UNITED STATES FOOD AND DRUG ADMINISTRATION

PART 15 HEARING

USE OF FECAL MICROBIOTA FOR TRANSPLANTATION TO TREAT CLOSTRIDIUM DIFFICILE

Silver Spring, Maryland

Monday, November 4, 2019

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P R O C E E D I N G S

(9:01 a.m.)

DR. GRUBER: Well, good morning. My name is Marion Gruber. I am the Director of the Office of Vaccines Research and Review at the Center for Biologics Evaluation and Research. On behalf of the agency and Dr. Peter Marks, who is the Center Director of CBER, I would like to welcome you today to the Part 15 public hearing on the "Use of Fecal Microbiota for Transplantation", also referred to as FMT, to treat Clostridium difficile infection that are not responsive to standard therapies.

The agency does recognize the critical importance of the microbiome and that manipulating the microbiome, such as is done with the fecal transplant procedure, to treat or cure very sick people is exciting science. But it is also important to note that FMT does carry some risk. Of note the FDA, as of today, has not approved any FMT for any use but the agency plays a critical role in supporting product development, while assessing the risks and benefits to patients of all unapproved therapies.

FDA works to achieve a balance between issuing patients' safety on the one hand and facilitating the access to unapproved treatment for unmet medical needs, on the other hand. We acknowledge that FMT shows promise in treating C. difficile infection which has not been responsive to other therapies. And we have developed a, currently in place, Enforcement Discretion policy to specifically accommodate the immediate needs of very sick patients with C. diff not responsive to standards therapies and whose illness can be life-threatening. In this, Enforcement Discretion policy is explained in the Guidance document that the FDA issued in July of 2013.

We appreciate the opportunity to hear today from all our stakeholders on the topics of clinical evidence of effectiveness. On the topic of safety and the impact of FDA's current enforcement policy on FMT product development, and we appreciate your thoughts on the future and path forward. The FDA will consider scientific data and other information obtained from today's public hearing as we continue to consider ways to

support the development of FMT to safely and effectively treat C. diff infection not responsive to standard therapies and the impact of the enforcement policy on such development. Thank you.

DR. FINN: Thank you Dr. Gruber. My name is Theresa Finn, I'm the Associate Director for Regulator Policy in the Office of Vaccines, Research and Review at CBER at FDA and I'm going to be the presiding officer for this hearing.

As the presiding officer it's my job to provide some administrative remarks and to give you an overview of the logistics for today's hearing. So, as stated in the Federal Register, the purpose of today's hearing is to obtain input on the state of this science regarding FMT to treat C. difficile or Clostridioides difficile, or more commonly C. difficile or C. diff infection not responsive to standard therapies. Including the available clinical evidence for safety and effectiveness of FMT for this use and to understand better the impact of FDA's Enforcement Policy on FMT product development.

So FDA will, as Marion has said,

consider the scientific data and other information from this hearing as we continue to consider ways to support the development of FMT to treat C. difficile infection not responsive to standard therapies and the impact of the Enforcement Policy on such development.

In our FR notice, we requested input from all stakeholders on four basic topic areas; the clinical evidence for effectiveness, safety evaluation, the impact of FDA's current Enforcement Policy on FMT product development, and future and path forward. Before we begin the hearing, I have some administrative announcements, then I'll ask the panel to introduce themselves and then I'll provide some -- an overview of the logistics for the meeting.

So, first the administrative announcements. First of all, please silence your cell phones or other mobile devices because they may interfere with the audio in the room today. And I'd like to just point out that we do have people online as well as you folks in the room. Secondly, we ask that all attendees sign

in at the registration tables outside the meeting room. Importantly, the restrooms are located in the lobby, past the coffee area to the right and down the hallway. And finally, copies of today's presentations will be available upon request. Contact information is also available at the registration table.

So before, as I mentioned, I was going to ask my panel members to introduce themselves and after that I'll talk about the logistics. So, first.

DR. GRUBER: Marion Gruber, Director, Office of Vaccines, Research and Review at CBER.

DR. FINK: Doran Fink, Deputy Director for Clinical Review in the Office of Vaccines, Division of Vaccines and Related Products Applications.

DR. CARLSON: Paul Carlson, I'm Principal Investigator in the Office of Vaccines, Division of Bacterial Products.

DR. DREHER-LESNICK: Sheila Dreher-Lesnick, Regulatory Coordinator in a Division of Bacterial, Parasitic and Allergenic Products, OVRR.

DR. STIBITZ: Scott Stibitz, Chief of the Laboratory of Near Coastal Pathogens and Cellular Immunology. Our lab does CMC review for FMT products.

DR. SLATER: Jay Slater, Director of the Division of Bacterial Parasitic and Allergenic Products.

DR. STEELE: Matthew Steele, Team Leader in a Division of Vaccines and Related Products Applications.

DR. FINN: Thank you to our panel members. Now for some logistics. For media inquiries, our press officer today is Megan McSeveney, she's way at the back standing up. If any members of the media are here today, please sign in and if you've questions or interest in speaking with FDA about this public hearing, please reach out to Megan.

The hearing is intended to give FDA the opportunity to listen to the comments from the presenters. So, panelists and other FDA employees will not be available to make statement to the media. Although there are no rules of evidence for this public hearing, there some

general procedural rules. No participant can interrupt the presentation of any other participant and only FDA panel members will be allowed to question the presenters. There will be an opportunity for open public comment at the end of the meeting once all the presenters have finished.

Public hearings are public administrative procedures are subject to FDA policies and procedures for electronic media coverage. Representatives of the electronic media are permitted, subject to certain limitations, to videotape, film, or otherwise record FDA's public proceedings, including the presentations of today's speakers. This hearing will also be transcribed, and copies of the transcript can be ordered through the docket or accessed on our website, approximately 30 days after today's hearing. Today we have, I think, 15 speakers registered.

Each of them will have 10 minutes to present. If a speaker finishes early, we intend to move on to the next speaker. This means that speakers may find themselves being called upon to

give their presentations before the time that is listed on the agenda. Although we might be adjusting the schedule to accommodate this, we will finish our scheduled breaks at the time listed on the agenda so that each section will start at the time listed on the agenda.

For the speakers, and pay attention, we have colored timer lights on the podium to guide you through your allocated -- your allotted time. The light will indicate when you begin speaking, it will be green and when to stop. When the light turns yellow you will have two minutes before the red light goes on. If you've not concluded your remarks by the end of your allotted time, I apologize in advance, but I will interrupt you and ask you to stop. Please remember that the hearing is being transcribed, so please be sure to use the microphone when speaking.

If you didn't register to make an oral presentation but you'd like to do so there will be an opportunity at the end of the hearing when you may be able to speak during the open public comment period. This is scheduled to begin after we've heard from patients and patient advocates.

If you're interested in speaking at that time, please sign up at the registration table outside the meeting room no later than 10:00 a.m. for a five-minute speaker slot. And I think we already have one person who's indicate they're interested in speaking during this time.

We strongly encourage everyone to submit your comments to the docket. The Federal Register notice has details on how to make comments to the docket and comments can be submitted until January the 21st of 2020. This hearing is being webcast, I mentioned already that we have a lot of folks scheduled -- registered to listen online, but the webcast is not interactive.

So, before we begin, I want to thank everyone, including our panelists and speakers for participating today. I look forward to a very productive hearing. And with that, I will ask our first speaker who I think is presenting in lieu of Carolyn Edelstein, it's Dr. Majdi Osman, to step up to the podium. Thank you.

DR. OSMAN: Wonderful, thank you very much and thank you for the agency for convening

this meeting today. So, in this presentation what I hope to do over the next 10 minutes is walk through our observations of Enforcement Discretion and the impacts on access, safety and innovation. As well as talking through some of the evidence gaps and recommendations. And the key takeaways that I hope you come away with from this presentation are firstly, that through Enforcement Discretion access, safety, and innovation have been successfully balanced. Secondly, Enforcement Discretion should remain in place so long as patients have an unmet needs that lack access to an approved product. And lastly, product development for FMT based therapies appears robust and can coexist with Enforcement Discretion.

So, at OpenBiome we operate like a blood bank but for stool. We manufacture material in a CGMP facility, have provided 50,000 treatments to over 1,200 hospitals and clinics in the U.S. under Enforcement Discretion and have also provided materials for 49 clinical trials as well as 16 single patient emergency IND's under FDA IND oversight. Reaching a total cumulative

enrollment across these studies of 950 participants.

With respect to access, Enforcement Discretion has been successful in enabling and overcoming key barriers to access for treatment. Ninety-eight percent of the U.S. Population now is within a two-hour drive of a FMT provider. But beyond universal geographic access, we've also seen that Enforcement Discretion has enabled clinicians to serve patients who otherwise would not be met by clinical trials today.

Data published by Colleen Kelly and colleagues recently show that only 25 percent of patients who were eligible for an FMT are eligible for clinical trials. Seventy-five percent of patients are excluded because of comorbid diseases such as IBD and IBS that are very common in this population. And this means Enforcement Discretion -- commissions can serve these patients. But stepping back and looking at the epidemiology of C. diff, you know, OpenBiome, we serve 10,000 patients every year. But there remain 110 to 140,000 patients who have C. difficile infection that could potentially

remain unserved and of those 35 to 40,000 patients have multiply recurrent C. difficile infection. Meaning, these are potential participants for clinical trials.

So, the last point in access that I'd like to highlight is that there are two specific patient groups who I think we've observed, have been particularly served by this policy, and firstly, severe and complicated disease. This is a very different disease phenotype to recurrent C. difficile infection and there are no industry trials in severe CDI and very limited treatment options. These are patients who are from progressed to last-line therapies or salvage therapies right at the outset, it's often bowel resection. And the mortality rate is 57 percent and in data published recently by a group from Mount Sinai, they showed a 77 percent reduction in the odds of mortality following FMT using OpenBiome material. And using their number needed to treat to three to prevent one death and we extrapolate that to our population of severe complicated patients that we've treated. It means that nearly three to 4,000 patients have

received -- have -- nearly three to 4,000 deaths have been averted.

In pediatrics, the second group, there have been no industry trials currently available for this population and similarly we've seen an 85 to 85.5 percent cure rate in this population using FMT OpenBiome. And stool banks sourced FMT is recommended in the NASPHAGAN position statement that was published earlier this year. And so, Enforcement Discretion has shifted the burden of sourcing FMT in these cases from practitioners and patients and mitigating a tradeoff between cost, time, and quality.

So, moving on to safety, we've observed that Enforcement Discretion has enabled scaled donor screening programs to be developed. They've enhanced FMT's safety and they've also formed into international consensus guidelines. Just speaking to our own experience at OpenBiome, we screen for ESBL and other MDRO's as well as other enteropathogens, and this proceeded the 2019 gene safety alert. In which the case reports recently published showed that the donor was not screened for ESBL at this hospital based

FMT program. But putting this into context, you know, overall the pass rate for being a donor in our experience at OpenBiome is 2.5 percent as we published in the New England Journal last week. And it costs around $3,600 per person for equivalent kind of stool testing and screening in a physician's office and ultimately what this means is that patients, regardless of geography can access safely screened stool for FMT.

And lastly on safety, you know, the other point to highlight is that Enforcement Discretion has allowed the development of stool banks to perform network wide centralized safety monitoring. And the features highlighted on this list, you know, are very challenging to perform in -- at a smaller scale and ultimately what this has meant is that there are no reported, definitively related serious adverse events from OpenBiome FMT material.

So, in terms of the evidence, so we followed up -- so real-world evidence has been successfully collected in the context of Enforcement Discretion alongside randomized control trials. We followed over 5,000 patients

treated at over 1,000 facilities. In terms of safety, observed no definitively related serious adverse events that were reported and in terms of effectiveness, a 79 percent cure rate with a third of these patients being treated for severe and severe complicated C. difficile infection.

And this is broadly in keeping with the real-world evidence when looking at randomized control trials comparing FMT to placebo or vancomycin. But there are weaknesses with such real-world evidence; under-reporting, misclassification bias and this certainly speaks to a mechanism that's needed that's guided by regulators for reporting safety and effectiveness that's scalable to the unmet clinical need.

So, in terms of innovation, Enforcement Discretion has enabled and supported innovation in this space and from what we've observed in the last six years, there is a robust pipeline for new therapies in this space. And, you know, the direct impact of Enforcement Discretion on enrollments, well we have sort of two hypotheses on that point.

Firstly, that Enforcement Discretion has raised awareness amongst physicians and patients regarding microbiota based therapies and overall, we expect -- reasonably expect that this has increased the number of patients entering the pipeline for enrollment. However, potentially, and I think it's reasonable to expect, that there may be some negative impact on the conversion of these patients into trial participants.

But the question then is overall what has the impact been on enrollment and, you know, using the data that we have, publicly available data on enrollment rates. It appears that if we look at trials for approved drugs that have occurred prior to Enforcement Discretion compared to the enrollment rates in trials currently of microbiome-based therapies for C. difficile infection they do not -- there doesn't appear to be such a considerable impact on enrollment, ultimately. And, you know, I'm sure there will be data presented from internally that these groups have, but, you know, ultimately at OpenBiome we are willing to support and will

continue to offer support for industry CDI trials. Because we believe that an approved product is of public health benefit.

So, in summary, you know, we do believe that Enforcement Discretion has had a positive impact on access, safety, innovation and as well as some of the evidence that I've walked through today. So lastly, in terms of gaps, you know there are gaps with Enforcement Discretion. You know, there's a lack of standardized donor screening, standardized oversight and regulatory guidance as well as the collecting and monitoring -- reporting of safety and clinical outcomes that are scalable to the size of the unmet need. And in terms of recommendations that the 2016 Draft Guidance has some limitations and that IND requirements are insurmountable for most health centers. You know, OpenBiome, we provide most of our material to community-based gastroenterologists and IND physicians and these requirements would likely mean restrictions in access for stool bank provided FMT. Potentially pushing patients to physician directed FMT or discouraging clinicians from providing FMT at

all.

And in terms of where we go from here, well, Enforcement Discretion should continue as long as there is a lack of available approved alternatives for addressing this serious and unmet clinical need. The Australian recommendations recently published align -- echo some of the features that Diane Hoffman and colleagues published in terms of how stool banks could be regulated. And in addition, you know, we think it's of critical importance that there be some forum, whether an independent advisory committee, review and update and monitor screening standards for FMT.

So, you know, in closing, OpenBiome, you know, we're now six years into Enforcement Discretion. In this room, after six years, there are physicians who've been able to provide FMT from screened, rigorously sourced, FMT from stool banks. After six years there are patients in this room who have been able to access FMT when they've run out of any other options, when there were no treatments available left for them, and they'd come to the end of the therapeutic ladder.

Patients who have been able to regain their lives after C. difficile infection, and so, you know, the decision taken by FDA in 2003 has enabled all of this and they should be commended for following this policy in 2013. We look forward to continue working with the agency in order to achieve these objectives and so, thank you for your attention.

DR. FINN: Thank you. Before I ask the panel if there are any questions, could you just tell me, is your lights -- were they working?

DR. OSMAN: They appeared to be, yes, yeah.

DR. FINN: Okay, good.

DR. OSMAN: Yeah, yeah.

DR. FINN: All right, thank you.

(Laughter)

DR. OSMAN: A few seconds over. Apologies.

DR. FINN: I -- because I can't really see them too well from here.

DR. OSMAN: Yeah.

DR. FINN: Before I ask the next person, are there any questions from the panel? Okay, so moving to the next person then, who is

Kevin Horgan. Dr. Horgan? From Seres Therapeutics.

DR. HOGAN: Good morning, I'm the Chief Medical Officer of Seres Therapeutics based in Cambridge, Massachusetts. Seres Therapeutics is a company developing novel treatments based on the microbiome to treat a variety of different diseases including recurrent C. diff infection. We've completed two clinical trials of our novel therapy for recurrent C. diff and we've got a third study in progress. The ongoing study is a Phase Three study. In the seven years since Seres was formed, particularly with respect to understanding C. diff infection, we've learned some important lessons. One of which was an insight from the analysis of our phase 2B, recurrent C. diff clinical study and is relevant to a question that the FDA has posed for this important meeting.

What additional scientific information is needed to determine the safety and effectiveness of FMT for C. diff infection that is not responsive to standard therapies? The key lesson we have learned is that accurate clinical

trial results, determining the efficacy of treatments for recurrent C. diff infection, can only be achieved if the diagnosis of recurrent infection is correct and the patient's enrolled in the clinical trial. Use of PCR testing alone without toxin testing means that recurrent C. diff infection is diagnosed incorrectly in many patients and leads to inconclusive and misleading outcomes in clinical trials evaluating therapeutic interventions.

