FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
CENTER FOR DRUG EVALUATION AND RESEARCH

FECAL MICROBIOTA FOR TRANSPLANTATION: SCIENTIFIC AND REGULATORY ISSUES CENTER FOR BIOLOGICS, EVALUATION AND RESEARCH (FDA) AND THE NATIONAL INSTITUTE FOR ALLERGY AND INFECTIOUS DISEASES (NIH)

[This transcript has not been edited or corrected, but appears as received from the commercial transcribing service. Accordingly, the Food and Drug Administration makes no representation as to its accuracy.]

Bethesda, Maryland

Friday, May 3, 2013

A G E N D A

Session III: Clinical Experience

Moderator:

RICHARD GORMAN, MD
NIAID/NIH

Panelists:

LAWRENCE J. BRANDT, MD
Albert Einstein College of
Medicine/Montefiore Medical

COLLEEN R. KELLY, MD
Brown University/Women's Medicine

Collaborative

DAVID T. RUBIN, MD
University of Chicago

SACHIN S. KUNDE, MD
Helen DeVos Children's Hospital

ALEXANDER KHORUTS, MD
University of Minnesota

Session IV: Looking Forward: Future Possibilities and Regulatory Considerations

Moderator:

SCOTT STIBITZ, PhD

CBER/FDA

Panelists:

JOHAN S. BAKKEN, MD, PhD
University of Minnesota

HERBERT L. DUPONT, MD
University of Texas, Health
Science Center

LEE JONES
CEO, Rebiotix

JAY SLATER, MD
Director, Division of Bacterial,

Parasitic, and Allergenic
Products,
CBER/FDA

* * * * *

P R O C E E D I N G S

(8:29 a.m.)

DR. MILLS: Good morning, everyone. We're going to go ahead and get started soon. We're actually, again, just about on time. This has been the most amazing meeting for that.

So, I'd like to introduce the moderator for the first session, Dr. Richard Gorman. He's the associate director for clinical research at the Division of Microbiology and Infectious Diseases at NIAID.

DR. GORMAN: Thank you, Melody. And Melody has also asked me to make a few remarks about yesterday.

Anyone who has ever made Apple Jack, which is fermented apple cider, or created their own homemade wine or a sourdough starter, has very little idea about the community of organisms that contribute to their success or failure, and yet, the products are generally pretty well received, much like the fecal -- I'll call it the FMT.

And like any well-functioning

community, when you put together a team that you want to be effective or a committee that you want to be effective or group that you want to have move things forward, you need a balance between similarities and differences. You need similarities so the group can have cohesion and you need differences so there are synergies between the people with differences, and yesterday was one of those times, by the end of the day, when I realized that the organizers of this meeting had caught lightening in a bottle and they had put together a group of people with enough similarities that we all could talk about the same subject and enough differences that we were looking at it through very different lenses with the same goal in mind.

As a recovering pediatrician and a newly formed scientific administrator, I was impressed with the amount of both energy and tension in the room yesterday. From the clinicians I heard the tension between primum nil nocere, which is Latin from "first, do no harm", and the therapeutic imperative, I've

got sick people in front of me and I need to do something to help them.

From the microbiologists I heard the creative intellectual curiosity that drives them to understand things that started with bio films and move to signaling between bacteria and now we're talking about biological ecosystems and, for the first time, I recognized a group of people who may be moving past Pasteur, and I was impressed.

And they have a balance with the practical applications of their work and will my discoveries move forward.

So, as a bureaucrat, I've learned a whole new language of storming, forming, norming, and performing, and this group is somewhere between the brainstorming -- I think that's past, you're forming your ideas and your goals, and you're now moving into one of the most difficult periods where you're going to be normed, where you're going to have normative systems that you have to begin to place, and that brings into play my sister agency, the Food and Drug Administration.

The Food and Drug Administration's approval is the most valuable approval on the planet and to get it is sometimes felt as an incredible burden, sometimes you feel like you're trying to solve the Gordian knot or clean out the stables, but once you've got it, you've got something that you then afterwards take for granted, the safety, purity, and effectiveness of the products that we use everyday in our clinical care.

