider at 1 month, 6 months, 1 year, and 2 years after FMT as well as direct communication with patients at least annually up to 10 years after FMT. Follow-up information collected will be designed to assess potential short-term and long-term safety and effectiveness.

Anticipating changes in therapy from current FMT to use of other gut-related microbiota products in coming years, the Registry will be constructed with the flexibility to collect methodological and follow-up clinical information for all forms of gut-related-microbiota products and for a variety of indications besides CDI and IBD.

3.2 Site Selection

Sites currently performing FMTs will be allowed to participate in the FMT registry. Sites may utilize any method of FMT treatment or may provide other gut-related microbiota products.

Sites selected to participate in the registry must demonstrate that all study staff have completed human subjects protection and HIPAA training prior to enrollment. Study staff must pass training on informed consent procedures, the electronic case report form (eCRF) system for data recording, and reporting procedure for unexpected events. Sites must demonstrate proper data protection procedures prior to participant enrollment. All site Principal Investigators must sign an Investigators Agreement and confirm IRB approval prior to site activity starting.

Sites will be chosen based on the following criteria: 1) FMT volume; 2) geographic location; 3) ability and willingness to comply with the requirements of registry participation; 4) have an IRB-approved protocol. In the initial phase, we will include the centers of the investigators on this proposal (n=5) and 20 centers from our listserv of 70 centers representing thought leaders in FMT with an interest in clinical investigation. To enhance representation of a geographically diverse population in the registry, centers will be related to their location in population-based regions. Using the projected number of FMTs at each center, we will enroll the number of centers in each region required to achieve a proportion of FMTs in the registry from a region to approximately mirror the proportion of the U.S. population in that region.

4 STUDY ENROLLMENT

4.1 Subject Inclusion Criteria

Participants will be eligible for participation regardless of age, race, ethnicity, or gender. Pediatric patients may participate if consent is given by a guardian.

4.1.1 Recipient Inclusion Criteria

- Ability to give informed consent
- Receiving FMT or other gut-related microbiota product within 90 days after providing consent
- Access to internet and/or telephone

4.1.1.1 Donor Inclusion

- Ability to give informed consent
- Providing stool sample for FMT

4.2 Subject Exclusion Criteria

- Incarceration

4.3 Strategies for Recruitment and Retention

Participants who are being seen in clinical practice as an FMT recipient (or FMT donor) or as a recipient of other gut-related-microbiota products will be approached in a private room to receive information about the registry protocol, the option to participate in a biorepository sub-study, review the informed consent documents, and to ask questions and review the risks and benefits of participation. Participants will have as much time as they would like to review the documents and ask questions regarding participation.

4.4 Subject Withdrawal

4.4.1 Early Withdrawal of Participants

Participants may end their participation at any time by notifying the study staff of their desire to halt participation. This may be done in writing or by secure internet connection. Registry mailing address and electronic address will be provided to all participants.

4.4.2 Data Collection and Follow-up of Withdrawn Participants

When participants notify study staff that they no longer wish to participate, study staff will request final-visit information from the participant and their healthcare provider. If the participant informs the study staff that they wish to withdraw consent, no further data will be sought from them or their healthcare provider. Data that was previously collected when the patient was actively enrolled will be retained in the registry.

4.5 Costs and Payments

This is not a clinical treatment study and all costs associated with the care and treatment of patient receiving FMT and follow-up will be paid by the patient or their insurance provider. No costs will be incurred by participants related to participation in the Registry. Continued patient participation will be encouraged with a $10 gift card for providing health information each year beginning 1 year post-FMT.

5 STUDY PROCEDURES AND EVALUATIONS

The only study procedure will be data collection regarding methodology of FMT, characteristics and health outcomes of recipients of FMT or other gut-related-microbiota products, and baseline characteristics of donors of stool for FMT.

5.1 Data Elements

Data elements that may be collected for the FMT registry are shown in Supplements 1-6. In order to make the data elements as broad and inclusive as possible, the FMT Registry Steering Committee developed the data elements based on current guidelines and published recommendations[48-50], their own treatment protocols/experience, and feedback from 15 additional large FMT practice sites. *Supplement 1* details the data elements related to FMT technique including donor and recipient screening. For sites that employ a donor questionnaire, *Supplement 2* provides potential questions used on a questionnaire, based on those used for blood transfusion. *Supplement 3* shows the data elements for baseline characteristics of donors and recipients and for FMT treatment indications, while *Supplement 4* provides effectiveness outcomes data elements. Finally, *Supplements 5* and *6* detail data elements for short-term and long-term safety outcomes. Patients will be followed at regular intervals for up to 10 years after FMT for pre-defined and spontaneously reported adverse events and for pre-defined outcomes of effectiveness. Investigators will enter follow-up data at 1 month, 6 months, 1 year and 2 years post-FMT, and patients will then provide data annually up to 10 years.

5.2 Study Specific Biospecimens and Biorepository Sub-Study

No biospecimens will be collected as part of this registry. However, participants have the option to enroll in a Biorepository Sub-Study and provide stool specimens to be stored in a biorepository that will be linked to their registry data. The biorepository will be maintained by the American Gut Project at University of California at San Diego. Currently, we plan to link data from at least 1,000 FMT procedures for participants in the registry to this biorepository, with 3 stool specimens for each FMT: a donor stool specimen and 2 recipient stool specimens (before and after FMT). The Biorepository Sub-Study protocol is described in *Appendix A*.

6 ASSESSMENT OF SAFETY

Details about participant risk and potential benefits are detailed in informed consent. AEs experienced by participants involved in this registry will be reported to the site's IRB in accordance with their procedures.