It's a fundamental medical principle that accurate diagnosis of the target disease in crucial in clinical practice and the conduct of clinical trials. Emerging data show that the use of highly sensitive PCR testing leads to the incorrect diagnosis of recurrent C. diff infection in many patients. Because PCR cannot distinguish colonization from infection. In contrast PCR, toxin testing is more accurate for diagnosing true infection. And this explains the Infectious Diseases Society of America and the European Society of Clinical Microbiology and Infectious Diseases recommendations for toxin testing in the diagnostic evaluation of recurrent

C. diff infection. Accurate diagnosis is arguably even more important in clinical trials, investigating the efficacy and safety of novel therapies.

This is why, in the Seres Therapeutics ongoing Phase Three study, we require toxin testing for diagnosis and only toxin positive patients are eligible for enrollment. The toxin negative patients are carriers of C. difficile, most probably, without true infection who do not warrant additional treatment and should not be enrolled in a therapeutic clinical study. The data from our ongoing clinical trial are very consistent from data from other settings on the relationship between PCR testing and toxin testing. In our ongoing study and in multiple published studies, 30 to 50 percent of PCR positive patients have no detectable toxin. These 30 to 50 percent of PCR positive patients, without detectable toxin, most probably do not have recurrent C. diff infection. The lesson we have learned from our prior clinical trials, is that enrolling such patients in a clinical trial leads to inconclusive and misleading outcomes.

So, in summary, the accurate evaluation of the safety and effectiveness of therapy, including FMT for recurrent C. diff infection, requires the use of toxin testing for diagnosis. We would like to emphasize the placebo controlled, double-blind clinical trials under an IND, with toxin testing for diagnosis are the only way that the safety and efficacy of a therapy for recurrent C. diff infection can be objectively and accurately determined.

I'd like to make an additional comment in light of the very recent reports of the serious adverse events associated with FMT in the New England Journal of Medicine and at the American College of Gastroenterology meeting last week. Minimizing the risk of donor-derived products such as FMT to patients can only be done by both donor screening and also manufacturing procedures to eliminate potential pathogens from the donor-derived product. This is why Seres Therapeutics uses both donor screening and pathogen elimination procedures to optimize the safety of our spore-based donor-derived products.

These procedures are complimented by rigorous testing prior to distribution to confirm lack of contamination and provide us with confidence in their safe administration to patients. I thank you for your attention.

DR. FINN: Thank you. (Applause) Does anybody have any questions for our speaker? Okay, we will move on then to the next person who is Lee Jones from Rebiotix Ferring. Dr. Jones.

MR. JONES: Good afternoon -- good morning everybody. My name is Lee Jones and I'm the Founder, President and CEO of Rebiotix, which is a Ferring company. We're here today to address key issues regarding the FDA's policy for Enforcement Discretion for using FMT for C. diff unresponsive to standard therapies. In particular, I'm here today to weigh in on question number three which is the impact of the FDA's current enforcement policy on FMT product development. Just by way of background, Rebiotix has had a long collaborative relationship with the FDA on microbiota therapeutics. I founded the company in 2011 and in 2012 we had our first FDA meeting. In 2013 we

submitted our first IND in March; this was before the first public hearing on FMT and before the Enforcement Discretion program was announced. Today in 2019 we're recruiting for our Phase Three trial in anticipation of ultimate registration.

So, before we came to this meeting, we did a meta- analysis of peer reviewed, published literature looking for evidence of clinical effectiveness and safety for using FMT for C. diff. There were 55 published studies that we evaluated which doesn't -- do not include studies for commercial registration. In those 55 published studies only eight RCT's were conducted and this literature was reviewed from 2010 to June of this year. Out of the eight RCT's they represented 14 differently processed, dosed, and administered FMT preparations over a varied patient population. The centers conducted the RCT's used only FMT from their research center with no outside stool bank material. Of the eight RCT's only three compared FMT to non-FMT controls, all of them are very small and none of them are conducted in the United States. Further note, that of the 55 published studies reviewed,

49 percent had no systematic collection of adverse events and no -- or reported no adverse events at all.

So why is this important to what we're talking about today? Because I -- what I wanted to show is that this is -- the results are encouraging but there's a very low level of rigorous clinical evidence. The studies reflect the pioneering characteristics of the work that's been done and deserve recognition, but collectively do not provide sufficient clinical evidence of safety and efficacy for commercialization of FMT for C. diff. Rigorous and well controlled and statistically powered studies are needed and companies like Rebiotix are doing this work to get product licensure.

But the FDA policy has caused major obstacles to completing this work. We're here today to talk about the impact of the enforcement policy and I can speak to that. In our own clinical studies, we have seen a profound impact in study enrollment over the years. Beginning with our first study in 2013 where there was no commercially available FMT until today we've seen

a four-fold decrease in patient enrollment as measured by patients per site per month. Even though we've used the same enrollment criteria, the same product and some overlapping sites. We are dealing with an orphan indication and the patients were hard to come by to begin with and its been exacerbated by the policy.

So, as the enrollment timelines have increased so have the clinical timelines have expanded. Which has led to an increase delay of patient access to approved therapy. Cumulatively to date, just enrolling our studies, we've used over four years of time and if we had enrolled at the rate of our first RCT it should have only taken us about 28 months. So, the impact of Enforcement Discretion has slowed our clinical development and delayed patient access to FDA approved therapies by over two years, just in enrollment alone. And it's added 10's of millions of dollars to the development costs.

As you saw earlier, these slides were presented at DDW by OpenBiome and you can see that the commercialization of non-regulated FMT is greatly increased due to the enforcement policy.

So that as he said earlier, 98 percent of the United States is within a few hours of receiving OpenBiome product. This has caused overwhelming competition for clinical studies subjects and has caused a broken patient referral network. So, the enforcement policy consequences as we've seen them; there's fractured referral patterns, we've gone from patients being treated at specialized disease experts to whoever can buy FMT on the internet.

The patients themselves actually have not fared that well either because, according to this poster presented at ID week on real-world evidence of FMT use and outcomes in patients with C. diff, 36 percent of the patients were given an FMT after their first episode of C. diff, exposing them to unnecessary cost and risks. And they don't -- this treatment doesn't even follow the current treatment guidelines or FDA guidance. It's promoted unfair competition. So, while it's cost companies more time and dollars in seeking licensure, it's enriched a national stool bank and it's caused potentially unreported patient safety issues. Finally, it's delayed

innovation for C. diff products because it's difficult to start new next-generation product clinical studies when there's such a competition for trial subjects.

I think the one thing that, you know, I really want to make clear here is in the rush to capitalize on the enforcement policy, the one big group that's been left out of the discussion are the patients. There are people at the -- you know, true people at the end of these processes that are looking for therapies to treat their diseases and they're getting left out of the equation. Because it's delayed -- these delays in recruitment for these studies have delayed patient access to FDA approved safe and effective therapies.

So how can we remedy this? Rebiotix, of course, has been working on this for quite some time. We've increased the number of sites to compensate for competition from the stool banks. We've minimized the number of subjects per trial, using smart-trial design. We've increased the patient recruitment programs and put significant more investment in social media advertising and

clinical site referrals. We've delayed implementation of new product clinical studies and the same indications so as not to cannibalize at current trials. And finally, actually, we ended up selling the company even though early on in 2018 we really anticipated being able to finish our trials in 2019, and so we were looking for a commercial partner. We found out that this has been helpful to ensure enough cash to complete clinical studies.

And you may be asking yourself why is this important? Well, it's important because typically, small companies are the ones that are doing all the innovation and, in this environment, today those small companies are not sustainable.

So, what can the FDA do to help out this situation? First and foremost, the FDA needs to formalize and enforce the 2016 Guidance and cause stool banks that are distributing products outside of their own clinics to apply for IND's and conduct statistically powered clinical trials for licensure. To adequately collect, document, and report adverse events; to

adequately screen donors and stool donations consistent with current IND CMC requirements and have GMP manufacturing controls in quality systems implemented, just like all the other companies that are going through this process. And finally, the FDA should address improper marketing of stool bank material. It's been marketed as safe and effective and implied that it's FDA approved which encourages improper and uninformed use. Also, we are dealing with an orphan patient population in the recurrent C. diff group and we need the FDA's help in continuing to talk about revised clinical trials.

So, in conclusion, I believe that the enforcement policy has had negative impacts but that can be remedied by FDA action and we're looking forward to continuing to work with the FDA to have this happen. (Applause)

DR. FINN: Thank you very much. Let me ask if there are any questions? Not hearing any. I think we can move, then, to the next speaker who is Paul Kim.

MR. KIM: Good morning, I'm Paul Kim, partner at Foley Hoag and speaking as counsel to

the MTIG, the Microbiome Therapeutics Innovation Group. MTIG is a coalition of innovative companies leading the research and development of FDA approved microbiome therapeutics and microbiome-based products to address unmet medical needs, improve clinical outcomes, and reduce healthcare costs. Our current members include Takeda Pharmaceuticals, Rebiotix, SeedHealth, Seres Therapeutics, Siolta Therapeutics and Vedanta Biosciences. Leaders of many of whom are present today.

Through its collective voice, the MTIG membership works together to accelerate microbiome therapeutic product development and enable the field to reach its potential to benefit patients. Ground-breaking drug products that modulate the microbiome have the potential to address a wide spectrum of health challenges. The impact of the microbiome is best understood in recurrent C. difficile infection, but additional clinical research is underway on the microbiome's role in other areas including inflammatory bowel disease, irritable bowel syndrome, outcomes of cancer immuno therapies,

asthma, urinary tract infections, and chronic inflammatory disease.

The foundational importance of the microbiome in treating disease and the therapeutic potential of microbiome modulation began with research into FMT. At present, the safety and efficacy of FMT has not been fully demonstrated in randomized, double-controlled -- double-blind controlled clinical trials or been evaluated by the FDA. FMT is commonly administered for the treatment of recurrent CDI in patients who fail other current treatment options. Although FMT appears to reduce the risk of CDI recurrence, a teeny accurate estimates of safety and efficacy is limited by the quality published trials.

In addition, a majority of the published trials are limited in their scope due to study size, lack of meaningful statistical outcomes, and non-standardized drug manufacturing and lack of diagnostic rigor. Notably, a 2019 Meta-analysis which examine the impact of trial design on clinical outcomes, found that FMT was associated with significantly

lower cure rates in randomized trials; 67.7 percent compared with open- label studies, 82.7 percent. Additionally, the published data on FMT includes studies and reports by authors with known but undisclosed affiliations with leading stool banks, further calling into question a possible bias of results.

FDA has determined that FMT administered to treat CDI meets the definitions of a biological product and of a drug subject to premarket review and approval as a drug under the Public Health Service Act and the Federal Food Drug and Cosmetic Act. MTIG supports this determination as a matter both of law and of public health. Clinical trials to demonstrate safety and efficacy, carried out of compliance with the agencies investigational new drug regulations are important public health safeguards that are required for FDA approval and the commercial distribution of FMT.

In 2013, however, FDA took the position that the agency would be exercising Enforcement Discretion to allow FMT to be used to treat CDI not responding to standard therapy without

requiring compliance with IND regulations. Provided physicians obtained adequate informed consent from their patients, including acknowledgement of the investigational nature and potential risks of FMT. In response of growing broad distribution of FMT and ongoing concerns about the potential transmission of infection, FDA issued the March 2016 Draft Guidance, narrowing the IND exemption. Provided that the treating physician obtained informed consent, including a discussion of reasonably foreseeable risks, that FMT product is not obtained from a stool bank and that the stool donor and stool are qualified by screening and testing under physician supervision in providing that the FMT product treat the patient.

At present, the 2016 draft guidance has not been finalized which has created an unintended situation in which stool bank companies and clinics screen donors, process samples and distribute or administer FMT treatments at commercial scale. Without complying with IND requirements and without establishing safety and efficacy of their drug

products through high quality effective clinical trials. These sales, as we've seen from the previous presentations, are national and international in scope and are distributed through interstate commerce. These products are often labeled as safe without appropriate data to support this claim. Given that safety reporting in FMT is generally optional and much less stringent than would be required under FDA supported trials. Evidence of over-broad and frequently unsubstantiated safety and efficacy claims of unregulated commercial FMT products have been submitted in the past through the agency.

In addition, there are multiple instances of advisors to stool bank companies listed as authors on published data, policy briefs supporting stool banks, and position statements endorsing limited FDA regulation without disclosing such affiliations. These individuals also publicly present data that promotes the efficacy of FMT from studies that did not study stool bank products, in many cases, without disclosing potential conflicts of

interest. FDA articulated important safety concerns in the June 13th, 2019 safety alert informing providers and patients of the potential risk of serious or life-threatening infections with the use of fecal microbiota for transplantation. In this report instance, the donor stool and resulting FMT were not tested for antibiotic resistant organisms prior to use.

Given that former requirements for adverse event reporting or safety monitoring are required under the IND regulations but are not mandated under the 2016 Draft Guidance. MTIG believes, at a minimum, that the demonstrable health risks warrant immediate revision and finalization of the Guidance. Current under-regulation or voluntary passive reporting to an FMT registry will inevitably under-report adverse events and is inadequate to protect patients' safety. Consistent with years of agency practice and precedent, MTIG concurs with FDA's regulatory classification of FMT as a drug project subject to IND requirements that protect patients' safety and ensure clinical investigations conducted in concordance with the

law.

And the IND process incorporates two vital components; the protection of patients' safety while instituting requirements for developing substantial evidence of safety and effectiveness. This is the ideal framework since it is permissive of research while assuring patient access and maintaining scientific rigor. MTIG also strongly disagrees with critics who argue that compliance with IND regulations can impede patient access or clinical practice in relation to FMT. This claim is belied by FMT -- FDA's many decades of supporting product innovation for the benefit of patients while mitigating risks. MTIG agrees with FDA, that patients should access FMT treatment through clinical trials and supports continuing patient access to physician prepared FMT with donor controls and informed consent; consistent with FDA's Draft Guidance.

But MTIG also supports consistent and equitable FDA oversight and regulation to ensure that sponsors and manufactures of commercial scale FMT products, like stool banks and FMT

clinics, implement and adhere to the same rigorous clinical, manufacturing, and quality controls. To which other microbiota drug sponsors must currently adhere to in clinically developing new drugs for licensure. Enforcement Discretion should not extend to unregulated commercial scale FMT stool banks and clinics that have not established safety and efficacy through FDA regulated clinical trials; given the dramatic growth in scope, national breadth, and substantial sales of such unregulated products since FDA first issued its Draft Guidance.

These entities should also not be allowed to make claims about efficacy or safety of their products to patients without demonstrating such claims in rigorous, well controlled trials. We applaud the agency for its continuing work in protecting patients and for convening this public meeting as we believe patients, clinicians, the scientific community, and Congress are all eager to work with and support the agency in its statutory mission to promote the public health and to sustain innovation. We encourage you to consult sister

public health agencies within the Department of Health and Human Services including the CDC and NIH, regarding safety and efficacy considerations surrounding use of FMT products from commercial stool banks. We believe the agencies have important views in data that may assist you in revising the Draft Guidance to better protect public health.

In conclusion, MTIG's member companies are committed to patient access to therapeutic microbiota-based products that are proven safe and effective. Patients and clinicians stand to benefit from products with FDA approved safety, efficacy, manufacturing controls, and rigorous post-marketing surveillance to ensure their long-term safety. FDA approval of microbiome-based therapeutics that have been shown to be safe and effective through clinical trials will meet great unmet medical needs for patients. Thank you for your time.

DR. FINN: Thank you very much. (Applause) I don't see anybody with any questions so I think we could move to the next person who is Dr. Smith from Finch Therapeutics

Group. Thank you.

DR. SMITH: Hi, great, I'm Mark Smith. I'm CEO at Finch Therapeutics and as some of you guys know I started working on C. diff nearly a decade ago after watching my wife's cousin suffer through 18 months of C. difficile recurrences. I started OpenBiome in 2012 to help patients like him gain access to FMT and subsequently started Finch Therapeutics to develop licensed products that will further secure and expand access to microbial therapies. As a result of these experiences, as a patient ally, a stool bank operator and now a drug developer, I feel that I have a unique perspective on the field which I look forward to sharing with you all this morning. I'm confident that together we can find a path forward that balances the interests of all these diverse stakeholders.