I once had the good pleasure to sit next to Richard Ferber, who is a scientist who studies sleep and pediatric sleep in particular, and he told me that people, when they think about sleep and they come in to complain to their pediatrician about their child sleeping, remember two days -- the worst day they ever had, and last night.

And I sometimes think about the FDA the same way. When I think about them, I think about the worst day I ever had with them and the last time we ever had with them, and for all my FDA colleagues, I'm sure you're sitting there looking at me and saying, I

remember the worst day I had with Rich Gorman too. But they're here -- we don't know which FDA, sometimes, we're going to get. Are we going to get the FDA that still worries about preventing the next thalidomide or are we going to get the FDA that allowed surfactant to be tested on sick neonates where you effectively drowned a baby to give them surfactant to let them breath. And if anyone has ever seen that process, pouring liquid down a baby's lungs to save their life is just an amazing concept and somebody let that get through the regulatory pathway. Congratulations to the FDA on that one.

There's an old African proverb, and this is the last thing I'm going to do before I introduce the first speaker, which says that if you want to go fast, go alone, and if you want to go far, go together. I hope this group hangs together and goes far.

Yesterday we talked a lot about microbiology and today we're going to talk a little bit more about clinical, and without any further ado, I'd like to introduce

Lawrence Brandt from the Albert Einstein College of Medicine and the Montefiore Medical Center.

DR. BRANDT: I think that was one of the best introductions I've ever heard. That was wonderful. Thank you.

I'm going to be speaking today about fecal transplant and giving an overview, and just to take one second and thank the organizers of this meeting for inviting us and putting this together. It's been a wonderful program so far and I hope we can go forward together.

So, let's talk a little bit about Fecal Transplant Therapy and give you this overview. My disclosures are from Optimer Pharmaceuticals, I'm on their speakers bureau and I get a small amount of money to do some research on C. Difficile.

So, we're going to start from the top and go right through this, a little bit about the organism, it's a gram- positive, anaerobic, spore-forming rod. The spores are long-lived. They produce toxins; that's the

damaging agent. They are ubiquitous, and they're transmitted by fecal-oral means.

If one looks at how important this is, you can see that starting in approximately the year 2000, 2001, we noticed that hospitalizations related to C. difficile infection have gone up significantly, whether just by themselves or as part of an all-listed diagnosis group, and here we're talking about 700,000 new cases of C. difficile infection per year in the United States.

If one looks at where that fits into healthcare associated infections, it accounts for about 10 percent of infections right behind surgical site infections, which follows catheter and urinary tract infections, so this is a very important kind of infection that we will see and we're seeing more of it.

If we look at mortality, mortality has also gone up. It's sort of plateaued a little bit since 2004, but you can see that this has a very significant mortality curve.

If you look at the mortality risk in patients with just -- if you can use that term

-- C. difficile infection versus C. difficile infection that occurs in association with another disease, you can see that primary C. difficile infection, 4 percent mortality, secondary C. difficile infection, a 12 percent mortality. This, compared with no CDI at all, in which the mortality risk here was 2 percent, so the presence of C. difficile infection, at the least, doubles your mortality.

The average cost, we're talking significant dollars -- primary CDI, about $10,000 per case, per stay. In secondary CDI, it's about $31 - 32,000, and the cost is a little smaller without C. difficile infection. So, it's important in terms of patients' well being, it's important with regards to the cost of hospitalization, and it's important, of course, with regards to mortality.

How does C. difficile manifest itself? Well, you can have a carrier state, and as we discussed yesterday, about 3 percent of people will be a carrier. You can have C. difficile associated diarrhea increasing in

severity, that can translate into a colitis, it can then become a pseudomembranous colitis, which is a little more severe. The colitis can be fulminant, can be associated with a toxic megacolon. There are atypical manifestations of C. Difficile, and then the disease can be recurrent, and recurrent disease, in a sense, is the bulk of the discussion for today.