6.1 Adverse Events

Based on numerous case reports and small clinical studies in the literature, it appears that FMT for refractory CDI is generally well-tolerated and safe, although occasional adverse events (e.g., febrile

episodes) have been reported[39,50]. Importantly, a prospective systematic evaluation of both immediate and short-term predefined adverse outcomes in a large number of patients undergoing FMT is currently lacking. In the absence of any consensus guideline on practice standards for FMT in the U.S. and the lack of regulatory oversight for the treatment of refractory CDI, the committee has learned through polling of sites performing FMT that there is a wide variation in the practice of FMT. This variance in practice also raises potential concerns about risks for both short-term and long-term risks. As discussed in section 5.1, to broadly capture adverse outcomes in recipients of FMT that may be indicative of a safety concern, we have developed two data entry fields: 1) Short-Term Adverse Outcomes (within 30 days)—Supplement 5, and 2) Long-term Adverse Outcomes (up to 2 years reported by the physician and 10 years reported by the patient)—Supplement 6. Adverse event information will be provided by the FMT provider site at four time points post-FMT: 1 month, 6 months, 1 year, and 2 years. In addition, patients will be contacted directly by email and text at least annually for up to 10 years to provide follow-up information via a dedicated portal maintained by the Icahn School of Medicine at Mt. Sinai.

6.2 Classification of Events

6.2.1 Relatedness

The site Investigator will assess the relationship of SAEs to FMT, as related or not related, based on clinical judgment and using all available information, and may include consideration of the following factors:

- Possible alternative causes of the SAE, including the disease under treatment, pre-existing conditions, concomitant use of other drugs, and presence of environmental or genetic factors.
- The temporal association between FMT exposure and onset of the SAE.
- Whether the manifestations of the SAE are consistent with known actions or theoretical toxicity of FMT.

The causal relationship between FMT and the SAE will be assessed using one of the following categories.

1. Not Related:
   - Temporal relationship is lacking (e.g., the event occurred before FMT); or
   - Other causative factors explain the event (e.g. pre-existing condition, other concomitant treatment);
2. Possibly Related:
   - Positive temporal relationship (e.g., the event occurred within a reasonable time frame following FMT); and
   - The SAE is possibly explained by FMT and/or, and there is a lack of other causal factors.
3. Related:
   - Positive temporal relationship (e.g., the event occurred within a reasonable time frame following FMT); and
   - The SAE is more likely explained by FMT than by other causes.

6.2.2 Expectedness

Related or possibly related SAEs will be assessed as to whether they were expected or unexpected based on current knowledge regarding the effects of FMT. Events known to be associated with FMT, CDI, or IBD include the following:

- Diarrhea
- Constipation
- Abdominal pain
- Fever
- Sedation complication
- Bleeding
- Perforation
- Bacterial infection
- Viral infection
- Fungal infection
- Parasitic infection

Events that are determined to be expected will be reported through the annual event summary report to the Sponsor and OSMB.

6.3 Serious Adverse Events (SAE)

The only type of adverse event that may occur related to participation in the FMT registry is breach of privacy/confidentiality.

Clinical SAEs that are recorded in the registry will have the standard definition, which includes the following:

- Death
- Life-threatening (patient was at substantial risk of dying)
- Hospitalization (initial or prolonged)
- Disability or permanent damage
- Congenital anomaly/birth defect
- Other important event (may jeopardize patient and may require to prevent one of other outcomes)

6.4 Reporting Procedures

All spontaneous and pre-specified AEs reported by participants or healthcare providers will be recorded in the Registry database. Predefined short-term and long-term AEs are presented in *Supplements 5* and *6*. Analyses of all AEs (including spontaneous and pre-defined AEs and SAEs) will be provided to the Registry Steering Committee and the OSMB at least twice yearly for their review. Summaries of AEs (including spontaneous and pre-defined AEs and SAEs) will be submitted to IRB and NIH during the annual review of the registry.

Breach of privacy and suspected unexpected SAEs will be reported to the Registry Steering Committee Chair and Co-Chair and the OSMB within 5 days of identification of the event. These events will also be reported to the local site IRB per local reporting criteria.

All participants are given a toll-free number to contact the Investigators directly if they have any safety issues or concerns.

7 Registry Oversight

7.1 Steering Committee

The FMT Registry Steering Committee will oversee the FMT Registry. This Steering Committee will report to the AGA Center for Microbiome Research and Education Scientific Advisory Board, which reports to the AGA Governing Board. The Steering Committee will be comprised of the individuals listed on the FMT Registry Protocol as Principal Investigators (PIs) and Co-Investigators. Two PIs, Drs. Laine and Kelly, will serve as the Chair and Co-Chair of the Steering Committee and will be responsible for the daily management of the registry and its associated activities (e.g., site selection, recruitment, IRB requirements, data management). The contact PI, Dr. Wu, as Chair of the AGA Center for Microbiome Research and Education Scientific Advisory Board will serve on the steering committee in an *ex officio* capacity. The other members of the steering committee, comprised of the co-investigators, include representatives of key organizations that have helped to develop the registry and have an interest in its execution (IDSA, NASPGHAN, CCFA) as well as experts in clinical epidemiology and information technology.

7.2 Observational Study Monitoring Board

An independent OSMB will be established to monitor the registry performance and data in order to protect the safety and privacy of participants and to ensure the integrity and credibility of the registry. OSMB members will have no involvement in the FMT registry and no vested scientific or financial interest in the registry. OSMB members will include a data scientist with experience in epidemiology and registries, and at least two other members with expertise in clinical investigation, FMT, and/or the gut microbiome. It is anticipated that the OSMB will meet at least twice yearly and will review information on the registry conduct and results, including recruitment and retention, deviations from registry protocol, breaches of confidentiality, characteristics of participants, and safety and effectiveness outcomes. The OSMB will produce minutes for each meeting and provide any comments or recommendations regarding registry conduct or participant safety/privacy to the FMT Registry Steering Committee.

7.3 Data Access and Publication Committee

A Data Access and Publication Committee will be established to review requests from investigators to access and perform analyses of registry data for purposes of scientific presentation and publication. This committee will ensure that the request is appropriate and within the scope of the

registry. It is anticipated that all appropriate requests for data will be granted. Once approved, data requests will be forwarded to ACI Clinical for processing. The investigators will be asked to adhere to the data sharing agreement, which includes credit to FMT Registry and the R24 as the source of the data on subsequent publications, abstracts, and other presentations.

7.4 Funding Sources and Conflicts of Interest

The FMT Registry is funded with a grant provided by the National Institute of Allergy and Infectious Diseases at the National Institutes of Health.