I'll start with a very brief introduction to Finch. Finch is focused on utilizing data from clinical experience with FMT to develop next-generation microbial therapies --

SPEAKER: Can you speak up?

DR. SMITH: Yes, apologies. Is that better? Got to get the mic in front. Finch is focused on utilizing data from clinical experience with FMT to develop next generation microbial therapies that overcome the limitations of currently available options. We have two different therapeutic approaches and we decide which strategy is best suited for a specific indication based on data from interventional clinical studies. For recurrent C. diff, we're developing an oral therapy that contains complete microbial communities derived from healthy human donors, delivered in an oral capsule. For IBD and other conditions, we're developing therapies that contain selected microbes, each grown in pure culture.

One of the key questions that we're here to discuss is the impact of Enforcement Discretion on clinical development. And I agree with my colleagues that enrollment in placebo-controlled studies is difficult when patients have open-label access to FMT. However, we have demonstrated that while difficult, it is feasible. We've nearly

completed enrollment in a large placebo-controlled study, and we understand that others are also close to study completion at this point. Against this backdrop of enrollment that is challenging but feasible, we believe that it is especially important to consider the impact of policy on near-term public health.

There aren't many patients -- there are many patients who can't enroll in industry trials because they aren't eligible, as is been discussed earlier. Many more patients can not participate in trials because there aren't sites nearby. There are 11 states that don't have any industry trial sites and 12 states with only one. Furthermore, there just aren't that many spaces in our trials relative to the clinical need. There are 100-fold more RCDI patients than all the industry trials together will enroll. Enforcement Discretion is critical to serve the many patients who can't enroll in our trials and in this space, we must consider that patients without access may pursue high-risk, at home procedures.

We founded Finch to serve patients and

the communities that support them. While Enforcement Discretion makes our job as developers harder, I think it is important that we stay true our mission to improve the lives of patients, even when it is difficult and at times at odds with our near-term objectives. We believe that it is essential that patients continue to access FMT in parallel to developments of new products. While I support the current policy because it provides access to a life-saving therapy to patients that otherwise would not be served, I do think there are serious challenges that we need to consider as we evaluate long-term solutions.

We believe the most significant draw-back of the current policy is the lack of uniform standards for comprehensive donor and stool screening. The unfortunate patient death this summer is an important reminder of how real these risks are. While Finch and other groups screen for MDRO's and many other risk factors, there're not uniform mandatory standards that all providers must follow, and the current environment does not provide oversight of

institutions that prepare FMT treatments locally. Some of which may not perform the same level of donor screening. As we have seen, this creates significant risk for patients. To enhance patient safety, we see an urgent need for FDA approved products that are produced under robust CMC protocols and have been reviewed by the FDA.

These considerations directly inform my thoughts on how the agency can facilitate patient access while also protecting patient safety and supporting innovation and product development. We believe that the current policy of Enforcement Discretion should continue until products with more robust manufacturing controls in clinical data are available for approval by the FDA. We strongly believe that the controls and safeguards that come with an approved therapy will serve patients better than the products available under Enforcement Discretion today. Once licensed products are available, we believe Enforcement Discretion should be phased out. We believe that close collaboration between FDA and industry will be key to expediting this desired

transition from Enforcement Discretion to approved therapies.

The agency has clearly demonstrated its commitment to partnering with the industry by granting breakthrough therapy designation to three companies developing products for recurrent CDI. As on of those companies, we've greatly appreciated the communication and guidance that we've already received from the agency and look forward to continued collaboration. To further expedite the licensure of products, we believe that the risks inherent to the current policy should be considered when evaluating new products for regulatory approval. As an example, enhanced post-marketing requirements may be considered as a strategy to accelerate the replacement of unregulated products with approved alternatives while still ensuring that robust safety and efficacy data are collected.

To conclude our commentary on the impact of current policy and paths forward for the field, we believe that patients will benefit most from continuation of a policy of Enforcement

Discretion while we all continue to work expeditiously to develop improved licensed alternatives.

Next, I'll quickly address two additional topics the agency requested commentary on. The first is the impact of current policy on incentives for development. As you can see, there's been significant investment in the industry including well over a billion dollars invested after Enforcement Discretion was implemented. I think investors see the agency's clear commitment to development through several expedited programs, in significant engagement efforts, like the hearing today, as a sign of the agency's commitment to innovation in this space. Rather than seeing Enforcement Discretion as a threat, many see it as an important validation of the approach. Clear public guidance from the agency on the plan for Enforcement Discretion when approved products are available, would reduce uncertainty in the investment community and help all involved plan appropriately.

The second additional topic is around

the expected generalized ability of clinical data across different types of microbial therapies. As I mentioned at the outset, we're developing both, donor-derived and cultured products, and so thought deeply about the merits of each approach. For donor- derived products, we believe that currently available efficacy data from FMT and recurrent CDI is likely to be generalized both to other minimally modified, donor-derived products if the dose and delivery methods are comparable.

In terms of safety, we believe that currently available FMT safety data is also generalized both to other donor-derived products if and only if similar or more robust screening and manufacturing protocols are followed. So for example, if you consider the two unfortunate ESBL cases this summer, we do not believe these events reflect on the safety of donor-derived products that are screened for the agents involved. For products that contain a selection of microbes grown in pure culture, we believe that currently available efficacy and safety data for FMT is less generalizable considering the significant differences between this approach

and the transfer of a diverse, intact, natural microbial community. While we believe that this product strategy's also likely to be well tolerated, the ecological dynamics of a few strains may be quite different than the dynamics of those same strains when delivered as components of and intact, natural community. As a result, it will be important to evaluate the strategy in the clinic.

So, as I've discussed, we believe that Enforcement Discretion provides a critical short-term solution for patients. We believe it should continue until there is an approved therapy available and we believe that we all need to keep working together to expedite that transition as much as possible.

Thank you for the opportunity to share my reflections and more generally, thank you to everyone here for coming together to find solutions that work for patients. Tens of thousands of patients and their families have already benefited from the creative and compassionate efforts of the past five years and I hope that many more will be served by the next

generation of therapies that will soon follow. Thank you. (Applause)

DR. FINN: Thank you. I think we have a question?

DR. FINK: Hi.

DR. SMITH: How are you doing?

DR. FINK: I actually have two clarifying questions. The first question is: If and when a licensed FMT product or other microbiome-based product becomes available for this disease indication, do you have any thoughts about what considerations should guide how the Enforcement Discretion policy is phased out? Specifically, with regards to the speed of the phase-out process.

DR. SMITH: Right. Yeah. I feel that it's going to be important to ensure that there's continued supply for patients throughout that process and the extent that, you know, a manufacturer of an approved therapy like Finch Therapeutics is able to demonstrate that it can supply the need for, you know, all patients that are potentially, you know, in need of this therapy. Then I believe that should inform a

more expeditious phaseout into the extent that, you know, there's a potential for manufacturing short-fall, I think that that should be considered to ensure that patients continue to have access.

DR. FINK: Okay and my second clarifying question is that, often at public meetings we ask speakers to disclose any potential conflicts of interest. This is a not a requirement for this forum, but in the interest of full transparency, could you please clarify your current relationship and Finch Therapeutics' current relationship with OpenBiome?

DR. SMITH: Yeah, absolutely. So, I currently do not have a role at OpenBiome, either operationally or in the management or governance of the organization. Finch Therapeutics has a partnership with OpenBiome in which we collaborate on manufacturing of products and we have licensed access to certain data and know-how from OpenBiome in order to support the development of our own products.

DR. GRUBER: Can you repeat that?

DR. SMITH: Yeah, absolutely. I was just saying that I do not have any operational or governance role at OpenBiome. And Finch Therapeutics has a collaboration with OpenBiome in which we have licensed access to data and know- how from OpenBiome to support the development of our own therapeutic programs at Finch.

DR. FINK: Thank you.

DR. SMITH: Yeah. Absolutely. Any other questions?

DR. FINN: If there are no further questions, I think we can move on to the next speaker. We've -- moving now into the folks who have identified themselves academics. Our first speaker is Ms. -- Dr. DuPont, Dr. DuPont.

DR. DUPONT: Thank you. While you're looking at my conflicts, I would like to thank the agency for allowing me to present our data and provide our thoughts on FMT in C. diff. While I performed an FMT in 1970, eight years before C. diff was discovered as a cause of post-antibiotic colitis. Our program really began in 2013 when we wanted to address and identify microbiome

reversal possibilities to improve health with C. diff -- recurrent C. diff as the cornerstone of that program. And we began doing FMT studies as soon as the FDA allowed us to do that. What I will present this morning is our experience with FMT in CDI under IND and under Enforcement Discretion. We'll talk about route of administration and adverse experiences.

I'm going to make -- provide our thoughts on continuing the FDA enforcement policy. I want to comment on the use of placebos in FMT trials and I want to provide one thought about how we can meet the needs, clinical needs, for clinical trials with the use of Enforcement Discretion. These are 148 subjects treated in randomized clinical trials under IND working with the FDA and I want to indicate, it has relevance to this hearing. In working with the FDA with these IND trials has been efficient and helpful. If you look at the first column, you see the route of administration and I've -- these are randomized trials but I'm just re-dividing them into the route of administration and the type of product; fresh, frozen, lyophilized and how it

was administered.

We found that with lyophilized oral product, we only needed to increase the amount of product being used. But once we did that, we were able to achieve cure rates comparable in all groups, ranging from 75 percent in the low dose lyophilized product by colonoscopy up well into 90 percent for the various products. Looking at route of delivery and looking at efficacy, we saw once we increased the lyophilized inoculum size for the oral administration, the route of delivery had no significance in terms of efficacy in curing C. diff patients for 60 days after FMT.

Looking at the adverse experiences, keep in mind these are sick people, they've had C. diff, they're currently suffering from C. diff effects; very high frequency of nausea, vomiting, abdominal pain, flatulence, urgency, fever. But the percentage or the frequency of adverse experience did not correlate with any of the products or route of delivery. With regard to serious AE's we provide them here, what we've seen in these IND trials.

Between seven days and 270 days after

FMT we've had these serious AE's and they're listed here. With regard to deaths, we've had three deaths. One was recurrent C. diff 270 days after FMT, obviously a reinfection and both in two cerebral vascular accidents. Our Data Safety Monitoring Board looked at these cases thoroughly and felt they were unrelated to FMT. We cannot be certain about that, but we believe, with a reasonable degree of certainty, these were not FMT related.

Now with regard to the enforcement policy of the agency, we have treated 55 patients, and this is sequential. Really, we started off with the IND trials, we developed our products, we developed our tools, now we're beginning to do the Enforcement Discretion -- enforcement policy subjects. And these -- there are 19 cancer patients at MD Anderson with C. diff were treated with 95 percent cure in 60 days. One liver cancer related death. In the other patients we treated 36 patients with a cure rate of 78 percent. We are actively working with industry and we welcome that relationship. I feel a responsibility to develop -- help develop products in this area and

want very much to be part of programs going forward with industry.

I'll makes some comments in conclusions and thoughts about our studies and about FMT in general. We've used eight donors in all of our studies, primarily three donors and when we look at the efficacy response rate in recurrent C. diff by donor, looking at the three donors that have given most of the product, their efficacy is almost identical; 83 percent to 86 percent with similar AE profile. We've been screening aggressively for antibiotic resistance in ESPL production by Enterobacteriaceae for more than a year. Have had no adverse experiences in that regard.

We believe that FMT is curative and safe in recurrent, otherwise unresponsive, CDI. Providing sufficient dose of FMT product is given and a cryoprotectant is used in processing. The route of delivery doesn't really matter, we believe. Our recommendation is to continue the FDA enforcement policy, allowing multiple groups to perform FMT for recurrent C. diff because of the incredible public health need. However, we

are very concerned about industry and ability to do clinical trials; more on that in a minute.

I want to underscore the fact that this is a fatal disease. Looking at death certificates in Texas, C. diff has been associated with fatalities in hospitalized patients in almost a straight line going up, beginning in about 2001. And we're seeing this rise in nursing homes. This is a very serious infection. I raise the question about placebo control trials and wonder if we can be a little more creative in using some active controls. Certainly, we have to have very aggressive rescue therapy built into it. The other thing is that treatment centers shouldn't just be study centers. They should be management centers and when a patient is enrolled in a clinical trial and fails, they should be treated and managed if they fail treatment and wellness should be achieved. Very important point.

So, the enforcement policy of the FDA has decreased the opportunity of clinical trial. One of the ideas that I would put forth is the creation of centers of FMT research and treatment

among the larger centers, like our own. There are maybe eight, ten, twelve, centers who have a natural referral base. Just like the NIH VTU's for vaccines and biologics, this center could be organized through contractual basis with centers with funding from industry. And a large percentage of clinical patients, I believe, could be studied through a mechanism like this. This would not be the only mechanism by which studies could be done. But I think we have to address very actively how industry can move these products through because all of us want to remove the "F" from FMT. This is the group in Houston that is dedicated to reversing dysbiosis abnormal microbiome to improve health in patients with diseases from various disorders; certainly C. diff is our primary concern right now. Thank you. (Applause)

DR. FINN: Thank you. Does anybody have any questions? No. Thank you. So, moving to our next speaker, who is Diane Hoffman. Dr. Hoffman, thank you.

MS. HOFFMAN: So, good morning everyone and thank you for the opportunity to

speak with you today. My comments stem from a three-year grant that I and co-investigators from the University of Maryland received in 2014 from the National Institute for Allergies and Infectious Disease to examine the current regulatory framework for microbiota transplants. A significant component of that work focused on the regulatory framework for fecal microbiota transplants for recurrent C. diff that is not responsive to standard therapies.

Since the end of that grant I've been guest editing an issue of the Journal of Law Medicine and Ethics that is being devoted to the promises and challenges of microbiome- based therapies. Specifically, microbiota transplants. A number of the articles focus on regulatory issues and the publication will be coming out next month. But today I'd like to share some of the points that I and my co-authors made in one of the articles titled, "The Impact of Regulatory Policies on the Future of Fecal Microbiota Transplantation".

In addition to myself, the authors of the article include Dr. Alexander Khoruts,

Professor of Medicine and Medical Director of the Microbiota Therapeutics program at the University of Minnesota and Dr. Francis Palumbo, Professor and Executive Director of the Center on Drugs and Public Policy at the University of Maryland, School of Pharmacy. In the article we explore the potential paths the FDA may take in regulating FMT and how the agency's decisions may impact patient access as well as research and innovation. Both on FMT and on other stool-based biologics. While I don't have time to go through all the points in the article, I wanted to highlight a few that might be relevant to the agency's decision making.

As regard to the impact of the FDA's Enforcement Discretion policy on the development of what we refer to as complete community FMT products or donor-based products, we believe it has had both positive and negative effects. On the one hand, the relatively high -- light regulatory burden for conducting research under Enforcement Discretion facilitated a rapid transition from a cruel procedure that involved preparation and administration of raw,

homogenized stool to an easily administered, purified, and cryopreserved microbiota product. That is centrally manufactured from rigorously tested universal donors.

Under Enforcement Discretion, you already heard, academic clinical investigators have been able to perform a number of studies on FMT including comparing the effectiveness of fresh and frozen microbiota, routes of administration and various doses of treatment for recurrent C. diff. They've also made preliminary assessments of clinical safety and efficacy for FMT in higher risk recurrent C. diff patient groups. For example, those with inflammatory bowel disease, advanced liver disease, and organ transplant recipients.

On the other hand, the Enforcement Discretion policy that allowed liberal clinical practice of FMT for recurrent C. diff has resulted in an enormous missed opportunity to collect clinical outcome data in tens of thousands of patients. We believe there are a number of reasons for continued Enforcement Discretions or something that I'll talk about that will allow

continued access to FMT. If Enforcement Discretion is discontinued before approval of some FMT product, and the primary stool bank in this space, OpenBiome, shuts down, the main risk and loss will be to access to FMT for the vast majority of patients. Since current clinical trials are IND exclude the majority of recurrent C. diff patients. If FDA decides not to continue Enforcement Discretion after a new stool-based drug is approved and OpenBiome closes, the cost of the new drugs will likely be a major barrier to access.