How often do we see recurrent disease? Well, in general, 15 percent of patients. And it's not really important to the clinicians, for the most part, to differentiate and distinguish relapse from re-infection. It is important for the clinician to differentiate post-C. Difficile irritable bowl syndrome, which can present with diarrhea. That's an important differential diagnosis.

For those that have a recurrence, about 30 to 45 percent will now have a second recurrence. If you have a second recurrence, your chance of having a third recurrence can be up to 60 percent. Once you have a third

recurrence, you're not really getting rid of that organism without something special being done.

Treatment failures are starting to increase, now occur in about 20 percent of patients, and these relapses can continue for years. The record holder in my practice is nine years. Nine years of C. difficile. There's no universal treatment algorithm, and none of the treatment recommendations are evidence-based.

Well, why do we get this recurrent C. difficile infection? It could be impaired host response, it could be an intestinal microbiome that has been altered.

And here's a figure that shows that patients who have asymptomatic carriage of the organism have an innate ability to make substantial amounts of anti-toxin A antibody, and that is protective. Patients who have just one single episode have the ability to develop that antibody. Patients who have recurrent C. difficile seem to be limited in their ability to produce an immune response

that is effective.

There also is the concept that patients with recurrent C. difficile infection, as we heard yesterday, have a decreased diversity of the fecal microbiome, and they have a decrease in their phylogenetic richness, and specifically, their Bacteroidetes and Firmicutes are reduced and we don't see that in patients with just one bout of infection, we do see that in patients that have recurrent infection.

You know, the microbiome is really getting to be a hot topic, and if you look at this graph, you can see that in blue we have 2012, in redish we have 2002, and you look at all of the different sub-specialties in medicine, gastroenterology being the fourth column, and you see how the publication and journal articles has just, you know, gotten dramatically so rich over the last decade or so.

Well, we recently authored ACG treatment guidelines for C. difficile and these were published last month in the

American Journal of Gastroenterology. So, I'm not going to go through all of these, but what they do is they talk about the antibiotics and the treatments that are appropriate for mild to moderate and severe C. difficile -- if you don't get a response, how the Vancomycin changes, if you have complicated disease, how the Vancomycin changes again, and when you should consider surgical therapy.

If you're talking about recurrent C. difficile, though, you notice that for the first recurrence you use the same treatment as for the initial episode, if you have a second recurrence, you can use a pulse or a tapered Vancomycin regimen, never really proven to be better than the standard regimen in a controlled, finely designed way, and now you see that for the third recurrence, one could either use a pulse-tapered Vanco regimen, or one can consider a fecal transplantation.

The best that we could come up with in this universe of people who were writing this guideline, we agreed that this was a conditional recommendation based upon

low-quality evidence. What does low-quality evidence mean? It means that there was no randomized control trial and this was published before -- or was written before the trial came out in The New England Journal of Medicine, and my guess is today it would be moderate quality evidence.

The rationale for fecal transplantation in C. Difficile is that you can avoid prolonged and repeated courses of antibiotics, you could reestablish the diversity of the intestinal microbiome and thereby you can reestablish "colonization resistance".

This is not a new procedure. It actually goes back to the 4th century China when Ge Hong described use of human fecal suspension by mouth for a variety of illnesses, food poisoning primarily or severe diarrhea.

In the 16h century, now we had a menu of ways that stool could be served. It could be served as a fermented fecal solution, fresh suspension, it could be dried, it could

be infant feces, and now the panoply -- there was a panoply of diseases with diarrhea and abdominal pain and fever and vomiting and constipation -- fecal suspension was actually called "dragon yellow soup" and was called "dragon yellow soup" to make it a little bit more attractive rather than describing what it actually was.

Yesterday we heard an excellent discussion on veterinary medicine, and it actually dates back to the 17th century, and we discussed transfaunation, which is the transfer of fecal contents or fresh feces from healthy horses to treat horses with chronic diarrhea, and we learned about rumen transfaunation to refaunate cows, as an example, that had been off feed because of mastitis or other illnesses.