All investigators are required to conduct themselves at all times in accordance with Good Clinical Practices. Investigators are expected to commit themselves to ethical and professional conduct of clinical research. Commitment to preserving the physician's, medical community, and public's trust is ensured by conducting research at the highest scientific and ethical standards. Disclosure of any potential conflict of interest strengthens this trust. The COI review process will be:

- An AGA COI disclosure form and confidentiality statement is to be completed by all Investigators, including Steering Committee, OSMB members and Data Access and Publications Committee members, at the start of the project and updated at least annually thereafter, for 1 year post appointment/tenure.
- The content of the disclosure is the responsibility of each Investigator. The Investigator is expected to complete the statement, sign and submit it in writing to the AGA prior to engaging in research. It will then be forwarded to the AGA Institute Ethics Committee, who will report the existence of a conflict, if present, to the subcommittee, committee or task force chair as appropriate.
- The Ethics Committee is authorized to disqualify a candidate for Registry committees or the OSMB who fails to make a disclosure or who does not agree to resolve the conflict prior to assumption of their position.
- The disclosure statement is required to be completed even if no conflict exists.
- Disclosure and confidentiality statements will be held in a confidential file maintained by the national office. Access to the file will be available to appropriate AGA staff, the AGA Institute Ethics Committee, and the AGA Institute Governing Board only.
- Members adversely affected by this policy may request the Ethics Committee review the issue and recommend to the Governing Board that application of the policy be waived for compelling reasons.
- Reporting financial interest to the AGA Institute does not replace the need to comply with federal COI requirements.

8 Statistical Plan

8.1 Sample Size Determination and Power

As noted in the AHRQ's Registry User's Guide[51], registries are used to provide precise estimates of outcomes in real-world practice and document that potential adverse events occur at less than a pre-specified incidence with a predefined level of confidence. Plans for the FMT registry include a sample size of approximately 4,000 patients, which will provide precise estimates of incidence rates for common and rare events. For example, if the incidence of an outcome after FMT in the Registry population is 5.0%, the 95% CI will be 4.4% to 5.7%, indicating a precise estimate of treatment effect. The planned sample size will also provide high confidence in ruling out rare adverse events. If an adverse event does not occur in the planned population of 4000 patients, we will have 95% confidence that the adverse event occurs at a rate of less than one in a thousand patients undergoing FMT.

The FMT registry also will support comparative effectiveness studies focusing on different methods of delivery of FMT (e.g., colonoscopy, enema, upper GI endoscopy, nasogastric or nasointestinal tube). Statistical power for comparative effectiveness studies will depend upon the incidence of the outcome and the distribution of use of the different methods of delivering FMT. For example, assuming an outcome that occurs in one out of 1,000 FMT procedures using one delivery method, there would be 90% power to detect a difference between an incidence of 0.001 and 0.008 assuming that 2,000 patients were exposed to each of the two delivery methods. For more common outcomes, the statistical power for specific relative risk estimate is greater. For example, with 2,000 patients in each group there would be 90% power to detect a difference between two approaches for which the incidence rates of events were 3% and 5% (i.e., RR=1.67).

8.2 Interim Monitoring and Early Stopping

The Registry will have no formal interim analysis or early stopping plan. Regular monitoring of the safety and effectiveness data will be performed by the Registry Steering Committee and OSMB. Regular review of analyses of safety and effectiveness will occur twice yearly. In addition, breaches of privacy or suspected unexpected SAEs will be reported to the Registry Steering Committee Chair and Co-Chair and the OSMB within 5 business days after the event is identified.

8.3 Statistical Methods

The registry will be designed in a manner that will facilitate statistical analyses for the purpose of signal detection, generation of descriptive data, and the conduct of comparative effectiveness studies. There will be several major advantages of the registry design as opposed to a system of spontaneous reporting. Most importantly, a prospective cohort of patients who undergo FMT with collection of predefined outcomes will allow accurate estimation of incidence rates. In contrast, systems that rely on spontaneous reporting have incomplete numerator data and lack denominator data. The ability to calculate incidence rates greatly facilitates both descriptive epidemiology and signal detection.

As noted above, registries are used to provide precise estimates of outcomes in real-world practice and document that potential adverse events occur at less than a pre-specified incidence with a predefined level of confidence. Thus, descriptive statistics with 95% confidence intervals will be determined for the safety and effectiveness outcomes to provide precise estimates of incidences. As mentioned above, if an adverse event does not occur in the planned population of 4,000 patients, we will have 95% confidence that the adverse event occurs at a rate of less than one in a thousand patients undergoing FMT.

To increase our ability to study unanticipated adverse events, we will include a retrospective control group of patients with recurrent CDI identified from insurance claims using Optum Insight Life Sciences, Inc data. Using these data, we can determine the incidence of relevant outcomes in a group of patients with recurrent CDI treated with antibiotics rather than FMT. The incidence of relevant outcomes in this group can be compared to the patients treated with FMT in the registry. To assure the feasibility of this approach, we have conducted a preliminary analysis of these data to identify the number of patients who will be included in the control cohort. Recurrent CDI was defined as having a physician-made diagnosis of CDI (ICD-9 008.45) treated with 3 separate courses of antibiotics with metronidazole, vancomycin, or fidaxomicin (at least one of which were vancomycin or fidaxomicin). The 3 antibiotic prescriptions had to be at least 10 days apart and the third course needed to be started within the 90 days following the CDI diagnosis. We identified 4,313 patients meeting this definition with mean follow-up of 1.70 years. The sample size should be sufficient to address questions on relatively rare outcomes. For example, at age 68 years (the median age in our control cohort), the probability of death in the next 12 months is 1.75% and the expected survival is 18.8 years (CDC lifetables). With an average follow-up time of 1.70 years, assuming equal number of subjects undergoing FMT and equal follow-up time, we would have 90% power to detect a hazard ratio of 0.77 for a difference in survival rates between FMT and antibiotic treated patients.

As mentioned above, the FMT registry also will support comparative effectiveness studies focusing on different methods of delivery of FMT. Comparative effectiveness studies rely on the ability to adequately account for differences between the treatment groups. The FMT registry will facilitate this by collecting robust data on the indications for therapy and other covariates that describe the recipients and the methods of delivery. Such data will support standard statistical methods including logistic, Cox, and other regression methods, and the development of propensity scores and risk scores for risk adjustment.