While an approval of a new drug is likely to result in insurance coverage of the product, if the cost is substantial, insurers will likely limit coverage and consumers will be required to pay a significant amount out of pocket. The increase in cost for patients may push some patients to try to find a physician who will perform a FMT with donor stool from a family member or friend of the patient. If stool product from a stool bank is not available, however, there will likely will many fewer physicians willing to perform the procedure. As

they will be required to screen donors, test stool, and prepare that stool for administration. Although Medicare does cover FMT for recurrent C. diff, the reimbursement is not sufficient to cover the costs of the rigorous donor screening done by stool banks. Which you heard costs over $3,000.

Furthermore, blending stool may require specialized equipment, such as biological hood certified by -- for biosafety to operate level two operation, which many physicians do not have. A final concern about an FDA policy that would limit access to stool from stool banks has been the potential for many more "do it yourself" FMT's which comes with significant risk. Primarily from inadequate donor screening and testing for infectious diseases and pathogens. However, additional non-infectious risks, such as obesity, diabetes, neuro-psychiatric disorders and others also may be increased due to less stringent donor selection; relative to those established by the stool banks.

In terms of a way forward, if FDA

terminates its Enforcement Discretion policy for stool banks currently operating, stool banks would probably not pursue a traditional IND for approval as a biologic because of the costs. As a majority of these stool banks are not for profit or associated with academic medical centers, the bank would have to raise significant investment funds to do so. That would be unlikely given the minimal intellectual property it could obtain in the donor stool. However, the possibility that stool banks could operate under an ongoing observational clinical trial could allow them to continue to provide their donor stool for the treatment of recurrent C. diff. By an ongoing observational clinical trial, we mean one that -- where the safety data would be collected and -- I'm sorry -- safety data would be collected and -- as well as data on effectiveness. But the banks would need not make progress toward obtaining a biological license.

We propose that the inclusion criteria for participation in trial be very broad. Permitting any patient with recurrent C. diff to enroll if their treating physician believes they

would benefit from an FMT. Participating physicians would be required to report adverse events and data on effectiveness to the stool bank; which would have to submit regular reports to FDA. Such an observational study would require collection of data that is currently not being adequately captured by stool banks or by the IND studies being conducted for FMT products in clinical trials.

You've already heard about the study by Dr. Colleen Kelly and others recently that they published, indicating that these IND trials do not reflect the population that needs the procedure. Efforts would need to be made to simplify data collection and report new requirements for physicians who may otherwise refuse to participate. But operating under an IND for an ongoing observational trial, stool banks might be able to provide an alternative engine to FMT research. Unconstrained by the goal of product approval, stool banks could focus on fundamental questions of mechanism, formulation, and optimal delivery. Funding this work will be challenging, however, stool banks

may be able to take advantage of current FDA regulations that allow for cost recovery of drug manufacturing for research purposes.

Finally, there is precedent for the idea of an ongoing or permanent IND. In the late 1970's, some may know of this, the FDA administered a compassionate IND program allowing a small number of patients to receive medical marijuana from the National Institute of Drug Abuse. The program started in 1978 and had patients enrolled for approximately 30 years.

In conclusion, FMT has emerged the first, true, microbiota therapeutic and has proven to be highly effective in treatment of recurrent C. diff. It has been widely incorporated into clinical practice under the FDA's Enforcement Discretion policy which allows its administration without collection of systematic data on its safety, efficacy, or long-term physiological effects. The rapid adoption of FMT has been driven by the large demand from patients and enabled by availability of FMT products from stool banks. Termination of the Enforcement Discretion policy, at this time,

might accelerate ongoing placebo-controlled trials being conducted by several commercial developers. However, doing so will likely impair access to FMT for many patients who have no other treatment options available to them. It also may force many patients into less safe, "do it yourself" protocols, which are viable options that are not available for other drugs. Thank you so much for your attention. (Applause)

DR. FINN: Thank you very much. Do we have any questions? Yes.

DR. FINK: So, this is less of a question and more of a clarification or a confirmation on behalf of FDA and that is just that we can clarify that there is no requirement for products being studied under IND, that the products be developed to licensure.

MS. HOFFMAN: Thank you.

DR. FINN: Do I -- anybody else have questions? No. Okay. So now, moving on to our next speaker, Amanda Kabage. Dr. Kabage.

MS. KABAGE: Good morning, I am Amanda Kabage. I'm a researcher and bioethicist at the University of Minnesota for the microbiota

therapeutics research program, working alongside Dr. Alexander Khoruts. But today I'll also be speaking as a former recurrent C. difficile patient myself and recipient of FMT.

So, I'd like to start by giving you a little picture of the kind of person I am. Before I got sick with C. diff, I was balancing a full-time research job at the university, studying the genetics of pediatric cancer while simultaneously getting my master's degree in science policy and bioethics. I love to travel and I'm the kind of person who will spontaneously buy airline tickets and find myself in another country a few weeks later. I'm a runner, I love to go to the gym. These days I lift weights and I used to play racquet ball quite frequently. So, I've always been a very active, adventurous person.

And then in 2012 I became sick with C. diff and every single aspect of my life came to a screeching halt for 14 months. That's how long I was sick. I went through many antibiotic treatments that didn't work and each came with their own debilitating side effects that were

sometimes worse than C. diff itself. One particular antibiotic was -- caused such severe neurological side effects that I ended up in the emergency room because I couldn't remember what I had done an hour prior. It was a really terrifying experience to go through. But there was this particular moment for me when I really realized how sick I had become and how malnourished I had become. It was one morning when I was in the shower, and clumps of hair that had started falling out, and being a cancer researcher, I thought to myself, "this is what happens to chemo patients, not to C. diff". But then I got FMT and in days I started feeling better and I knew it worked. One month later I was back at the gym and two months later I was on an airplane again and I got my life back. And despite 14 months of suffering, I still consider myself one of the lucky ones.

Being in this field I consider my case to be moderate in comparison to a lot of the horror stories I've heard, and I had access to FMT. If Enforcement Discretion were to go away patients far sicker than I was will not have access and they

will suffer, and many will die. Enforcement Discretion has given tens of thousands of people access to a life-saving therapy. It was the moral thing to do. It's not to say we haven't had challenges or that mistakes haven't been made along the way, but it was the right thing to do. And so, I'd like to briefly discuss some of the impacts Enforcement Discretion has had on this field and propose a solution forward.

One of the major oversights was the missed opportunity to collect data on 50 to 100,000 patients who have already been treated with FMT under Enforcement Discretion. The lack of this data has limited our scientific understanding of safety, efficacy, and mechanisms of FMT. This data is crucial for a new emerging field, like microbiome, where we don't know a lot about this yet. We could've obtained an impressively large data set of real clinical world experience, that I might argue, is even more valuable than data we're collecting from clinical trials.

My career started out in genetic epidemiology, so I'm a little biased, but also no

stranger to no large-scale observational studies. I know they can provide valuable information that clinical trials simply cannot capture. In my opinion, from the beginning, Enforcement Discretion should have been coupled with outcome data collection. But it's not too late to mandate it. The continuation of Enforcement Discretion would allow us to collect safety and efficacy data on a much larger C. difficile population than clinical trials can capture. There's an efficient way for doing so using patient registries.

Again, when I would go back to my work as -- in genetic epidemiology I helped develop registries for pediatric cancer patients. The childhood cancer research network has data on over 90 percent of cancer diagnosis for kids in this country, and that's a far cry from the data we've been able to collect on C. diff patients. But, again, I emphasize it's not too late to start capturing that data. We're already doing this at the University of Minnesota. I personally have created a patient registry in which we capture data on all of our patients receiving FMT under

Enforcement Discretion.

We collect medical history data so we can understand the type of patients that we're working with. And we ask physicians to provide safety and efficacy data at multiple time points; one to two weeks after receiving FMT and to collect longitudinal data we collect it at one month, two months, six months and one year. Physicians who wish to use our FMT product are required to provide this data in order to continue having access to our FMT product. Asking physicians to provide a minimal amount of information is not unreasonable. Our industry only takes a couple of minutes to take -- to complete.

So, I always considered that the gold standard in drug research is the randomized clinical trial but there are limitations with RCT's. In this situation we found ourselves in, I think it's important to ask: Are the participants that are participating in these clinical trials representative of the patients who will be receiving FMT after the FDA approves a product? Is this data generalizable to all

patients who have received FMT under Enforcement Discretion? And in my experience as a researcher in this field, I think the answer is no.

Recurrent C. difficile patients, by their very definition, are incredibly sick individuals which is why they require FMT in the first place. Many of these patients have comorbidities and they are excluded from clinical trial participation. You can go into clinicaltrials.gov and see the eligibility criteria for each of these trials. They all exclude patients who are immunocompromised, those who have IBD, those who have history of GI surgeries, and even people with IBS, which we know is a generalized term applied to a lot of undiagnosed GI problems. In our practice already we know that IBD patients with C. diff respond differently. We know that post-infection IBS is very common. We need large-scale observational studies to understand the complexity of these patients. Safety and efficacy data from these minimal number of clinical trials is simply not adequate.

If I was sick today, I would not be

eligible for any of these clinical trials based on a former misdiagnosis of IBD and an IBS diagnosis. My data would not have been collected without Enforcement Discretion, but instead I am a published data point for our research program at the University of Minnesota. And it's not to say that clinical trials are unnecessary, I just think we've found ourselves in a situation where clinical trials and Enforcement Discretion need to coexist successfully. It's been argued that clinical trial recruitment has been struggling because of Enforcement Discretion. I don't agree. I think it is the very strict eligibility criteria that limits the patient population. If 100,000 patients have recurrent C. diff and only about 10,000 are being treated by OpenBiome, there's 90,000 some patients leftover.

But the pressure of this recruitment struggle put us in a situation where a proposal was drafted listing conditions for which C. diff patients could still receive FMT under Enforcement Discretion but trying to help recruitment in the clinical trial research. And as bioethicists I was really deeply concerned

with what I had read. When I read this proposal, it seemed reasonable at first. Patients with severe cases of C. diff could still get FMT from their doctors as well as those who live too far from clinical trials sites or simply didn't meet eligibility criteria. But what the proposal lacked was an option for people who simply don't want to be part of a clinical trial. Research participation must always be voluntary, free of coercion, as stated by the Belmont Report. The fact that a violation of human subjects' ethical guidelines was even suggested should sound alarms. Are we willing to sacrifice patient autonomy for financial gains?

I empathize with participant recruitment because it's not an easy task. In my 12 years of research experience, I can probably count on one hand how many times I've met my recruitment goal. It's hard work but the burden of participant recruitment must always fall on the investigative research team and not on patients seeking treatment. This is just not an acceptable solution but mandating the collection of safety and efficacy data through patient

registries is. I know this situation we've found ourselves in is unique but FMT is unique. It's not like other drugs and we know that. We've only touched the surface in this new field of microbiome research, and we should proceed with caution and optimism, learning from our experience with C. diff, especially as we move into treating many other indications that show promise.

We need to consider off-label use and really consider the restriction of any FDA approved products to solely C. diff. I fear that if we allow off-label use for other indications, we could potentially find ourselves in dangerous situations as we found with this summer with the unfortunate death. Enforcement Discretion brought FMT into the spotlight and into the headlines and gave access to C. diff patients who are looking for an end to their suffering the same way I was. There's plenty of science already to show this is safe and effective for this disease. It has saved tens of thousands of lives, including mine, and it would be highly unethical at the point to even consider terminating Enforcement

Discretion knowing we have a treatment that works. I'm here today because of Enforcement Discretion. Thank you very much. (Applause)

DR. FINN: Thank you. Any comments?

DR. GRUBER: Yeah, so I just wanted to thank you for your -- sharing your story with us and also for your comments and perspective. I wanted to make one comment. It's maybe more a clarifying comment in that you mentioned at the beginning that because of Enforcement Discretion many, many sick people have been receiving this therapy and it may have been a missed opportunity to collect data. I just wanted to clarify that under the Enforcement Discretion policy, the agency cannot mandate or require data collection. Just wanted to make that point. Thank you.

DR. FINN: I'm sorry but there are no questions to the panel. Is anybody else on the panel have any further questions? No? All right, so then moving on then, we have our last speaker before the break is Dr. Javitt. Dr. Javitt, thank you.

DR. JAVITT: I want to thank the panel for allowing to present my thoughts about the

prevention and treatment of antibiotic associated C. difficile. I would like to describe the pathogenesis of antibiotic associated C. difficile colitis and the mechanism underlying the effectiveness of FMT and other strategies. I would then like to focus on the alternative strategy for C. difficile prevention and treatment. This strategy leverages the generic drug, Ursodiol, or Urso, who's active ingredient is ursodeoxycholic acid. Unlike FMT, Urso presents a viable approach for the prevent of C. difficile and could reduce the need for FMT treatment.

Okay. Many individuals, including some sitting in this room have spores of C. difficile lying dormant in their colon. The reason the spores remain dormant is the presence of bile acids that suppress C. difficile germination as explained in this slide. Normally, the liver produces what are generally referred to as primary conjugated bile salts, or acids. These are metabolized of cholesterol and provide a major pathway for removing cholesterol from plasma. When the gallbladder contracts

after a meal and the primary conjugated bile salts enter the intestine and reach the colon, there are two bacterial enzymes produced by the normal gut microbiome that convert the primary conjugated bile salts to unconjugated secondary bile acids. These secondary or intestinal bile acids, deoxycholic acid and lithocholic acid, suppress the germination of C. difficile spores.

How do I get this to go forward? Okay. The impact of some antibiotics on the formation of secondary bile acids is shown in this slide. Antibiotics can suppress or even eliminate the normal intestinal bacteria that produce bile salt hydrolase and 70 hydratase, which prevents the formation of secondary bile acids. Without the suppressive effect of the secondary bile acids, dormant C. difficile spores begin to germinate and produce the toxins that lead to C. difficile infection. What makes matters worse is that the primary conjugated bile salts actually stimulate the germination of C. Difficile.

Now if I can -- just want to fast forward here. Okay. This next slide illustrates the difference in the biological effects of primary

conjugated bile salts and secondary intestinal bile acids. This is a cell-culture study. If you want to germinate C. difficile spores in cell- culture you add a primary bile salt, as shown in orange, such as sodium taurocholate which maximizes growth. Now if you add deoxycholic acid in different amounts, which actually are less than you find in a normal colon, there is virtually complete suppression of growth.

Now this slide looks like the last slide but actually if you look closely this is Ursodiol, ursodeoxycholic acid and it is a surrogate that will accomplish the same effects as deoxycholic acid and a variety of different strains of C. spores. So, we turn in to FMT, we can now appreciate that it's successful because it restores the intestinal bacteria that produced the enzymes that convert the primary conjugated bile acids to the secondary bile acids. The restoration of these bacteria allows conversion of primary to secondary bile acids to resume the suppression of C. difficile germination. So that the Usro is a surrogate for the effects of

successful FMT. Now, Ursodiol was approved by the FDA in 1987 as Actigall and is widely available as a generic. And as you can see, it's currently used for the treatment of primary biliary cirrhosis which is now called cholangitis, cholestasis of pregnancy, neonatal cholestasis, and gallstone prevention. And what we're proposing is that that one can use it for the prevention and treatment of clostridium difficile.

And this is the first report of successful use of ursodeoxycholic acid in a patient who had multiple episodes of recurrent C. difficile and as you see in the bottom the patient refused to discontinue Urso because of fear of another recurrent episode. Which is not an unusual response of a patient. So, what I refer to as bridge therapy which can be used either for the prevention or the treatment of C. difficile, is that in prevention if you start an antibiotic which has a bad reputation such as Clindamycin you can give ursodeoxycholic acid at that time. The antibiotic will suppress the bacteria, the normal gut microbiome, but the patient will not get C.

difficile because he's on Urso. And if you continue it long enough, we propose 56 days, it allows the person's own microbiome to come back. And so, we think this is an alternate strategy and suggested to you for your recommendations. Thank you. (Applause)

DR. FINN: Thank you very much. I don't think we have any questions, so that brings us to the end of this session. We have now a break until 11:10 and then we will come back with a group of clinicians followed by the patients. So, we have rather a long break until 11:10 but I want to make sure that we don't miss people who might not yet be here for their scheduled time. So, thanks very much we'll reconvene then at 11:10. Thanks.

(Recess)

DR.Finn: If everybody could take their seats. So, we really should try to start on time here because we have two groups to hear from, the clinicians as well as the patient people who identified themselves as patients or patient advocates. And then I mentioned that we had an opportunity for people to give comments in an open

public hearing forum and that those people would be able to speak for five minutes. So, I have just heard that we have six people signed up to speak. Each of those people will get five minutes to speak and in case they were not here at the beginning, as we move into that I will remind you, for those public hearing folks you will be getting five minutes and the yellow light will come on when you have one minute left. So, our first person now, is Dr. Kahn, Stacy Kahn.