And yesterday I learned that in horses, this is also given by the upper tract to accomplish the same purpose. So, both routes have been used in veterinary medicine.

In the more current literature, 1958, the first use of fecal transplant in the

English language given by enema to treat pseudomembranous colitis thought to be due to Micrococcus pyogenes. Three critically ill patients, "dramatic" response within 48 hours.

First use for C. difficile infection also by enema, 1983; 1991, Dr. Aas and colleagues, including Dr. Bakken, who is in the audience here, gave the fecal transplant by nasogastric tube, same year done by Lund-Tønnesen, gastroscopy and colonoscopy. We wrote a single case report in 2000 using colonoscopy, and because it was in the English language, that sort of filtered throughout the United States a little more easily. Two thousand-ten, Silverman published an article that taught people how to do this by themselves. I think this is a little bit of a problem area, but it does work and we'll probably discuss this later this afternoon.

So, how do we do this? Well, the first thing you have to do is you have to choose a donor. I'm not sure it really matters what donor you use. I don't think there's great evidence that it has to be a

spouse or an intimate partner or a relative. It can be a total stranger. And now we're thinking about, and Alice Koritz has used a standard donor or a universal donor and that, to me, actually makes the most sense.

There are certain exclusions for donorship. One cannot have used antibiotics within three months. Why? Because antibiotics can damage or perturb the intestinal microbiome for a period of time that can last three or sometimes four months. Patients that have recurrent or problematic diarrhea, constipation, irritable bowel syndrome, inflammatory bowel disease, colorectal cancer -- you look at the list and you say, you know what we're thinking about is anything that we can conceive of being transmitted to the recipient and changing the behavior of that recipient's body and predisposing them to any disease, we would rather not use those individuals.

And then we test the donor, and as we heard from Dr. Tarr, this probably isn't a perfect way of testing, it's the one we have

now. And in the NIH protocol that Dr. Kelly will talk to you about after me, we do all the tests that you see here -- we culture, we specifically test for Listeria, we specifically test for certain vibrios, we do an ova and parasite test, of course we test for C. difficile, we test for H. pylori antigens, Giardia antigens, cryptosporidium, we do an acid-fast stain, and we test for Rotavirus.

We test the blood for hepatitis A, B, C, syphilis, HIV 1 and 2. We just don't go on the street and collect any poop that we see.

So, the protocol that we use -- this is my particular protocol -- protocols have not been studied and validated and no one can say that their protocol is superior to anyone else's. I stop antibiotics two to three days before the procedure. When I say antibiotics I mean Vanco or DIFICID or whatever they're on. Some people continue the antibiotics right up to, and some people through, the transplant.

We clean the patient out -- reduces the volume of stool, reduces the volume of C. difficile, we give them a large-volume typical colonoscopy prep the evening before the procedure, and right before the procedure we give the patient Loperamide because we want them to hold the stool better.

None of these things have been tested either. As far as the donor is concerned, I like to give the donor a gentle laxative, such as Milk of Magnesia, the night before the procedure because I usually stir this by hand and I don't want to have to use a chisel to get the stool into solution.

We try to use the stool within six to eight hours. Is that the right amount of time? Never been studied. Maybe it's four hours, maybe it's twelve hours, but six to eight. And the stool need not be refrigerated.

Then, we take the donor stool, we suspend it with a non-bacteriostatic saline by hand or by blender, we filter it through gauze into a canister. The use of a hood is

recommended, as you'll see from a slide one or two from now, we don't use a hood, but a hood is recommended. I think this is the safest stool that we, as gastroenterologists, will ever see in our lives. We use a 60 cc catheter-tip syringe connected to "suction" tubing to administer the suspension into the ascending colon, and we administer about 300ccs of the suspension, which contains approximately 60 grams of stool.