9 QUALITY CONTROL AND QUALITY ASSURANCE

9.1 Confidentiality and Security

The registry will collect only clinical data and test results. There is a theoretical risk of breach of confidentiality or a data security loss although exhaustive efforts will be made to minimize this inherent risk. All sites must demonstrate proper physical and electronic security measures in order to participate in the registry.

To protect the confidentiality of the participants it is required:

1. Separate all direct participant identifiers (i.e., names, social security numbers, medical record numbers, etc.) from outcome information stored in the registry
2. Securing in a separate location and limiting access to information linking codes assigned to the registry information with direct participant identifiers
3. Limiting access to information contained within the registry to investigators and approved study staff

All data from healthcare providers will be entered into the registry through the eCRF system maintained by Viedoc™. The electronic data capture system is 21 CFR Part 11 compliant. All computers will be used to collect and send data during implementation of the study or to receive or store data at the central location will be password protected. A password will be required to open Windows® and a second, different password will be required to open the electronic data capture system, Viedoc™. This closed system requires a unique identification for each user.

Electronic forms will be stored on a secure dedicated server with appropriate firewalls. The system will use 128- bit encryption (SSL certificate). This technology is the same as that used for online e-commerce applications to protect consumer information such as name, address, and credit card details. The system has a secure login along with audit control mechanisms to meet HIPAA standards. Servers are scanned for viruses and systems are in place to detect attempts at unauthorized entry. The data base server is backed up daily internally. All transactions to the database are stored in archive logs as re-do data and are accessible to enable quick recovery of all data should the need arise. Backup files are written nightly to back up servers. Weekly, a monthly backup copy is stored off-site in perpetuity.

For follow-up beyond 2 years, the ePRO system allows the registry staff to automatically contact the patient for follow-up information. For example, patients can receive an automatic text message or email that opens to a follow-up electronic questionnaire for long-term follow-up. The link to the ePRO also will be embedded in the patient education app that will include content (videos and written information) approved by the steering committee related to FMT indications, pre-procedure checklist, potential adverse events, and post-procedure follow-up. The app will be maintained at Sinai AppLab, Icahn School of Medicine at Mount Sinai and will be made available to all FMT patients enrolled in the registry.

9.2 Data Access

The AGA will create a dedicated landing page for the FMT registry on its Web site, through which data access requests can be made. Interested investigators will be asked to submit a brief application including their research question(s) and requested criteria and variables. The Data Access and Publication Committee will review these requests to solely ensure that the request is appropriate and within the scope of the registry. It is anticipated that all appropriate requests for data will be granted. Once approved, data requests will be forwarded to ACI Clinical for processing. The investigators will be asked to adhere to the data sharing agreement, which includes credit to FMT Registry and the R24 as the source of the data on subsequent publications, abstracts, and other presentations. We will transmit (PHI) de-identified and aggregate data to approved applicants via

the web portal, along with appropriate documentation that describes the study methods and procedures used to collect the data, details about the codes, definitions of variables and metadata, variable field locations and other information relevant to the data use. Payment solely to cover the costs of data retrieval will be required.

Data from the eDC deployed FMT registry database will receive secure data transfers from the Mt. Sinai ePRO application per a data transfer agreement with the data processing center and Mt. Sinai to assure no PHI is transferred. Upon termination of the grant, all data and in an agreed format (SAS, ASCII) will be electronically transferred by ACI Clinical to AGA via the secure website.

9.3 Training

Each site will receive training on the data collection procedures and entry of data into the electronic registry. Each site will need to provide documentation of receiving and passing a training course in human subject's protections.

9.4 Records Retention

In accordance with federal law all records will be kept for a minimum of three years after the study has closed.

10 Ethics/Protection of Human Subjects

10.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6; 62 Federal Regulations 25691 (1997).

10.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials and all participant materials will be submitted for IRB review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require IRB review and approval before the changes are implemented in the study.

10.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to participants and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the participant. Consent forms will be IRB-approved, and the participant is required to read and review the

document or have the document read to him or her. The investigator or designee will explain the research study to the participant and answer any questions that may arise. The participant will sign the informed consent document prior to any study-related assessments or procedures. Participants will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

Minors may participate in the FMT registry. The minors and their legal guardians will undergo the consent process. Written consent must be provided by at least one guardian and, to the best of their ability, assent will be obtained from the minor.

The consent process will be documented in the clinical or research record.

10.4 Inclusion of Women, Minorities, and Children (Special Populations)

Due to the complexity of state and federal requirements governing the participation of prisoners in research, prisoner-patients shall not be approached for participation in the research registry. All other participants regardless of age, gender, race, or ethnicity will be approached to participate in this observational study. Due to the nature of observational research, AGA will monitor the progress of the study for gender and minority inclusion.

Due to the research activities, data collection, being no greater than minimum risk, children will be asked to participate. Consent for participation will be given by the child and at least one legal guardian. If the child reaches legal age, the participant will be consented again at the next patient interaction. There are only limited case reports and small studies of children who have received FMT for recurrent CDI with and without underlying IBD.[40,41] To date FMT appears both safe and effective in children with recurrent or refractory CDI. Although age-specific rates and patterns of disease associated with CDI in children is poorly characterized, there has been a marked increase in CDI-associated hospitalizations from 7.24 per 10,000 in 1997, to 12.8 in 2006[53]. Another large database analysis revealed a median age of diagnosis was 4 years and found that the 7% had one or more underlying complex chronic condition. Even with advances in medical care over the past several decades, the mortality rate in children with CDI remains stable at 4%.[54] The experience of FMT as a primary treatment for IBD is also quite limited with mixed results.[55,56] Despite limited data, FMT remains a potential therapeutic option for children with FMT and IBD. Sites that enroll minors will provide appropriate informed consent and assent per IRB protocols.

11 PUBLICATION POLICY

The Data Access and Publications Committee will establish requirements for publication of abstracts and research papers derived from FMT Registry data (e.g., acknowledgment of the FMT Registry and R24 support).