DR. KAHN: Good morning and thank you to the organizers and to the FDA for hosting this important hearing today. I would like to shift the focus to talk about the clinical impact of enforcement discretion and availability and access to FMT in a very special population, and that is of children. The data on C.diff and FMT in children is incredibly limited. In January of this year our European Society for Pediatrics Gastroenterology Hepatology and Nutrition along with our North American Society partnered to draft the first guidance ever on the use of FMT in children with C.diff. Although we cited the lack of evidence and studies in children with

C.diff, we universally agreed that FMT should be available to children following appropriate indications of recurrence C.diff and that it should be considered a viable option and that especially important is the need for further research in this area. Our consensus statement as well as papers by several other leaders in the field, both pediatric and adults has noted that there are several potential benefits from stool banks and I would just like to highlight why these are so important for children. First of all, family members of children with C.diff have a higher risk of exposure and infection with C.difficile and therefore may not be ideal donors. As a clinician who has been performing FMT for many years I can tell you that among my early cases I was doing individual directed donor stool and had an aunt fly from New York to Chicago to donate stool for her nephew with recurrence C.diff. This is not a viable option. This is not access. Family members in addition are highly motivated to help. I assume most of us in this room have children or have nieces or nephews or family members and we know that when those

individuals are ill that we will do almost anything in our power to help them. This does not lead to the ideal process for donor selection and recruitment as these family members may feel that their confidentiality is compromised by the rigorous screening process in FMT. In addition, recently there have been several studies that universal donors may be better in terms of outcomes compared to individual donors. I also know personally and from the experience of my colleagues that stool from bank donors is much safer than what I can provide on an individual basis due to their comprehensive and extensive and rigorous screening process as well as the fact that they bio-bank samples which can go -- we can later go back and test additionally for further conditions and infections. As an IBD specialist I can also tell you that I do not want family members donating for my patients who have underlying IBD, family members may share familiar risk factors from FMT and in fact, may not be ideal donors in any circumstances. And finally, universal donor FMT is much easier, much faster and much more cost effective than what we can do

as clinicians.

This summer many of us in the room attended the Rome Two International Consensus Conference on Stool Banking on Fecal Microbiota Transplantation and Clinical Practice. And again, although there was little discussed around the treatment of CDI in children, the conclusion was that FMT is a safe and effective treatment for CDI in children. And although the certainty of evidence was low, the strength of recommendation was strong, finding that there is sufficient evidence to support the safety and efficacy of FMT in children with CDI. Furthermore, that CDI presents a growing health concern in young patients who are also more likely to have community acquired CDI. In children who do not respond to standard antibiotic therapy, or who have recurrent or severe CDI, maybe candidates for and benefit from FMT. So, why is this so important and what does this matter and in terms of enforcement, discretion. Well, it has been incredibly important for our pediatric patients and although the vast majority of patients with C.difficile are adults we do know more and more

about the incidence of C.diff in children. We found data from the CDC' Emerging Infection Control Program in 2011, that rates of CDI are increasing with an overall incidence in children of 24.2 per hundred thousand persons. Furthermore, that out of an estimated almost 17,000 cases, the vast majority of these cases are community associated. This means children are coming in without any clear antibiotic exposure, healthcare exposure, or other known risk factor, meaning that many of these other treatment pathways and diagnostic pathways are not sufficient in children. We also know that C.diff is increasing in hospitalized children and this nice study from my colleagues looking at the annual incidence of CDI cases based on the number of discharges is just remarkable. You can see that children in every age group, the youngest children 1 to 4, a dramatic increase in incidence from just over 30 percent to close to 80 percent. And what you can see from each of these age groups is that since 2003 the rates of CDI in our children in hospitals is going up.

I would like to also highlight that

through our pediatric FMT registry which was created through a grassroots effort and the support of our NASPGHAN Pediatric GI Society, we have collected retrospective data on the safety and the efficacy of FMT in children. We found that CDI disproportionately impacts our sickest children, as has been noted by several of the other presenters we see high rates in IBD at almost 33 percent. Thirty percent of our patients in pediatrics are immuno-compromised. Twenty percent have a feeding tube. Another ten percent have reflux. Another six percent have a malignancy or have had a somatic stem cell transplant. Almost three percent respectively have short bowel syndrome or have a history or solid organ transplant. So, although we do not see the rates that you all do in adults and we do not usually see the severe illness, or thankfully, the mortality, these are our sickest children. If we leave these infections unchecked there will be consequences in terms of morbidity and mortality in children.

From our registry we have published more data on 335 children from across the United

States from 18 centers, both academic and in clinical practice from rural and city settings and we followed them for two months after their FMT. And we found, based on our real-world experience, an 81 percent cure rate with this single FMT, and an overall cure rate of 87 percent. In general, it was incredibly well tolerated by these children regardless of the delivery method and severe adverse events were rare, less than five percent and mostly consisted of individuals with IBD flares, where it is quite difficult to distinguish an active infection with C.diff from an IBD flare. Importantly, there have been no deaths today reported.

I would also like to share a patient's success story. This patient was treated by my colleague, Dr. Alga Gyall whose also one of the pioneers in pediatric FMT and IBD specialist at Children's Mercy Hospital in Kansas. This young patient, Jaden, suffered tremendously with a diagnosis of Crohn's Disease at age three. This is considered very early onset IBD and is an incredibly difficult condition to treat. He had C.diff for over a year before getting FMT. He had

debilitating diarrhea, stomach pain, was unable to go to school. He had been on antibiotics for well over a year, and she provided him with treatment from FMT from a stool bank and cured him of his C.diff and he remain well today.

There are also emerging applications for FMT which we have yet to discuss and I am hopeful that some of the other colleagues who are presenting today will highlight this as well, but my pediatric colleagues at John Hopkins have looked at other applications for FMT in children. This very busy graft shows on the left of the stash line a donor, and as you can see, the blue bars indicate multi-drug resistant genes. To the right of the bar we followed these patients before transplant and after transplant. And what you can see without even looking at this specific classes of resistance, that over time we had a dramatic and statistically significant decrease in multi-drug resistant genes in the patient receiving FMT that was sustainable for up to 24 weeks. So, we know that there are applications beyond this.

I would also like to highlight the

letter that we drafted --

DR. Finn: I am sorry but your time is up. So, we will have to --

DR. KAHN: Okay. Can I just do my last line on (inaudible) consequences please?

DR. Finn: Sure.

DR. KAHN: Thank you. I am the only pediatrician here representing so obviously I have got a lot more to cover then some of the other people who have multiple -- people talking on adults and clinicians, so. There are no randomized control trials of FMT for children with C.diff. This is incredibly important as you consider the enforcement discretion policy. Furthermore, commercialized micro- therapeutic products are not available for children and have not yet been studied and are not being studied in children. It is also important to note that our current antibiotic strategies for treating children with C.diff are not FDA approved for children in most cases. Institutions may therefore stop offering FMT and the alternative is long term antibiotics which is expensive, can cause adverse events, can harm, and may increase

vulnerability to (inaudible) and resistant organisms. And I would just like to thank everybody who has helped put this work together and all of my pediatric colleagues who could not attend today. Thank you for allowing me the extra minute. (Applause).

DR. Finn: Thank you. Do we have any questions from the panel?

DR. FINK: Yes, just more of a clarification again just to thank you for pointing out that there are no microbiome therapy products available for children, which is the case for any population. There are no microbiome therapy products approved for any indication at this time.

DR. KAHN: Oh, of course, thank you.

DR. Finn: Okay, so moving on to the next speaker is Colleen Kelly, Dr. Kelly.

DR. KELLY: Thank you for having me. I am a clinician. I have been performing FMT since 2008, but I am here today speaking on behalf of the AGA and the FMT National Registry Steering Committee. So, the AGA is a professional home to over 16,000 clinicians including research

scientists and others interested in the field of gastroenterology. In this presentation today, I am going to enter -- address work that has been done, including data on the FMT National Registry. We are going to talk about safety and efficacy in the first 250 patients treated, as well as AGA's Position Statement for Guiding Principals Moving Forward. But before I get into the registry data, I would like to just briefly step back and discuss a recently accepted multi-center long term follow up study from our group. This involved 533 patients who had been treated with FMT for C.difficile since 2011. They were contacted at various time points in follow up using a structured telephone interview as part of the routine clinical care. We were successful in contacting 208 of these people. As you can see, 10 percent of them had died. The main follow up post-FMT in this group was 34 months, but we had follow up data as long as 7 years. And as you can see, the sustained cure after FMT was 75 percent and close to half of these patients had reported use of antibiotics for non-CDI indications post FMT, though only 11

percent of them experienced a recurrence. The full paper will go into detail, but we did look into new conditions that were reported post- FMT and 50 percent of these patients reported new conditions that had developed. I listed the kind of important ones on the right. There were two new IBD, a variety of oncologic conditions and one auto immune. So, the FMT National Registry is an NIH funded study. It is an observational for we aim to enroll patients from 75 clinical sites across the U.S. The AGA is the lead organization, partnering with other professional organizations and collaborators to collect this data. It is broad based and its inclusion criteria includes patients who we have already talked about today that are often excluded from clinical trials. We used a web based platform to get patient data collected at the sites at 30 days one year and 2 years post FMT, and patient collected data was -- we aim to go on for up to 10 years. So, I am going to present to you today the first 253 patients who have reached the short term 30 day end point. And as you can see here, the majority are female and white, which we see

other C.diff studies. Most were over the age of 55, though eight percent were children and all received FMT for an indication C. difficile infection, which ranged in severity from mild to moderate and about 20 percent received it for severe or severe complicated infection. So, similar to all published reports on effectiveness of FMT in C.diff, the effectiveness was quite high. At one month after FMT, 89 percent of these patients experienced cure. Most of them with a single FMT. We actually have follow up data now on 152 patients reporting at six months post-FMT. And as you can see the long term cure is quite good, supporting that FMT appears to be a more beneficial long term solution for these patients in that 95 percent remain -- of those who achieved initial cure remained cured. Of the 14 patients who initially failed FMT, eight were subsequently cured at that six months follow up point. Adverse events were reported at one month post-FMT. There were no deaths at that time point and two infections were reported as possibly related to FMT, though the investigators at both of those sites thought it was unlikely

just because of the proximity to the FMT. They indicated possibly related. There is a (inaudible) bacteremia in a patient who had severe diarrhea pre and post-FMT. And an intro-pathogenic E.coli that came up on a multi-plex PCR panel of a patient who was having frequent soft stools, thought that to be a colonizing organism. There were -- most patients you can see, did not have any hospitalizations. And of those who did, they were thought to be most likely not related to FMT with the exception of a few patients, two who experienced C.difficacy or recurrence. One colonoscopic perforation which occurred at the time of FMT and was treated with a subtotal colectomy, as well as a urinary infection and three others which were not reported. Safety evaluations at six months out-post FMT, have -- again are available for these 150 patients. And there have not been four deaths. None of these are thought to be related to the FMT. One was a COPD, another with dementia, ovarian cancer and a septicemia. Other serious infections you can see have been reported at that

six months time period. The queries are still out as to the relatedness and we are contacting each of the sites to get more information there. And new conditions have been diagnosed in 15 percent of patients in the Registry. And the most common new condition reported has been a diary of predominate IBS, which is quite common after C.diff infection, whether or not patients receive FMT. So, in conclusion, as the FDA is determining where to go, I would like to offer and share these dieting principles which were developed by the AGA center for gut microbiome research and education. The AGA supports continued patient access to FMT for treatment of C.diff infection that fails standard therapies where there is evidence supporting its safety and efficacy. For other indications, or the weaker evidence-base, AGA supports the use of FMT only in the context of formal clinical trials or single patient compassionate use with appropriate scientific ethical and regulatory review. The AGA does not support the use of FMT outside the supervision of a licensed health professional. The AGA recognizes a continued need for

systematic data collection on short and long term outcomes of FMT for all indications including treatment of C. difficile infection. And the AGA supports continued innovation in the development of microbiome-based therapies that are standardized as manufactured products and have demonstrated safety and efficacy in appropriate clinical trials. On behalf of the AGA and its membership I want to thank you for allowing me to comment today. (Applause).

DR. Finn: Thank you. One question Colleen, on your last, second to last slide, you say you support continued patient access to FMT. I presume by and through enforcement discretion at this current time?

DR. KELLY: Correct. That is correct.

DR. Finn: Thank you. Dr. Gruber.

DR. GRUBER: Yes, I have a question. Can we bring up, I think it was your last slide, where you say that you acknowledge and recognize a need -- continued need for systematic data collection on short and long term outcomes of FMT for all indications, including treatment with C.diff? Now, we heard a little bit about your

pregnant -- sorry, your patient registry, but how do you see you know, if there were (inaudible) for a systematic data collection on short and long term outcomes of FMT for all indications, what is the process really of you know, collecting, analyzing them and really making decisions regarding safety and efficacy of these products outside of (inaudible)?

DR. KELLY: So, earlier we heard from the researchers at the University of Minnesota and the ideal of you know, in order to use the materials from their stool bank, that their mandating this collection of efficacy and safety data and safety outcomes could then be reported. We would certainly encourage patients and people to participate in the Registry and enroll their patients. I have to acknowledge though, there are challenges to that. It is quite expensive you know, despite you know, having a generous from the NIH. We do not have a lot of money to pay sites to enter that data and clinicians who are performing FMTs are very busy. So, whatever mechanism we develop really cannot be overly burdensome. It has to be just very kind of stream

lined and is easy to integrate into clinical practice as possible.

DR. Finn: Thank you. Are there any other questions from the panel?

SPEAKER: No. (Applause).

DR. Finn: Our next speaker is Dr. Khanna.

DR. KHANNA: Hi, good morning everyone. I think I had some slides. Thank you. I am presenting here on behalf of a relatively large program that we have been -- we have had since 2012. We have two clinicians, several research fellows, research coordinators and lots of patients who have gone through our program and while I have my (inaudible) slide up I will just describe how we went -- how we developed all of this. In 2012 is when I had the first hallway conversation with a colleague saying we have a recurrency of patients that need some microbiome replacement therapy. This started off from a donor directed therapy where they were using individual donors for individual patients, not cost effective, not really feasible. We moved quickly to standard donors using fresh stools and

if a donor forgets then you have got to prepped patient who cannot get a therapy. And then from that, about five years ago we have moved to a frozen stool bank where we screen donors at regular intervals. We bank the stool and we use that for patients. In my clinical practice I see between 300 and 400 patients every year who have been referred to me for management of recurrence C.diff. We look at the subset of these patients and about 25 percent of them do not truly have the diagnosis of recurrence C.diff, but they get referred to be managed for recurrence C.diff for fecal transplantation. I spend a lot of my time educating patients on C.diff because about 8 or 10 patients who I see in my clinical practice have never heard of C.diff infection before it happened to them and before it took over their lives. We do have a large program of microbiome replacement therapies in terms of clinical fecal transplants. We perform between 100 and 125 fecal transplants a year. And we are also are dispensed in several phrase one to phrase three clinical trials over the years. So, that is a little bit of background of where I am coming

from. Although for today, I am going to present on the variable efficacy of fetal transplantation, how it defers in clinical practice to open label clinical trials and to control clinical trials. And then I will talk about pathogenality of clinical microbiome replacement therapies in terms of both clinical trials and in clinical practice.

So, it has already been shown that FMT today is highly effective. Success rates are more than 85 percent in observation studies, including abnormalities and the reported success rates in trials range from 55 percent to 90 percent depending on what study you look at and what mode of deliveries looked at after a single therapy.

So, what about antibiotics? After a dose of antibiotics, the recurrence rates after three or more infections is within 50 and 60 percent. With microbiome replacement therapies, this is one of the abnormalities that was done, showed a 16 percent recurrence rate after a single infusion and 8 percent after multi infusions so, over a 90 percent success rate. We

wanted to do a study to look at what is the efficacy of a single FMT in a controlled setting. How does that differ in open label trials versus placebo controlled trials? So, we did a systematic review and metanalysis, and this is published data, where we looked at all clinical trials that included patients with recurrence C.diff who had managed it with FMT. And trials are different from each other. They have internal consistency, but one trial is different from another. We found about -- at that time we found about 13 clinical trials. There were six of them which had a controlled setting, meaning there was a non- FMT competitor group. Two Hundred and Sixteen patients who received FMT and 155 with no FMT. There were 400 patients in open label trials which did not have a control arm. These trials occurred over eight years and the follow up period is very able. They can follow up to eight weeks, although up to 13 weeks, but none of the clinical trials have extremely long term follow up and we think that perhaps after a certain of time it is a D-no if it happens again.