So, here I am at work, some people think doing what I do best, and I'm stirring up the stool and I'm trying to make a suspension out of it. Bottom right panel, I am filtering it through gauze and then we draw this up into a 60cc syringe and do the colonoscopy and then administer it through the colonoscopy as you see us doing here.

Some people use a blender. Actually, I've used both and I prefer the blender, so I'm in blended mode now. That is my modus operandi.

Now, this photograph is actually taken from Max Brenner Chocolates in New York.

This is one of the ways they serve their chocolates. I am not recommending that -- well, you know what I'm not recommending.

If one looks at the extant literature on fecal transplantation, just combing the literature, isolated case series, small case series, you see that about 450 cases have been done, most of them by the lower GI route. The cure rate is from a low of about 81 percent to probably a mode of 100 percent. The average is 93 percent throughout the world.

This is the summary of the Van Nood trial, which is a randomized trial reported in The New England Journal of Medicine, and they had three arms to the trail, a short course of Vanco followed by bowel lavage and then nasoduodenal infusion of a fecal transplant. That was compared with a 14-day course of Vanco in high dose and a 14-day course of Vanco in high dose followed by just bowel lavage, and you can see that on first go around, the cure rate was 81 percent with the fecal transplant. Because they had such small

numbers, they did a second fecal transplant in three patients, and that raised the cure rate to 94 percent. The other two arms, about 30 percent success, and the study was terminated by the review board at the interim analysis because they thought that it was unethical to continue. And note that the adverse effects were minor -- transient cramping and belching, and serious adverse effects, none.

And this is sort of the experience that's been reported throughout the world.

If one looks at -- I'm going to go through the next two or three slides quite quickly -- a study of fecal transplant in recurrent C. difficile, you can see that in general the lower route is more effective than the upper route and that enema, rectal tube seems to be -- have a higher resolution rate than colonoscopy and a lower recurrence rate.

What's not expressed on this slide is that many of the enemas -- not many -- some of the enemas and rectal tube insertions were done multiple times. The colonoscope was only done once.

And you can see that EGD and nasogastric tube, is about 75 percent with a recurrence rate of about 4 percent.

As far as the donor, there are differences in donor, but as you'll see from a future slide, which I quote Alex Khoruts, you can see the results with a standard or universal donor are just as good as the evidence with a patient identified donor, so I'm going to move forward on this.

As far as the diluent to use, I've used saline, I've used bottle water, I've used milk. I don't think it makes a difference. In terms of volume and stool weight, it appears as if more is better.

In terms of a follow up study that we did on patients who were followed for at least three months after the fecal transplant, and Mark Mellow was in the audience, who was one of the authors of this study, these were patients that were sick for a long time, but they responded promptly. Seventy-five percent of the patients responded within three days. They had a primary cure rate of 91 percent and

a secondary cure rate, meaning, if the first transplant didn't work, you then put them on Vanco again, which they responded to, or you did a second transplant, which they responded to, that secondary cure rate was almost 99 percent. Ninety-seven percent of the patients said, sure, I'd have another fecal transplant, and 58 percent of the patients said, not only would I have a fecal transplant, I don't want anymore antibiotics. Give me that as my first treatment.

The drawbacks of fecal transplant, some people consider it aesthetically unpleasing. At present, there's no reimbursement for this.

The cautions are the potential transmission of pathogens, and that can be a broad topic, or allergens.

The pros, it establishes the diversity of the intestinal microbiota, there's a decreased resistance of intestinal bacteria, it's inexpensive, and it's rapidly effective.

This is Alex's study in which he

looked at the microbiome after fecal transplantation for recurrent C. Difficile. I'm not going to spend any time on it. I'm going to go through these slides rather quickly. Basically what he showed, and I'm sure he'll talk about this a little bit, is that the stools resembled that of the donor and this resemblance can last for, oh, let's say, 130 days, and he has more recent data than that.