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Supplement 1. Donor/Recipient Screening and FMT Technique Data Elements (characteristics to be collected once at initiation of site)

A. Transplant material

- Donor Stool (full spectrum)
    - Fresh
        - Time from donation to delivery
    - Frozen
        - Time from donation to freezing
    - Source
        - Directed donor (known to recipient)
            - Related
                - Household versus non-household
            - Unrelated
                - Household versus non-household
        - Volunteer donor
    - Age-matched : yes, no, or unknown
    - Gender-matched: yes, no, or unknown
- Modified human stool (filtered/processed and/or enhanced)
    - OpenBiome
        - Batch/Lot number
    - Other stool bank
    - Specify bank
    - Batch/Lot number
- "Commercial" stool product
    - e.g. RBX2660, SER-109
        - Batch/Lot number
    - Other
- Cultured bacterial product derived from stool
    - e.g. RePOOPulate
- Microbial consortia not derived from stool

B. Donor Screening *(check all that apply)*

- Donor Selection
    - Donor screening Questionnaire (see Supplement 2)
        - AABB DHQ or AABB DHQ modified/derived
        - Other
    - Donor interview
        - Physician
        - Nurse Practitioner
        - Physician Assistant
        - Nurse
        - Research coordinator or assistant
    - Donor physical examination
        - Physician
        - Nurse
        - Research coordinator or assistant
        - Research Nurse
- Laboratory

- No laboratory screening done
- Screening laboratories unknown (FMT product)
- Stool
  - *Clostridium difficile* toxin by PCR
  - *C. difficile* toxin EIA
  - *C. difficile* culture (anaerobic culture for toxigenic *C. difficile*)
  - Direct stool cytotoxin with tissue culture
  - *C. difficile* by glutamate dehydrogenase (GDH) testing
  - Routine bacterial culture for enteric pathogens (E coli, Salmonella, Shigella, Yersinia, Campylobacter)
  - Culture for *Listeria monocytogenes*
  - Culture *for Vibrio* (*parahaemolyticus and cholerae*)
  - Fecal *Giardia* antigen or DFA
  - Fecal *Cryptosporidium* antigen or DFA
  - Acid-fast stain for *Cyclospora* and *Isospora*
  - Trichrome Ova and parasites exam (O&P)
  - Rotavirus via EIA
  - Norovirus PCR
  - VRE culture
  - MRSA
  - New Delhi-Metallo-beta-lactamase-1 (NDM-1)
  - Carbapenem-resistant Enterobacteriaceae
  - *Helicobacter pylori* fecal antigen
  - Adenovirus EIA
  - Fecal calprotectin
  - Fecal lactoferrin
  - Luminex xTAG® Gastrointestinal Pathogen Panel (xTAG GPP)
  - BioCode GI panel
  - RIDA®GENE Bacterial Stool Panel
  - FilmArray® GI Panel
  - Other____
- Serology
  - Norovirus
  - *Helicobacter pylori* serology (IgG, IgM or IgA)
  - JC Virus Ab
  - *Strongyloides stercoralis* Ab *(IgG)*
  - *Schistosoma* Ab *(IgG)*
  - *Entamoeba histolytica* Ab *(IgG)*
  - HIV, type 1 and 2 (Ab)
  - HIV, type 1 & 2 (qualitative PCR)
  - HIV p24 Ag test
  - HAV total Ab
  - HAV IgM
  - HBsAg
  - HBsAb
  - anti-HBc (IgG and IgM)
  - HCV Ab
  - RPR
  - Syphilis (TP) Ab test
  - FTA-ABS

- EBV Ab panel
- EBV PCR
- CMV IgG
- CMV PCR
- HSV 1 & 2 IgG
- Human T cell lymphoma virus 1 & 2
- Trypanosoma antibody
- Other____

C. Recipient Screening

- Site specific exclusion criteria (check if site protocol excludes patients with any of the following)
  - Age <__
  - Age >__
  - BMI
  - Medical conditions
    - List conditions
  - Pregnancy/lactation
  - Recent or ongoing antibiotic use
  - Allergy
  - Malignancy
  - Immunosuppression
  - Other___
- Laboratory (baseline screening of recipient)-check any which apply
  - HIV 1 & 2
  - Hepatitis A
  - Hepatitis B surface Ag
  - Hepatitis B surface Ab
  - Hepatitis B core Ab
  - Hepatitis C Ab
  - RPR
  - Other

D. Transplant material preparation

- Location of material preparation
  - Laboratory (research)
  - Laboratory (clinical)
  - Endoscopy unit
  - Pharmacy
  - Clinic/office
  - Other Patient care area (hospital room, infusion center)
- Approximate weight (grams) or volume (mL) of stool used in preparation
- Diluents
  - None/NA
  - Water
    - Volume___
  - Saline
    - Volume___
  - Glycerol
    - Percent___
  - Other

- Processing
  - Blender
    - Household
    - Commercial
    - Laboratory mixer
  - Manual mixing
- Filtration
  - None
  - Coffee filter
  - Medical gauze
  - Metal/disposable sieve
  - Laboratory microfilter
- Material Storage
  - Stool
    - Fresh (used within ____hours of passage)
    - Frozen stool (used within ____months)
      - -20°C
      - ≤-70°C
  - Other material (specify Openbiome, SER-109, RBX2660, etc.)
    - Room temperature
    - Refrigerated
    - Frozen
- Amount of material delivered
  - Volume (ml)
  - Number of capsules
  - Contents/dose (CFU) if non-stool product

E. Method of delivery

- Oral ingestion: capsule
  - Fresh capsule
  - Frozen capsule
  - Lyophilized capsule
  - Number of capsules used
- Oral ingestion: liquid
- Nasogastric tube
- Naso-intestinal tube
- Upper endoscopy
- Sigmoidoscopy
- Colonoscopy
- Enema

F. Delivery schedule

- Single dose delivery/ingestion
- Multiple dose
  - Number of doses____
  - Dosing Schedule
    - Daily
    - Weekly
    - Monthly
- Maintenance (chronic therapy)
  - Schedule

Supplement 2. FMT Donor Questionnaire Data Elements

Are you:

1. Feeling healthy and well today? Yes No
2. Currently taking any medication for infection? Yes No

Have you:

3. Taken any antibiotics within the past 6 months? Yes No
4. Had any fevers, vomiting, diarrhea or other symptoms of infection within the past 4 weeks? Yes No

In the past 8 weeks have you

5. Had any vaccinations or other shots? Yes No
6. Had contact with someone who has had the Smallpox vaccine? Yes No

In the past 12 months have you:

7. Had a blood transfusion? Yes No
8. Had a transplant (organ, tissue, bone marrow, dura mater- brain covering)? Yes No
9. Had a skin or bone graft? Yes No
10. Come into contact with someone else's blood? Yes No
11. Had an accidental needle stick? Yes No
12. Had sexual contact with anyone who has HIV/AIDS? Yes No
13. Had sexual contact with a prostitute or anyone else who takes money or drugs as payment for sex? Yes No
14. Had sexual contact with anyone who has ever used needles to take drugs or steroids, or anything NOT prescribed by their doctor? Yes No
15. Had sexual contact with anyone who has hemophilia or has used clotting factor concentrates? Yes No
16. *Female donors*: Had sexual contact with a male who has ever had sexual contact with another male (male donors circle "I am male)? Yes No I am male
17. Had sexual contact with a person who has hepatitis? Yes No
18. Lived with a person who has hepatitis? Yes No
19. Had a tattoo? Yes No
20. Had an ear or body piercing? Yes No
21. Been treated for syphilis or gonorrhea? Yes No
22. Been in lockup, jail or prison for >72 hours? Yes No

In the past three years have you

23. Been outside the United States or Canada? Yes No

List location/time spent:_____

From 1980 through 1996,

24. Did you spend time that adds up to three (3) months or more in the United Kingdom? Yes No

25. Were you a member of the U.S. military, a civilian military employee or a dependent member of the U.S. military? Yes No

<u>From 1980 to the present</u>,

26. Did you spend time that adds up to five (5) or more years in Europe? Yes No

27.. Receive a blood transfusion in the United Kingdom or France? Yes No

<u>From 1977 to the present, have you</u>

28. Received money, drugs, or other payment for sex? Yes No

29. *Male donors*: had sexual contact with another male, even once (female donors circle "I am female")? Yes No

I am female

<u>Have you EVER</u>

30. tested positive for HIV/AIDS virus? Yes No

31. used needles to take drugs or steroids or anything NOT prescribed by your doctor? Yes No

32. used clotting factor concentrates? Yes No

33. had viral hepatitis? Yes No

34. had any type of cancer (including leukemia)? Yes No

35. had sexual contact with anyone who was born or lived in Africa? Yes No

36. been in Africa? Yes No

37. had sex for drugs or money? Yes No

38. had any of the following gastrointestinal diseasesor problems?

a. Irritable bowel syndrome? Yes No
b. Crohn's disease? Yes No
c. Ulcerative Colitis? Yes No
d. Chronic diarrhea? Yes No
e. Gastrointestinal cancers? Yes No
f. Celiac disease? Yes No

39. received growth hormone made from human Pituitary glands? Yes No

40. Have any of your relatives had Creutzfeldt-Jakob disease? Yes No

<u>General Medical History</u>

41. Do you have any autoimmune diseases (for example: Rheumatoid arthritis, Multiple Sclerosis, Lupus) Yes No

If yes, please list:_____

42. Do you have any neurologic diseases (for example: Parkinson's, Autism, ALS)? Yes No

If yes, please list: _____

Supplement 3. FMT Treatment Indications and Baseline Donor/Recipient Characteristics

A. FMT Indication

- *C. difficile*
  - Refractory
  - Recurrent
  - Severe
- Inflammatory Bowel Disease
  - Ulcerative colitis
  - Crohn's disease
  - IBD-U
  - Pouchitis
- Irritable bowel syndrome
  - IBS-D
  - IBS-C
  - IBS-M
  - Other functional disorder
- Chronic constipation
- Obesity
- Diabetes
- Metabolic syndrome
- NAFLD/NASH
- Neurologic or Neurodevelopmental disorder
- Other

B. Baseline Characteristics

- Donor (if known)
  - Age
  - Race/Ethnicity
  - Gender
  - Height
  - Weight
  - Donor medical conditions (check any which apply)
    - No significant medical or surgical history
    - BMI ≥30
    - Hypertension
    - Hyperlipidemia
    - Diabetes type II
    - Depression/anxiety
    - CAD
    - Cerebrovascular disease
    - Asthma
    - Other___
- Recipient characteristics (baseline)
  - Age
  - Race/Ethnicity
  - Gender

    - Height
    - Weight
    - Medical co-morbidities
        - Metabolic (hypertension, diabetes II, hyperlipidemia)
        - Autoimmune (hypothyroid, RA, SLE)
        - Asthma/Allergic-Atopic conditions
        - Cardiovascular
        - Neurological conditions (MS, Parkinson, Alzheimer's, autism)
        - Psychological (depression, anxiety, eating disorder)
        - IBS
        - IBD
        - Immunocompromised from medical condition or medication
        - Other
    - Labs (glucose, cholesterol, HDL, LDL, triglycerides, ALT, alkaline phosphatase, bilirubin, albumin, BUN, creatinine)
- CDI baseline characteristics
    - Disease characteristics (pre-FMT)
        - Mild illness (recurrent)
        - Moderate (more severe but uncomplicated disease)
        - Severe
        - Severe complicated
    - Duration of *C. difficile* infection (weeks between initial diagnosis and FMT)
    - Number of CDI episodes
    - C. difficile strain
        - Nap-1
        - Non Nap-A
        - Unknown
    - Other treatments courses received (and number of courses of each, if known) for CDI prior to FMT
        - Metronidazole
        - Vancomycyin
        - Vancomycin taper/pulse dose
        - Fidaxomicin
        - Nitazoxanide
        - Rifaximin
        - IVIG
        - *Saccharomyces. boulardii*
        - *Lactobacillus GG*
        - Other probiotic
        - Other___
    - Immediate Pre-FMT treatment(s)
        - Antisecretory therapy?
            - No
            - Yes
                - H2 blocker
                - Proton Pump inhibotor
        - Probiotics?
            - No
            - Yes