In terms of exclusion criteria trials,

they are different from each other in terms of number of C.diff occurrences, the (inaudible) conditions that are allowed and things that have been mentioned earlier today. But trials are consistent within the trial. And in terms of C.diff occurs after condition therapy is defined, trials are very able in terms of number of stools, the need for antibiotic therapy, what kind of stool test is required to determine is C.diff has occurred. So, these are data and I will not go into individual line items, but the overall theme here is that 76 percent was the cure rate that was seen in all clinical trials, which is numerically lower from what is seen in open label observation studies. Probably because in open label observation studies people have the benefit of getting more than one microbiome replacement therapies. These are after one therapy.

When you look at open label clinical trials the cure rates are higher, about 82 percent in open label clinicals trials which do not have a controlled non-FMT arm. You compare to trials that have an do not have -- are not open label and have a non-FMT competitor group, 67 percent. The

other part that I would like to highlight, there is -- if you look at this high square number, that 78 percent, that means that there is a high level of heterogeneity within these clinical trials just saying that methodologies are different amongst different clinical trials. So, when we did more statistical analyses we found out that overall cure rates are different and lower and random controlled trials compared to open label clinical trials. And when we look at the antibiotic cure rates, which is the efficacy and the non- efficacy comparative group, that is about 43 percent. I must also state that a lot of these trials and clinical practice, the way this works is when somebody has their third or their fourth episode of C.diff infection and you are considering them for enrollment for clinical trial or clinical practice, these patients are first treated with an antibiotic therapy. The vast majority of them respond to Fidaxomicin or Metronidazol for their initial C. difficile symptoms. By the time they are enrolled into getting clinical fecal transplantation or immunotherapy, their diarrhea has resolved.

Through a fecal transplantation the vast majority of patients is to prevent the next episode from happening, rather than treating the active infection in the vast majority. The small faction of patients in whom therapies are not working, in those patients you can use this as a primary therapy. There is a very small fraction of patients who get this in the ICU setting and those patients this could be life-saving, life- altering because medications are not working. But in the vast majority of patients' medications are working. This success rate of 43 percent does not mean medication in itself has a 43 percent success rate for the active infection or symptoms it means that recurrence happens 60 percent of the times, but medicines do control symptoms when patients are actively having symptoms. We got critiqued on this study when we published it saying that you had some trials where success rates were low and that drove your results. So, we excluded some of the trials that had lower success rates and despite doing that still the overall success rates in multiple randomized controlled trials was only

approaching 72 percent. These were the placebo controlled trials. We also attempted to compare different methodology routes in this metanalysis and we found out that single FMT (inaudible) colonoscopy was superior to enema. Enema was inferred to oral in-colonoscopy and oral delivery were similar as far as the data that was available to us in this clinical trial after, in these clinical trials after a single microbiome replacement therapy.

Moving on further, trials are different from each other, but they have consistency within. What about clinical microbiome replacement therapy? I think the clinical therapies that are out there that are done in all of our offices are different from each other. There is not an existing approved product, but I can count the number of times I have been referred a patient who has received fecal transplantation and the clinical notes say, this patient has received an FDA approved stool bank obtained fecal transplant product for management of recurrent C.diff and the symptoms have recurred. This happened to me a few months ago and we then

figured out this patient actually had irritable bowel syndrome and did not have recurring C.diff, so did not improve from the FMT. Now, I see a very small number of patients who are referred from all over the world, or all over the country for C. difficile infection, but there are probably other patients out there who may be receiving therapy inappropriately. And also, there are clinicians who I have had personal infractions with who feel that fecal transplantation is an FDA approved therapy. There is a lack of universal consensus on different methodology competence and how FMT is done in terms of how we all recruit donors, how we screen and how we prepare the donors, how the stool is prepared and how the stool is stored. How patients are prepared, where -- how patients should have the stool installation done, endoscopically capsule, colono-scopically (inaudible). Studies are all different. And in terms of follow up and end points has as (inaudible) earlier, we do not have a mechanism to follow these patients long term. At our center we do like to follow them at least up to a year and then later we have sent questionnaires

every now and then to get more follow up data from patients. This was a very nice metanalysis published about a couple of years ago. I wish I had done this study and had thought of it. This is a study that looked at different methodology competence of microbiome replacement therapies and how often they were reported in different publications that were out there. And I tried to color code them for anything that was reported 75 percent or more, I put them as green. If anything was between 25 and 75, I put them as brown and if anything was reported 25 percent or less, I put them as red. So, you can imagine there is a lot of red and brown here and we would like to see a lot of green. In terms of number of donations per donor, number of donors deliberately tracking of donors ex cetera. Same thing as student collection and processing is non-uniform, not very well reported either. Lots of red here. How do we prepare (inaudible)? How do we take stool further and stool installation? If only better reported for the skills --

DR. Finn: I am going to interrupt you now so that we can move on to the next person.

DR. KHANNA: That's fine, I can stop here.

DR. Finn: Okay, thank you very much. (Applause). All right, so our next person is Dr. Kraft, Colleen Kraft.

DR. KRAFT: This is Colleen Kraft and I am an infectious disease physician and clinical laboratorian in medical microbiology at Emory University Hospital. I view our discussion today as a commitment to our current patients and our future patients as well. In order to keep all of these patients safe, but also to allow us to have eventually an effective microbiome respiration therapeutic that one day hopefully is not fecal transplant. I agree with Dr. DuPont on that one. Seven years ago, when I entered this field I thought that by now we would have had a licensed product that you would be able to give for patients with dysbiosis, which I define as disruptive loss of our protective bacteria in our intestines and that result in C.diff infection from this dysbiosis. At Emory Hospital we performed our first FMT for C.diff in 2012. And for five years I myself recruited and screened all

of our stool donors, mixed the FMT product myself with some of the same experiences as Dr. Khanna and kept track of all of the clinical outcomes for what became almost 300 patients. I knew all of the donors personally and along with Dr. Tanvi Dhere, my gastroenterologist colleague, we kept very close track of our recipient patients. We published in 2014 a case of diverticulitis that occurred after one of our FMTs for C.difficile to be able to inform others what we had experienced. We have been, and continue to be, retrospectively evaluating outcomes in our patient cohort. Focusing on at risk individuals including older adults and immune depressed patients. We have contributed our outcomes dated to multi-center retrospective chart reviews lead by Dr. Monica Fisher and others. Specifically looking at solid organ transplant recipients and patients with cirrhosis to be able to have larger numbers to determine any safety concerns or signals in these patients. On a more national scale that you have already heard from Dr. Kelly, this is also the hope of the AGA Fecal Microbiome Transplantation National Registry what it hopes

to achieve. It maybe that our prospective studies need to accommodate the evaluation of some longer term outcomes. We appreciate the opportunity at Emory to be a site, courtesy of Dr. Nadine Rouphael at our institution in the prospective DMID 130045 Study through the VTEU. That is prospectively studying long-term safety longer than 24 weeks, so, going up to one year. It is typical for many of our studies. The longer term studies are expensive and time consuming, but we are hoping that the knowledge gained in this VTU study will help us with resolutions on some of the current concerns that have been voiced today. While we have studied in our own patient cohort the durability after FMT for up to four years in some of our patients, we did find that there were no new medical conditions attributable to the FMT. However, this is limited by a retrospective survey and not in prospective studies as I have already discussed. For our current patients those of us who have been able to care for individuals with recurrent C.diff infection have been able to appreciate the quality of life improvement after FMT when

someone no longer has refractory diarrhea. And it is true that there has been variable efficacy. That has already been discussed by Dr. Khanna but has also lead to the determination of other medical problems as is also discussed by Dr. Khanna in a population where a few years no one would have even performed a colonoscopy in someone who carried a C.diff infection diagnosis. For instance, we recently had an individual, one of our clinical trials that was diagnosed with amyloid and I really believe that it is because of the interaction with specialists and people that knew to continue to test the patient for C.diff to understand the limitation of our therapeutics and to continue to look for other causes of diarrhea that are allowed that diagnosis to occur. I think that patient would have undergone indefinite C.diff treatment because of not being tested again. This has not been very emphasized in our literature, this sort of secondary gain from a better understanding of FMT and C.diff infection, but I think it has been a dramatic clinical practice change, at least locally, at Emory Hospital where we are much more

savvy about what our patients actually have.

For our future patients our investigation of the intestinal microbiome has allowed us to gain knowledge that the therapeutics that we give our patients, mainly antibiotics as an infection disease physician, their chronic illnesses and their nutrition all contribute to incredible intestinal dysbiosis. I am going to warn that as we discuss the risks of FMT, we have not even begun to scratch the surface of the risk of persistent intestinal dysbiosis and what that means for the risk of sepsis potentially, and also the risk of carriage of MDROs. This disruption of our gut garden even simplistically, allows the weeks of C.diff and multi drug resistant organisms to grow up, which studies such as Dr. Eric Pamer in his (inaudible) stem cell patient recipient populations have demonstrated risks from basic infection with persistent dysbiosis and persistent colonization. It is important that as we continue to push this field to understand the risks of an altered intestinal microbiome and find efficacious and reproducible ways to correct

it. We owe it to our patients to find a microbiome therapeutic that can restore our homeostasis, prevent further infections and I believe that will also reduce the pressure on the new antibiotic development needs by restoring the gut microbiome to more wild type diversity. We need continued focus on the right donor and right recipient. The publications of the individuals that were infected was very insightful to understand that a thorough clinical strengthening had been indeed performed on the donor. And I also would have clinically thought that the donor was very low risk. It is clear that the recipients were at very high risk, one patient with decompensated liver cirrhosis and another during the time of their hematopoietic stem cell transplant. I do believe though, that we can mitigate this risk in these fragile recipients. As a clinical microbiologist we can selectively culture as we have been doing at Emory, for Vancomycin resistant Enterococcus extended spectrum, Beta lactamase, Enterobacteriaceae and Carbapenem resistant Enterobacteriaceae. These are clinical

laboratory protocols that can validated and utilized to prevent such infections. In the study that Dr. Michael Woodworth and I have undertaken in renal transplant recipients, it is under FDA IND. We have even sought out CNBIGG negative donors. And we also monitor for recurrent herpes infection reactivation in our donors during collection and release testing. Again, we have determined the highest risk of transmission and concern for our recipients and we mitigate through laboratory testing. In summary we need to continue to pursue microbiome therapeutics. We need consistent follow up on our patients. We need to continue to study and understand the unknown risk of persistent dysbiosis. We need a continue focus on right donor, right recipient and we can mitigate the risk of the FMT through laboratory testing. I appreciate the opportunity to speak to you today. (Applause).

DR. Finn: Thank you Dr. Kraft. Are there any questions from anybody on the panel? Dr. Fink.

DR. FINK: I have one question. I

apologize if I mis-heard or misunderstood you, but could you just clarify, are you proposing use of FMT treatment and documentation of a negative response as part of the standard approach to diagnosis of conditions that might mimic C.diff?

DR. KRAFT: Maybe not that formerly. I am proposing that our understanding by using FMT to try to correct the dysbiosis in many of these patients has lead us to pursue other causes of their diarrhea and causes of their illness. And this did not happen typically -- I will just want to speak from the perspective of Emory because I do not -- we have not studied this nationally. But in general, we never would scope or evaluate individuals that had a C.diff positive. That was their final diagnosis and we stopped there. And so, what I am saying is that we moved on to other diagnoses because we had a better understanding of how we could eliminate and restore microbiome and when that did not work, then we moved on to other causes.

DR. FINK: Okay. So, I guess the follow up question would be, having you know, realized this now as you have changed your

diagnostic approach at all, you know, prior to recommending to FMT?

DR. KRAFT: It has changed our therapeutic approach. Our diagnostic approach remains the same in terms of PCR for C.diff, or PCR in toxin for C.diff. Our therapeutic approach is just to note that if people are in a cycle of recurrence and if they undergo FMT and they do not respond that we continue to look for other causes.

DR. FINK: Thank you.

DR. Finn: Thank you. So, now we are moving on to hear from our patients and patient advocates. Our first scheduled speaker is Christian Lillis. Thank you.

MR. LILLIS: As I am the first patient advocate to ever speak at one of these things, I may go over 10 minutes and I hope you will indulge me and that the audience will have tried to keep this fairly concise.

Judy Dexter, age 70; Donald M., age 52; Arnie Stone, age 87; Richard Progue, age 48; Mary Regina Burman, age 85; Edith, age 92; Josephine, age 79; Gail Memma, age 64; Joe Tardar Bono, age

51; Peggy Lewis, age 56. All the people I have just named died from a C.diff infection over the past decade. Some like my mother, died before FMT was in wide spread use. But others have died since, either because it was not offered in time or it was not performed properly. They represent the tens of thousands of Americans who die every year from this largely treatable infection. For comparison, more people die now from C.diff than from HIV AIDS, drunk driving or MRSA. We started POF WHEN FMT for C.diff was in its infancy. By the time of the source of our mother's infection was diagnosed it would not likely have saved her. We have watched as its use has proliferated. We were excited that there was a treatment that finally was available for 20 percent of C.diff suffers who do not respond to typical therapy. We were happy about the rise of biotic companies taking fecal transplant to the next level. And we have relations with many of these companies and with provider run and independent stool banks. I want to be absolutely clear. No one wants a fecal transplant. The sheer desperation it takes for someone to agree to have the poop of another

person transplanted into their body is mind boggling. But if FMT been an option for my mother in 2010 I would have asked the doctors for a bed pan, a bucket, and some privacy. We have always seen FMT as an intermediary step where we develop safe and effective microbiome formulations that can be safely grown. But I am frustrated that it has taken over six years and three draft guidances to get us this far. I am also angry. I have been angry every day since my mother died nine and a half years ago. I am also angry that after six years -- six years after F Tier released its first draft guidance you are still collecting data. Worse, it continues to be presented as just a question of science. But public policy is a moral and ethical pursuit. From military to housing, to drug approval we constantly aware of the potential benefit against the likely risk through an ethical and moral lens. FT has updated its draft guidance twice. The 2014 update illustrates where science stops and policy making begins. In it providers were told to use donors known to themselves or the recipient. What is the scientific basis for that? There is

not one. Just as there is no scientific reason why I, a healthy adult male, who has been with my husband for 18 years cannot donate blood. I could if we abstained from sex for a year, again, where is the scientific explanation? If married heterosexuals had to abstain for a year to give blood, you would see a near cessation of blood donations. Since very few people would forego sex for just a year so they can donate blood, it is a defacto band. There is a similar dynamic between the gay blood band and the lack of progress in regulating FMT. Though gay people have won broad acceptance and rights since HIV lead to the blood band in the 1980s, the same cannot be said of feces. There is no pro-pooh lobbies spending millions of dollars so people can have access to it. In fact, I can tell you most fecal survivors do not want to discuss the shit, but we have to. Both here in the realm of public policy and more broadly so that people are aware of C.diff. And to do so, we need FDA to be more forthcoming. Following the FMT safety alert in June on the death of the immune compromised recipient, lots of folks panicked.

We heard of people who were set to get an FMT but they were now afraid to. I know that at least two doctors who stopped providing FMT because the laboratory testing was cost prohibitive. For 139 days FDA provided scat details. No information was released on who was being treated, the status of the patients or the facility where the breach happened. Then on Wednesday a thorough but somewhat self-serving article was published in the New England Journal of Medicine. I really bristled when I read on the cover a Dr. Elizabeth Homan say that she and her colleagues wanted to set the record straight. With all due respect to Dr. Homan, it is not up to her whether half a million people who are struggling with C.diff this year find out the accurate information they need to make an informed decision to take an FMT, to join a clinical trial or any other treatment. That is the FDA's job. And it is not Mass General's decision to keep this information from the public and you had no right to sit on it. Since 2013 and estimated 150,000 people have died from C.diff. How many were prevented by an FMT or one of these

clinical trials. We do not know for certain, but I would guess it is several thousand or tens of thousands. Whatever regulations you ultimately finalize and enforce must take into account two things: The need to move microbiome therapies beyond fecal transplant as it is currently practiced and the need to maintain access to FMT patients who need it. So, how do we trend this needle? The answer is patients, patients of doctors, not patience. I am not sure how many of you were at FDA during the explosion of AIDS activism in the late 80's. Back then FDA was even adept to engaging patients. But actives fought to be listened to, to have a seat at the table and to be part of developing the policies to guide treatment and permit them access to drugs. When actives were shutting down highways and egging the façade of the FDA's buildings I know that was very disruptive, but people were fighting for their lives and it opened the space for so many advances in HIV medicine. A former microbiome executive who worked in the AIDS development in the 1980s said that he couldn't believe that actives were targeting the drug (inaudible).