            - list
        - Antibiotics?
            - No
            - Yes
                - Metronidazole
                - Vancomycin
                - Other
        - If yes, were antibiotics stopped? (yes/no)
        - Number of days off antibiotics prior to FMT
- IBD Baseline characteristics
    - Type of IBD
        - CD
        - UC
        - IBD-U
        - Pouchitis
    - Disease location/extent
        - Montreal classification for adults >18 y/o
        - Paris classification for children <18 y/o
    - IBD treatment pre-FMT
        - Antibiotics
            - IV
            - Oral
        - Probiotics
        - Diet
            - Type of diet
        - Mesalamine
            - Oral
            - Rectal
        - Thiopurines
        - Methotrexate
        - Steroids
            - Oral
            - Rectal
            - IV
        - Biologics
            - Anti-TNF
            - Anti-Integrin
            - Ustekinumab
            - Other
        - Cyclosporin or tacrolimus
        - Other
    - IBD history
        - Number of years since initial diagnosis
        - Bowel surgery (ever)
        - IBD-related hospitalizations (within 12 months prior to FMT)
    - Severity of IBD at time of FMT (quiescent, mild, moderate, severe)
    - Disease activity scores (if available)

Supplement 4. FMT Effectiveness Outcomes

A. Clostridium Difficile Infection

- Post-FMT treatment(s)
  - Probiotics?
    - No
    - Yes
      - list
  - Antibiotics?
    - No
    - Yes
      - Metronidazole
      - Vancomycin
      - Fidaxomicin
      - Other
  - Days post-FMT antibiotic stopped
- Cure (Resolution of diarrhea without need for further anti-CDI therapy)
  - Cured with single FMT
  - Cured with >1 FMT
- Failure/Recurrence
  - How recurrence was diagnosed
    - Symptoms only
    - Stool testing only
    - Symptoms and +stool testing (EIA)
    - Symptoms and + stool testing (PCR)
  - Time of recurrence (weeks post-FMT)
- Antibiotics received post-FMT for treatment of other infections
  - Agent
  - Indication
  - Months post-FMT

B. Inflammatory Bowel Disease

  - IBD severity at time point post-FMT
    - Quiescent, mild, moderate, severe
    - Disease activity scores (if available)
  - IBD related hospitalizations post-FMT
  - IBD surgeries post-FMT
    - Number of days or weeks post-FMT
  - IBD-related medications post-FMT
    - Antibiotics
      - IV
      - Oral
    - Probiotics
    - Diet
      - Type of diet
    - Mesalamine
      - Oral
      - Rectal
    - Thiopurines
    - Methotrexate

        - Steroids
            - Oral
            - Rectal
            - IV
        - Biologics
            - Anti-TNF
            - Anti-Integrin
            - Other
        - Cyclosporin or tacrolimus
        - Other
    - Other complications
        - Reclassification of disease type
        - Change in disease distribution
        - Abscess
        - Fistula
        - Perforation

Supplement 5. FMT Short-term Adverse Outcomes (within 30 days)

- *Procedure-related*
  - Sedation complication
  - Bleeding
  - Perforation
  - Other

- *Symptoms post-FMT (within 30 days)*
  - Diarrhea
  - Constipation
  - Nausea and/or vomiting
  - Bloating
  - Abdominal pain
  - Fever
  - Headache
  - Rash
  - Weight gain or loss
  - Other___

- *Surgeries or other Procedures*
  - Describe
- *Documented Infection (any)*
  - Specify site/organism
  - FMT related (related, possibly related, unrelated)

- *Hospitalization*
  - Reason for hospitalization
  - FMT related (related, possibly related, unrelated)

- *Life-threatening experience*
  - Describe/diagnosis
  - FMT related (related, possibly related, unrelated)

- *Death*
  - Cause of death
  - FMT related (related, possibly related, unrelated)
  - Site of death
    - Hospital
    - Home
    - Convalescent or skilled nursing facility

Supplement 6. FMT Long-term Adverse Outcomes (up to 2 years by physician report and 10 years by patient report)

- *Characteristics*
  - Height
  - Weight
- *Serious Infection (HIV, viral hepatitis, prion, etc)*
- *Use of new drugs*
  - Describe
- *Surgeries or other Procedures*
  - Describe
- *Diagnosis of any new condition*
  - Autoimmune (hypothyroid, ITP, RA, SLE, MS, celiac, Type I diabetes, Sjogrens)
  - Asthma
  - Allergy/atopy
  - Metabolic disease
    - Diabetes II
    - Obesity
  - Psychiatric disorder
  - Neurologic disease
    - Parkinson's disease
    - Amyotrophic lateral sclerosis **(**ALS)
    - Autism spectrum diagnosis
  - Cardiovascular disease
    - Myocardial infarction
    - Coronary artery revascularization
    - Cerebrovascular accident
    - Hypertension
  - Colon cancer
  - Other malignancy
  - Inflammatory bowel disease
    - Crohn's
    - Ulcerative colitis
    - IBD-U
  - IBS
    - IBS-C
    - IBS-D
    - IBS-M
  - Other
- *Hospitalization*
  - Reason for hospitalization
  - FMT related (related, possibly related, unrelated)
- *Life-threatening illness*
  - Describe/diagnosis
  - FMT related (related, possibly related, unrelated)
- *Death*
  - Cause of death
  - FMT related (related, possibly related, unrelated)

APPENDIX A: Biorepository Sub-Study Protocol

Title: Fecal Microbiota Transplant National Registry Biorepository

Principal Investigator: Rob Knight, PhD, Professor, Departments of Pediatrics and Computer Science & Engineering, University of California San Diego

1. Facilities

Samples will be received and stored at the Knight Lab BRF2 Room 1220D, Bay D on the University of California San Diego Medical School campus. The American Gastrointestinal Association's (AGA) administrative offices (Sonya Serra, 4930 Del Ray Ave, Bethesda, MD 20814) will track a deidentified list of participants in the FMT National Registry and the American Gut Project (AGP) barcodes assigned to those who consent to be part of the Biorepository.