Why, why were they bothering him? Why were they yelling at him and his colleagues? But he told me that in hindsight, those activists the best allies his companies could have had. They made sure that FDA, CDC, and NIH all got more funding. They changed policies so that things could happen more quickly. In fact, many of the policies that we are currently using to speed microbiome therapy development have their roots in AIDS advocacy. I know you all mean well. I know you are over worked and under staffed, that why a few of us advocates every year advocate to secure more funding and resources for FDA, CDC, and NIH. I know that everyone in this room is here because you want to help in this epidemic. But where C.diff and FMT is concerned you have done a pretty crap job of including patients. This is the third FMT public hearing, but only the first where C.diff speaking and then an actual patient advocate is speaking. That should not have taken six years. In that 6 years how many times have you had public testimony from C.diff patients. How many times have you solicited input from us? And how many times have you heard from academia

industry, lobbyist, whoever? And I understand that technically this is a public meeting and I do generally appreciate the effort made to invite me and Catherine here. It is a good start, but it is not enough. We need you to do better, not just on FMT, but on all C.diff treatments. As you know, and for good reasons, companies that are in the process of developing treatment cannot engage patients in their clinical trials, but we do. The Peggy Lillis Foundation is more than 40 active and trained advocates and nearly 1,000 families and patients who have survived C.diff in our network. You can engage any of these people to obtain the real world experiences of C.diff patients which guide policy just as must as scientific evidence. By the time I get back to Brooklyn tonight I will have spent about $600.00 to be here and if I was not the head of a C.diff related advocacy group, I would have taken a day off work. Sixty-three percent of families do not have $500.00 to cover an unanticipated emergency. Let alone come to Silver Spring, Maryland for a public meeting, but you could bring them here. Organizing around infectious diseases is

difficult because they tend to be acute. People either recover or they die. Most people do not embrace an identity around them as many do being a cancer survivor. Adding to that difficulty, most people, some 70 percent have never heard of C.diff, despite it being the most common health associated infection. I realize I have been a bit harsh. I hope you take it as the tough love that I intend. The future of FMT development has to engage robust engagement with patients and families on the front line of the C.diff epidemic. C.diff must be treated as a national emergency. You can make that happen. So, do it for Judy, and Joe, and Gail, and Donald, and Betty, and Peggy. Thank you.

(Applause).

DR. Finn: Thank you very much for that perspective. That was very important to hear. I think maybe have comments at the -- from the panel? No? I would like to make one point of clarification. You made your remark to the effect that FDA did not provide further information in its safety alert. And I would just like to point out that FDA, when something

happens under an IND or in the context of an IND, FDA is constrained in what it can say. So, just -- and I think we have next speaker up to the podium. This is Catherine Williams. Thank you. I think we heard from you before at a previous meeting.

MS. WILLIAMS: Yes, in 2013.

DR. Finn: Yes, thank you. Can you just make sure that you pull the mic down just a little bit so that we can hear you? Thank you.

MS. WILLIAMS: Hi, some of you may remember me as Catherine Duff. You may know that in 2013 I came and told my person of C.diff which involved eight episodes of C.diff over 7 years and basically took away my life for that entire time. It was not until the seventh and the eighth year of my journey that I was offered FMT and it saved my life, and I might have promised then that no other patient should feel as alone as I did in that battle. A lot of things have changed since 2013, but the most ironic thing today is that six and a half years later we are still fighting the same battle. As some of you may know, following my battle, I started the Fecal Transplant

Foundation. It started in order to provide education, increase awareness and advocate for patients and for the science of FMT. With the increase understanding of the importance of organisms that inhabit our bodies and following my participation in the NIH funded MT working group, the Foundation's focus has now expanded to include all micro biotic transplantation. We all know that life is nothing if not continually changing circumstances. In 2013 I was married, had two very small grandchildren and blessed to still have both my parents. But as Jerry Garcia writes, what a long strange trip it's been since then. I am now single, but I now have eight grandchildren. The youngest, six weeks old in Arlington Virgin, and that on November 21st of last year, the night before Thanksgiving, I lost my mother. And although that was the saddest day of my life, my family and I did not mourn her passing, but rather celebrated her long, well-lived, happy, pain free life. Her death was not a tragedy, but part of the circle of life. Peggy Lillis' death was a tragedy and the two friends that I lost to C.diff before I started the

Foundation were tragedies. Their doctors did not even recognize that they had C.diff. And in Frankfort, Kentucky there was no hope of them retaining an FMT. The actual cause of death was not found until their autopsies. These were both young men in their 40s and 50s. I miss my mom terribly every day. But we continue to celebrate her death while we learn that many tens of thousands of deaths every year from C.diff. My parents were married for 70 years. You do not see that much anymore. So, my mother and I, my father, her 5 grandchildren and her 10 great-grandchildren take great comfort in the knowledge that her life was full and long and happy. Perhaps if Peggy Lillis' physicians had diagnosed her C.diff earlier, or recognized her sepsis earlier, she would still be here. The lack of awareness of C.diff remains the first and biggest problem about C.diff. Though all that has happened, my dedication to helping patients and fighting for FMT has not waivered much to the chagrin of you here. But thankfully my desire to listen to patients and to my own heart and convey their situations and concerns has not changed

either. We have heard from my experts today from industry, academia, medicine and research, and my fellow advocate and dear friend, Christian. I had an inkling of what was going to be said today as I was preparing my remarks and unfortunately, I was pretty correct. Those who have seen the amazing power to quickly heal dying patients want continued access for FMT for people with recurrent C.diff, not responding to antibiotic therapies. And those who were primarily focused on financial profit would like nothing better than for enforcement discretion to end and access to FMT be denied so that there is a clear, easier path to profitability for their products. I have been on this earth a long time, long enough to know that each person on this earth is different and each patient is different. I what a wonderful, curious thing that is. And so, we need all the products. We need FMT. We need Vancomycin. We need difficile, we need Zinplava. We need the C.diff vaccine. We need the series of Rebiotix products. But at this time there is no other product that is as safe and efficacious as FMT. There is no denying that there is much still to

be learned about FMT. As many have said, we do not know what we do not know. But there is no denying that FMT at this time is the only thing that consistency works for between 80 and 90 percent of people with recurrent C.diff. And as we also know, the problem of antibiotic resistant bacteria continues to be a huge threat to the existence of mankind. At the PACCARE meetings the stated need was for novel, non- antibiotic treatments for bacteria that was resistant to drugs. I will never forget my frustration at presenting the facts about FMT and having those facts dismissed or ignored by most of those committee members. I purport that FMT is still a novel, non-antibiotic method of addressing drug resistant bacteria. That is not being utilized as it should be. Some of you here have said, and continue to say, that FMT is no more effective than placebo. I have had words with many of you who have said that. We all know that is currently what is known as an alternative fact, meaning, it is not true. As you continue to present that information it is ludacris, demeaning to patients, and does nothing to further your

legitimacy or credibility. In fact, it erodes it. We all know that recruiting subjects for clinical trials for C.diff is different than recruiting subjects for other non-acute conditions. Many of you may not know that I have been contacted by several patients who have confided to me that they were told, sign here if you want FMT, only later to go home, read the paperwork and realize that they were enrolled in a clinical trial without their fully formed consent. This is immoral, unethical, and properly illegal. We have heard not only the tragic death of the patient earlier this year falling n FMT. He was an already immune-compromised patient, where the material was inadequately tested for MDROs, but also of other patients saying they developed various problems following FMT and there are many of you who are quick to blame FMT on all those problems. But no one hardly ever talks about is that the problems caused by the current enforcement policy -- enforcement discretion policy, the particular language due to its lack of clarity and specificity, leaves treatment protocols up to the

discretion of providers. Most providers do not live in the verified world that those of you inhabit. They do not keep up on the latest research. They do not go to the AGA website and check it out frequently, or the IDSA, or the SFAR. Most providers have too many patients, too little time, too much paperwork and too little institutional support. This results in confusion and lack of awareness about the most recent recommended treatment protocols. With the result research and it often leads to horrendous protocols, compounding possibly permanent damage caused by C.diff or the antibiotics used to treat it. There is permanent damage being done to patients by multiple long term administration of antibiotics and various strengths and lengths of duration. You have probably heard me say, if you have heard me speak before, that in one year alone my insurance company, Tri-Care, was billed $275,000 dollars for Vancomycin for that one year and remember I had a seven year battle and unfortunately that is still not atypical. Most patients who eventually having FMT tell me that before their

FMT their doctor required them to fail multiple rounds of increasing strength and treatment durations of both Vancomycin, Flagyl, Difficid, followed by various methods of tampering and pulsing these drugs alone or in combination. And so, we continue to hear from many patients who are left with tinnitus, neuropathy, neurological conditions, reactive arthritis, all of which I suffer from and these happened to me and other patients because I did not receive FMT in a timely manner. Also, in regard to the current enforcement discretion policy, many doctors do not understand that the draft guidances issued by the FDA were never instituted. So, many of them believe that they are no longer allowed to use stool banks and that they must come up with a donor who is known to the patient. As we have heard, less than three percent of people who think they will qualify to be donors at open biome actually qualify. So, you can imagine the complications of a normal person identifying at testing and procuring FMT material from someone they know. The odds are statistically impossible to claim. The result of this misunderstanding by physicians

results in decreased access to FMT, which results in increased mortality and morbidity. Also, many insurers still refuse to cover FMT because of its remaining tag as an experimental procedure. It is certainly no longer an experiment that between 80 and 90 percent of patients undergoing for recurrent C.diff not responding in the standard antibiotic therapies have a complete resolution of their symptoms following FMT.

DR. Finn: How much longer do you have? We are quite over time. Just a few more minutes?

MS. WILLIAMS: In regards also to the enforcement discretion policy, it has resulted in further denial of access because many doctors, rather than try to understand the current policy, have just quit doing FMT. It is time to allow people to have FMT for many other indications also, with fully informed consent. Companies have no problem getting FDA to approve medications with black box warnings. Physicians have no problem engaging in procedures that have extremely high rates of complication. And yet we continue to fight this battle for an amazingly

effective and efficacious treatment. I can tell you that I hear every day from patients around the world who have had an amazing resolution of symptoms for almost any condition you can think of that FMT is currently being used for. However, those patients are only able to access these other clinics around the world if they have the financial resources to do so, which is very few patients. As we move forward while we are just beginning to understand the importance and significance of our biomes and the organisms that inhabit them, we can no longer deny that for now FMT, VMT, and other microbiome transplantations are likely to be key features in the future of medicine. Thank you to everyone who cared enough to attend this meeting. Please remember that the reason we are all here are patients. There are patients out there depending on FMT for their very survival. And please do not forget that the next patient could be you or a loved one. And would not you want to have FMT to try to save their lives. Also, it is untenable that patient advocates are not included in every aspect of consideration of this procedure and others. Let

us make sure FMT remains accessible. Thank you. (Applause).

DR. Finn: Thank you very much. It is very important to hear from patients and patient advocates. Does anybody on the panel have any questions? Okay, then I would like to move to the open public hearing part and I know we have some people signed up. We have seven people signed up. I am going to allocate five minutes each on the timer. To remind those people who are speaking, you have five minutes. The yellow light on the podium will go on when you have one minute left and I will cut you off after five minutes when the red light comes on. So, the first speaker that we have is Anna Wexler, Dr. Wexler from the University of Pennsylvania. If you could make sure that you introduce yourselves, just say where you are from just to verify that I have got the right name with the right person. Thanks very much.

DR. WEXLER: Thank you. Yes, I am Anna Wexler. I am from the University of Pennsylvania. I am a social scientist and a bioethicist in the Department of Medical Ethics

and Health Policy. Much of my research focuses on do- it-yourself medical movements, where individuals use experimental treatments on themselves in their own homes. Largely outside of physician oversight. And as we have already heard today from several speakers, there is a population of individuals doing FMT at home to try and treat various ailments. There is not much known about this population. However, there is a study by Colleen Kelly's group, myself and a few others that is hopefully going to be published soon that really takes the first empirical look at what has been called Do-It-Yourself, or DIY FMT. And what we have found, I would say perhaps not surprisingly because we see this in other DIY medical movements, is that the key factors that drive people to do this at home are the lack of access to healthcare providers, prohibitive costs, and frustration at the lack of effective treatment. And in some follow up work that I have been doing, an interview study of physicians who provide FMT, what I have been hearing across the board is that the DIY movement seems to have had two phrases. What I like to think of as the early

phase, is when people were doing FMT at home, mostly for C.diff because they cannot find a nearby provider, they really just did not have access to the treatment at all. But as FMT for C.diff has become more accessible and I think this is in large part due to FDA's enforcement discretion policy, those who need FMT for recurrent C.diff seem to have been able to access the treatment more widely. And so, I think what we are seeing now is the makeup of the DIY movement has shifted, there is still a population who seeks it out at home, but they seem to be comprised of individuals seeking it out for indications other than C.diff. So, why should we care about what people are doing at home? Well, unlike most, if not, all of their products are medical products, I should say that FDA regulates. The substance in question here is one that is and will always be widely available to the public. And because of that, I think in tandem with the safety and efficacy issues that we are considering here today, it is really crucial to consider the social and public health consequences of regulation especially as they relate to the impact on home

use. Or another way of thinking about this is what the unintended repercussions might be outside of the clinic. For example, if the impact of regulation is that there is a higher cost or less access to FMT, which I think is a very real possibility in some of the proposals that we heard today, we may end up in a situation where very sick and very desperate patients will be weighing the cost of getting FMT done from a physician or doing it themselves at home. And I am really concerned that we would see a resurgence of home or DIY use. And finally, I just want to say I have not really heard this brought up today, but I think there is a lot of work to be done in terms of patient education and communication. Again, this is -- we are talking about a substance that will always be readily available to the public. We cannot regulate what people do in their own homes. And so, because of this, in tandem with thinking about regulation, I think that both FDA and professional societies here should consider what more can be done to educate and inform those who might be thinking about seeking FMT at home. Thank you. (Applause).

DR. Finn: Thank you for that. Any questions? No. Okay, then moving to the next person, trying to read this here. Dr. Feuerstadt.

DR. FEUERSTADT: Thank you. Yes, Paul Feuerstadt. First of all, I would like to acknowledge the FDA for taking the time today, but also all the speakers. I think we have really had a nice group of individuals to give a nice round approach to this in the thought process. I bring a little bit of a different thought process here, in that I am part of a hybrid practice. I spend about a quarter of my time in academia teaching residents, fellows, medical students, etc. But then I spend 75 percent of my time in a private practice. So, I see both quaternary care patients, but I also see kind of primary and secondary care patients, more simplistic disease, but also much more complicated disease. I trained with Larry Brant in the 2000 time frame and he was one of the original thought leaders, at least bringing sort of the public idea of fecal microbiome transplantation being both safe and effective for the treatment of multiply recurrent

difficile. So, for me training under him, this was just the logical extension of treating patients that had really multiply recurrent disease or refractory disease. As a provider though, when I got into the community I took a couple of steps back and I reviewed the literature and I realized that there is a balance. There is a lot of patients that could really benefit from anti-microbial courses if given appropriately. But unfortunately, as I developed my practice and as I was an individual who moved off and moved away from my original training, I was one of the few providers who is interested in C. difficile. So, a lot of patients who had multiple occurrences were referred to me. And I think it is Catherine Williams, a couple of speakers ago, referred to, there is a lot of inappropriate anti-microbial use. And that inappropriate anti-microbial use in the community results in depletion of the microbiota in patients that cannot get rid of this infection, specifically wiping out the spore phase through strength of microbiota. As a result of this, I of course, had to do quite a few fecal transplants. And following your direction

a number of years ago, I went to the Yale Human Investigation Committee and I got the equivalence of an IRB approval to do this procedure, became the only one in the New Haven area doing this and the rest is history. Now I see about 300 to 400 patients a year with pretty much multiple recurrency difficile coming to me saying, I need fecal microbiota transplantation. And, of course, as we have heard already today, a lot of these individuals have not exactly been worked up appropriately yet, or might have gotten inappropriate microbials so, we removed an element of those patients who have IBS, or have other diagnoses, but still a lot of them are appropriate for fecal microbiota transplant. Of course, it is also important that these patients are coming to me not just for c. difficile but for other indications that was also alluded to earlier. And I always say we have to follow what the FDA says. You, all of you sitting at this table today have a really significant impact on all of us who are treating patients in the community and in healthcare systems. So, earlier this year, when you came and you issued

that guidance recommendation, that warning about patients who were immune depressed who ended up with multi-drug resistant sepsis, I had to take a step bank and I had to stop doing fecal transplant, at least the old way, colono-scopically screening donors. I had gone to the (inaudible) a couple of years ago and I said to them, look, I could certainly go to a stool bank right now and treat patients much more efficiently and effectively. And they looked at me and they said, well, what is the data behind the stool bank? And I looked at them and I said, well, they quote a 79 percent efficacy. And then they looked at me and they said, Paul, what is your efficacy? I said, it is 98 percent. They said, well, help us understand what the delta is, why would you use an inferior product? And my answer to them was, we have to realize that a lot of the patients that are being treated might not have been diagnosed properly. It is not a reflection necessarily of the stool bank quality but might be the indications. And they looked at me and they shut it down. They said, Paul, you have an efficacy that is excellent, why would you change

what you are doing? Well, a few months ago with the recommendations or the issuance that you made, I did shut it down. And I say, well, where does that leave me as a provider? As a provider, sure, I have prospective, randomized control trials that I can offer patients the opportunity to participate in. But, those inclusion criteria are really narrow. Certain companies offer opportunities for patients to gain access perhaps if they are not participating in the trial. And I understand fully just how complicated this is and we have heard multi different angles on this today. And I think it is up to you, as the FDA, to think really long and hard about what you have heard today and about access and availability. And the final thing I am going to say, just sort of piggy backing on the last speaker, was, one of the things that I did today, was I lived tweeted this event. With each speaker I put forward the most important bullet points. I tried to do it in as level a sense as possible. And within about an hour, I had a patient re- tweet back to me, well, I have recently done a home do-it- yourself fecal

transplant on myself. Why? Access. And I will leave it at that. Thank you so much for your attention.

(Applause).

DR. Finn: Thank you very much. Any clarifying questions? No, okay. Our next speaker is Eugene Yen. Dr. Yen, and North Shore University Health System, if you could just confirm that?

DR. YEN: Yes, thank you. My name is Dr. Eugene Yen and I am a community based gastroenterologist out of Chicago. I am going to try not to copy everything that Dr. Feuerstadt had said just because we are in very similar practice environments and see a very similar patient population. I was at the FDA hearing in 2013. And to echo the last few speakers, had access issues to FMT. They have approved, but they certainly have not changed. What has changed is that we have saved thousands of lives, patients with FMT. What has also changed are the IDSA guidelines for C.diff therapy. Dr. Khanna earlier had mentioned that that folks on oral therapies do well on C.diff and I agree with that,

but C.diff is multiple recurrence, so, what I would also emphasize is that besides the mortality and morbidity that I see and experience with patients with C.diff, probably the second most common thing that both the patients had said, was the devastating financial effects of this disease, and currently our first and second line courses of therapy whether it be a 10 day or a 6 week course of therapy can run patients in the hundreds or thousands of dollars for each course. Again, illustrating the importance of access to FMT, or a high volume site. We offer FMT under FDA guidance. I support ongoing enforcement discretion. We are one of the highest enrollers for clinical trials. So, we are just one example that these forces do not have to be mutually exclusive. For example, I specialize in the care of patients with inflammatory bowel disease. So, a lot of my recurrent C.diff patients have concommon IBD and would have been excluded from clinical trials. In addition, at our institution about 40 percent of our patients fulfill a wrong criteria for irritable bowel syndrome, either pre- existing or irritable bowel

post infection. So, while enforcement discretion and safety data are crucial, we are also involved in the AGA FMT Registry. Aside from the Registry, for the past decade we have collected safety and outcome data after seven days, after one day, after seven days, after one month, and then every six months, and annually. Trial enrollment is challenging for nearly all studies across all disease subtypes. It is a matter of collecting correct sites and investigators who can navigate the nuance nature of treatment pre and post-C.diff infection. With great respect to my colleagues in the room, recurrence C.diff infection is mainly a community-based problem and I am here to represent the clinicians in the community fighting this disease. In the setting of hospitals with local stool banks like mine, but also industry and universal stool banks who have been improving access to this life saving treatment. As a major metropolitan city, we are still one of the only programs regularly doing FMT in Chicago. And while I feel privileged to be surrounded by people and individuals and

organizations who are earnest and passionate about curing this disease, we as the actual practitioners do not have the luxury of waiting if access is limited while a licensed product emerges. So, I just wanted to thank everyone for allowing me to speak and for the patients for your testimony today. Thank you. (Applause).

DR. Finn: Thank you very much. Our next person who signed up was Dr. Byron Vaughn from the University of Minnesota. Again, please correct my pronunciation.

DR. VAUGHN: You are correct, Byron Vaughn from the University of Minnesota. I first just want to thank the members of the panel for allowing this. You guys have a very difficult job as regulators when you do your job well nobody notices, and so thank you. I want to highlight two things that I think are important to remember from today, and one phrase that I have not yet heard which is, standard of care. The IDSA Shea guidelines came out with a strong recommendation with moderate level of evidence for use of fecal transplant for second or more recurrence of C. difficile. And that is really I think, one of the

best examples of the community sense of how effective and useful this is. In my mind effectiveness is not really a question anymore for FMT. We know that it works. And to think that we need to study with further placebo controlled studies I believe is an error. It is obviously the choice, I think, of anyone in this room who had recurrence C.diff would absolutely choose an FMT. We do certainly need more data on safety. And safety is always a challenge in general, randomized controlled trials do not provide sufficient data on safety because they are designed to answer a specific question and a lot of our safety data does come from post-approved marketing studies, phase four drug trials. I think it is important though to realize that as we have a standard of care for C.diff that we need to be very careful in what we are allowing to be studied in the future for non-FMT products. When we compare a defined consortium or a different type of bacteria vag or virus or something else for C.diff, it really should be compared against full spectrum FMT product like you would see from a donor bank. So,

I think it is really just an important point that I want to make sure is conveyed that, in our community we do really think that FMT is the standard of care. It would be great to have a product that is fully licensed and FDA approved and reproducible like a drug, I think to get there though we have to demonstrate that it is non-inferior to FMT. And so, until that time comes I believe that we need to have the ability for stool banks to obtain FMT while at the same time, continuing to do safety studies. Thank you. (Applause).

DR. Finn: Thank you very much. Any questions? No? Okay. Our next speaker is Sabine Hazan.

DR. HAZAN: Okay, I will hold it. I am Dr. Sabine Hazan and I am a gastroenterologist in Malibu. And I have been doing clinical trials for 25 years plus, since my age. I am here because Steve Jobs said, it does not make sense to hire smart people and tell them what to do. Today, I say, it does not make sense to give a doctor a medical license and not let them practice medicine and do FMT when they feel it is

necessary. FMT is a patient-doctor relationship. A time where we as doctors tell our patients the risk of a procedure versus benefits. A time for conformed consent, a time for patients to choose quality of life versus quantity of life, and a time for patients to insert their number one rule of medical ethics freedom of choice. Twenty-five years ago, I was doing clinical trials on antibiotics, and antibiotics was the trend. We did the antibiotics for everything, acne, Crohn's, everything. Then two years ago it was biologics. Biologics for everything and in fact, I have done all the clinical trials, psoriasis, Crohn's, you name it, C.diff, Monoclonial anti-body, for every condition. And now we are in the microbial business. When we get in the microbial business and we have no idea how did it change, I get a little bit nervous as a PI. C.diff was kind of my bug in the clinical trial world. People would come to me or, sponsors would come to me because I had a high ability to recruit patients with C.diff. And I do not know why that bug came in. I think I blamed Dr. Neil Stollman for that

because 25 years ago I was at a posture at ACG, and he said the microbiome, not to say sh.t is the future. And I said, Neil if you make me play with it I am going to hate you. And sure, enough he did make me play with it. So, what happened was, I really did not want to do it because what doctor wants to play with poop, let us be honest. But what happened is, when clinical trials failed from my patients with C.diff and I felt to trust me with a disease I had to do something. So, the something was fecal transplant and what I have come to discover after 16 plus years of fecal transplant is, it actually cured 99 percent of my patients. Now, I do not have time as a mom, and as a gastroenterologist to a high population, and as a clinical trial doctor to write my data. However, the other data is that not only that it cures C.diff in 99 percent of my patients, but it improved 2 of my patients with Crohn's disease, 1 Alzheimer's, 2 Psoriasis and kept one of my metastatic mesothelioma patient who I submitted an IND to you guys through my portal, alive for 29 months. In fact, the longest metastatic mesothelioma that has ever lived, have lived only

16 months. Now how does it do it? So, I set myself on a path, because sticking mud on a wall and hoping it would stick does not really fly with me. So, I decided, well, you know, I have got all these patients that have been improved, let me send my stools to different labs. So, here I am sending it to you biome, biome, biome and all these other labs, and I got different results from my stool samples. So, I said, well, that is not really standardized. In fact, I even became a voice on the Microbiome Congress showing the problems of the microbiome world in the clinical trial setting. In fact, even at NIST's (inaudible) Jackson will be the first one to say it, the microbiome testing is far from being standardized. So, I created a laboratory that is cap and clear certified. I embarked a bunch of doctors, a lot of them are in this room, they do not know that they are part of the lab, but I decided that we are going to do a valid, verified, reproductible, I will say that looks of the microbiome at the specie level. So, we have 22 clinical trials going on right now looking at the microbiome per disease with the IOD, and believe

me I realize that I am shaking the beehive here, but it needs to happen. We started six months ago and we already have preliminary data. So, I am going to show Exhibit Number 1. Catherine, do you want to help me to pass this to these gentlemen. Preliminary data, we identified non-toxigenics. C. diff is in all of us. So, this is randomly picking a bunch of patients that came to look at their stools with my lab and out of 121 patients and now we are up to 300 patients, we identified non-toxigenic C.diff in everyone. So, what does that mean exactly? Does that mean that everyone has C.diff and we should all worry and go do fecal transplants? We do not know. We are at mile 1 at 300,000 miles here. So, what we did -- what I suspected is probably maybe what we thought and we look at the data and C.diff is actually a 10 million year old bug. Why is it all of a sudden is it killing everyone, and especially if it is in our gut maybe it is the hamburger full of antibiotics that we ate the night before that actually caused it, or caused its family, or caused C.diff to secrete the toxins.

DR. Finn: Excuse me, your time is up.

DR. HAZAN: This is very important. This is autism and I think people, parents -- one in 56 kids has autism. Does the consideration of fecal transplant and autism -- we need to see the data. This is a mother with triplets, you can see at the second level --

DR. Finn: I really encourage you to submit this information to the docket so that everybody can see it. And everybody who accesses the docket can see all of this.

DR. HAZAN: This would be Crohn's disease improved. Thank you.

DR. Finn: Please submit that information to the docket so that everybody can have access to it, not just the people on the panel. Thank you. (Applause).

DR. HAZAN: I think we need to allow patients freedom of choice for fecal transplant. We need to trust the doctors and we need to continue with the registry of Dr. Kelly so we can understand fecal transplant work model of 300,000. Thank you so much.

DR. Finn: Thank you very much for your perspective and for sharing your information.

Our next speaker is Dr. Jennifer Allegretti from Breckenridge Women's Hospital.

DR. ALLEGRETTI: Hi very close. I am Jessica Allegretti. I am from the Breckenridge Women's Hospital in Boston. And you know I was not going to initially going to speak today but hearing the testimony of many of my colleagues I really felt compelled. This is an opportunity that I may not get again, to speak to this distinguished panel. So, I will start by saying I really felt compelled to speak today both as an active C.diff clinician as well as a researcher in clinical trialist and I think that I have somewhat of a unique perspective. Since 2012 I continue to direct the FMT program at Breckenridge Women's Hospital. This program has grown to a very large referral network, serving much of New England. And I, like many others in this room, I perform hundreds of these a year despite a very thorough pre-screening process. I am still shocked that many patients still come to me after five, six, seven episodes suffering for greater than a year because knowing that access has improved, it still is not good enough.

I find this unacceptable. When I started my program, I was unfortunately still screening my own stool and I say unfortunately because I know I was not doing a good enough job at that time, knowing what we know now. I am extremely to open biome for providing material for my patients. That has not only improved access, but more importantly has definitely improved safety. I would not have the ability to screen material as thoroughly as they do. And again, feel extremely grateful that I live so close to them to have access, such personal relationships with them as well as access. I personally have been fearful for my patients after the potential of possibly rescinding enforcement discretion. I have felt this way since the draft guidance was released in 2016. I do not have an internal store bank at my facility like many of the speakers we have heard here today have. And, I would therefore, not have access to screened material should enforcement discretion be rescinded imminently. I again, fear that if I do not have access to this, many patients will go untreated and again, I do not have alternatives at this time. In fact, I

truly feel that there will -- excuse me. In fact, I truly fear there will continue to be a role for FMT in its current state even after, if, enforcement discretion is rescinded, especially for our (inaudible). Many of us in this room are working hard to collect robust safety data. And as you saw Dr. Kelly present earlier, we have collected seven year follow up data, again, showing no major safety signals. I think it is absolutely critical that any clinician who wants to offer this therapy in their practice be mandated to collect safety and efficacy data. I do not think that that is a huge ask. Recognizing that perhaps the FDA cannot mandate this, but we should demand it of ourselves. As a trialist and somebody who has run several of my own investigator initiated FMT trials, I am well aware that enrolling in trials is always challenging, but certainly possible. I fully believe there is room for both open label and I also consider this a standard of care therapy as well as clinical trials investigating novel agents. I offer both. I have an informed conversation with my patients and I review

available options. It must be a shared decision process between clinician and patient. I worry that when one or many of these products get approved and I sincerely hope that they do, access will be significantly limited yet again. I feel strongly that there should not be a rapid withdrawal of enforcement discretion policy after gains licensure. Thank you so much. (Applause).

DR. Finn: Thank you very much. Any clarifying questions? No. Okay. Then I have on my list one more speaker, Debra Stewart, a patient advocate.

MS. STEWART: Hi, my name is Deborah Stewart. I am not a patient advocate. I am a patient.

DR. Finn: Sorry, I apologize.

MS. STEWART: Just a little bit of background. The field I work in is patent modernization. So, I absolutely understand the economics behind a licensed product. I feel like this is one of those moments where it is the emperor has no clothes and I am going to say it. This is insane. The idea that you are going to

remove a safe, effective, supply of material that saves lives so that for-profit corporations can have a licensed product so people can join their trials. That is insane. We have a therapy that works. If they can work in tandem, happy for it. But to remove it so they can get patients for their trials and put people at risk seems absolutely insane. And it seems to me that no rational person would make that decision. Thank you. (Applause).

DR. Finn: Thank you very much. Is there anybody whose name I do not have on the list who wants to speak or say anything? Okay. So, taking that as no, I just have a couple concluding remarks. First of all, I would like to, on behalf of the panel, I would like to thank all of the presenters and everyone in the audience and those listening to the webcast. We appreciate your attention, your interest and the time and effort that all the people who spoke spent on their presentations. We will take all that we have heard today, as well as comments submitted to the docket into consideration as we move forward in this area. And lastly, I would like to thank the

FDA staff and (inaudible) and here in the great room for making this happen today. And thank you everybody for your participation. The hearing is concluded.

(Whereupon, at 12:52 p.m., the PROCEEDINGS were adjourned.)

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CERTIFICATE OF NOTARY PUBLIC

STATE OF MARYLAND

I, Mark Mahoney, notary public in and for the State of Maryland, do hereby certify that the forgoing PROCEEDING was duly recorded and thereafter reduced to print under my direction; that the witnesses were sworn to tell the truth under penalty of perjury; that said transcript is a true record of the testimony given by witnesses; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this proceeding was called; and, furthermore, that I am not a relative or employee of any attorney or counsel employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

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Notary Public, in and for the State of Maryland

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