2. Estimated Duration of the Study

10 years

3. Specific Aims

By collecting and characterizing the microbiomes of these samples, we aim to expand knowledge to help optimize practice in the transplantation of fecal microbiota or other gut-related microbiota products. Specific aims characterizing the FMT National Registry-AGP biobank partnership include assessing the short and long-term safety of FMT and other gut-related microbiota products, to characterize the effectiveness of FMT and other gut-related microbiota products, and to gather information and promote scientific investigation on the practice in North America.

4. Background and Significance

The gut microbiome functions in a symbiotic relationship with the human body at a level of complexity akin to an organ or tissue. Recent advancements in genome sequencing technology have been used to identify the tremendous diversity of these microorganisms, opening a new frontier for research into the role of the gut microbiome in health and disease. It is now well appreciated that intestinal microbiota constitute a microbial "organ" that is integral to overall host physiology, including pivotal roles in metabolism and immune system function. Initial investigations have demonstrated that alterations in the gut microbiome (dysbiosis) may play a role in a number of gastrointestinal and non-gastrointestinal disorders (e.g., Clostridium difficile infection (CDI), inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), nonalcoholic fatty liver disease, obesity, diabetes, metabolic syndrome, cardiovascular disease, cancer, and many others).

The first clinical therapeutic application of this knowledge has been the use of fecal microbiota transplantation (FMT) to treat CDI. FMT involves administration of fecal material (containing intestinal microbiota) from a healthy individual (donor) to treat dysbiosis and restore beneficial intestinal flora and phylogenic diversity. FMT, which transfers highly complex microbial

communities, has proven to be beneficial in the treatment of recurrent CDI in numerous case series and a recently published randomized controlled trial. Because of recent trends in the incidence and severity of CDI and the growing body of literature, including current treatment guidelines, which support FMT, the number of physicians who perform FMT in the United States is growing. There are ongoing efforts to refine the process of FMT, with stool banks to supply carefully screened donor material and commercially available encapsulated formulations. Furthermore, investigations of FMT for the treatment of other conditions, such as IBD, are underway.

A biorepository will facilitate analysis of stool specimens and linkage of these analyses to clinical data from the FMT National Registry, thereby allowing assessment of the association of clinical effectiveness and safety outcomes with the biological characteristics of stool specimens or other gut microbiota-based products.

5. Research Design and Method

This biorepository will prospectively enroll at least 1,000 patients who undergo fecal microbiota transplantation (FMT) at 75 sites throughout North America and their corresponding stool donors. All of these participants will first be enrolled in the FMT National Registry, administered by the AGA. Upon consenting to enroll in the registry, individuals will be given the opportunity to also enroll in this biorepository sub-study, after explanation of the biorepository and providing an additional signature on the registry informed consent. If individuals enroll in the biorepository, they will be provided an AGP sampling kit. The AGP barcode will be linked to the participant's FMT registry code (which contains no personal health identifiers). The stool samples will be mailed to the Knight Lab BRF2 Room 1220D, Bay D on the University of California San Diego Medical School campus.

For patients enrolled in the biorepository sub-study, stool samples will be collected from the recipients before FMT and at 1 month after FMT. For stool donors enrolled in the biobank, samples will be collected from the stool they have donated for FMT procedures. The Knight lab at University of California San Diego will perform microbiome data analysis in accordance with the methods of the American Gut Project which may include amplicon sequencing, metagenomics, metabolomics, and proteomics. The clinical data obtained as part of the FMT National Registry can then be linked to the analysis performed on stool specimens for investigations related to the aims outlined above for the FMT National Registry. The Knight lab will also house the biobank in BRF2 on the University of California San Diego Medical School campus.

6. Human Subjects

Participation in the Biorepository will be limited to individuals in the FMT National Registry; therefore, the same restrictions on participation apply as in the FMT National Registry Protocol.

7. Recruitment and Procedures Preparatory to Research

At the time of consenting to participate in the FMT National Registry, individuals will be given the opportunity to also enroll in the biorepository, after explanation of the biorepository and providing written informed consent. Participation is entirely voluntary.

8. Informed Consent

Informed consent to the Biorepository will be obtained at the time of consent to the FMT National Registry. Minors may participate in the Biorepository. The minors and their legal guardians will undergo the consent process. Written consent must be provided by at least one guardian and, to the best of their ability, assent will be obtained from the minor. The signed Biorepository consent forms will be retained with the FMT National Registry consent forms. The consent process will be documented in the clinical or research record.

9. Alternatives to Study Participation

The study is entirely voluntary and the only alternative is not to participate. Not participating will confer no disadvantage to the participant.

10. Potential Risks

There are no risks of physical harm associated with participation in the biorepository. Participation in the biorepository does involve the potential risk of breach of confidentiality and associated privacy of the participants.

11. Risk Management Procedures and Adequacy of Resources

The biorepository will not hold confidential data. The samples will all be de-identified. Linked clinical data will be held only in the FMT National Registry as described in the FMT National Registry protocol.

12. Privacy and Confidentiality Considerations Including Data Access and Management

The biorepository will not hold confidential data. The samples will all be de-identified. Linked clinical data will be held only in the FMT National Registry as described in the FMT National Registry protocol.

13. Potential Benefits

There is no expected direct health benefit immediately associated with a patient's participation in the FMT National Registry or biorepository. The biorepository samples may provide a valuable

resource for future research into FMT and related gut-microbiota products.

14. Risk/Benefits Ratio

There is no significant risk and no direct benefit to the participant.

15. Expense to Participate

This is not a clinical treatment study and all costs associated with the care and treatment of patient receiving FMT and follow-up will be paid by the patient or their insurance provider. No costs will be incurred by participants related to participation in the biorepository.

16. Compensation for Participation

No compensation.

17. Privileges/Certifications/Licenses and Research Team Responsibilities

PI: Rob Knight, PhD
American Gut Project Manager: Embriette Hyde, PhD
Project sample coordinator - Greg Humphrey, BS
IRB consultants: Brent Erickson, BA and Gail Ackermann, DDS

All individuals have completed CITI training and have collectively over a decade of experience in protecting patient privacy and information.

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