So, when should fecal transplant be done? For recurrent refractory disease? I think the answer is, yes. No, I think the answer is, absolutely yes. For severe disease? I think it's arguably less. I have had several patients that I'm reporting on now that I have done transplants on right before they were going to go to surgery for toxic megacolon and severe complicated colitis, and within hours, their condition improved enough so that the surgeon said, let's hold off. As first-line therapy? This is more argumentative and as we go on and we learn more about the relationship of bacteria and

the microbiota to different diseases, not necessarily GI, this becomes less of an issue or less of an indication. Possibly, post-C. Difficile irritable bowel syndrome, and I have cured several patients with this disorder.

The next step, Alex will talk about this, use of a frozen fecal material from a universal donor. He got just as good results from this as he did from the traditional, if you will, method of introducing the fecal transplant, and I think that this is the way of the future, the immediate future, because in this journey we're on now, fecal transplant, use of whole stool, is really just the first step, it's the introductory step of this journey.

As you heard yesterday, synthetic stool, if you will, 33 strains, and curing just two patients, but that's not 1,000 strains, now we're down to 33. Maybe we can get down to five or ten and that super strain is what we might be looking for.

Future areas of investigation? Well, the indications. Who should we do this

on? Should it be severe C. dif, complicated diseases, should we do it for a first occurrence? Is this safe? Other diseases, inflammatory bowel disease, irritable bowel syndrome, constipation. There are reports, I have experience with all these areas -- t here are patients that have definitely gotten better with this. Is this the right therapy? Is it safe enough to do?

Non-GI diseases. We know that the microbiome determines our general wellness and our health. When things go wrong in non-GI areas, maybe if you can change the microbiota, you can change this.

How do we give it? What route? The safety is probably the most important thing at the moment. And what products should we use? Should it be stool? No. Should it be an industrially created product that's been safe and vetted? Yes. Can it be a capsule? Possibly.

My time is flashing now so I won't show this. This really was shown yesterday by Dr. Young in which he had a beautiful diagram

of how infection with C. difficile is usually a transient phenomenon unless you perturb the micriobiota severely and then you wind up with a persistent dysbiosis, but you can take that persistent dysbiosis and reverse it by recreating more of a normal situation.

And whether or not we have to use whole stool, a consortium of bacteria, a single strain, or the bioactive molecule, is something that deserves a little bit of study.

The safety and ethical concerns, most important, acute infection, acute allergic reactions, these are easily dealt with. It's the long-term concerns. Is it possible that we're predisposing the recipient to some or even all of the diseases or conditions that the donor will develop in his or her lifetime because we are now replacing one stool with another stool? Have we created a clone of the donor? How long will the donor microbiota populate? How long will be the effect of that population on the recipient's colon?

For solutions, use the safest

product possible. Stool is the most problematic. Stool-derived product from a volunteer is probably better. The commercial preparation is probably the safest. And most important, I think we have to monitor the results carefully, and for that, I would like to suggest that we have a national registry for all fecal transplant where the data is there, it's available, and it can be studied.

And with that, I will end with a quote from Hippocrates, "All disease begins in the gut." Hippocrates -- I'm not that old, but -- we weren't classmates but I know that if Hippocrates were alive today he would certainly agree that health is determined by the microbiota in the gut and hopefully we can restore health with fecal transplantation and I thank you all for your attention.

(Applause)

DR. GORMAN: For the transcriptionist, please speak into the microphone and please announce yourself with your name if you have a question for Dr. Brandt. Questions?

DR. ORENSTEIN: Bob Orenstein, Mayo Clinic. Thank you, Larry, for another exceptional presentation. Also want to thank Dr. Gorman for an excellent way of framing the issues.

So, in the last day or so we've now heard, I think, three speakers talk about a national registry and concerns about safety. And I'm wondering if anybody has any ideas of who might fund that registry so that we could actually collect the safety data that everybody wants and how we might go about doing that.

DR. BRANDT: Did you want me to answer that question about how that should be funded? I think there are many people in this audience who could answer that question better. I think it should be a federally funded project and I think the data should be available to all who are interested in this area, and maybe we can discuss this later this afternoon.

MR. ROEHR: Bob Roehr. What is the value of a registry without comparators?

DR. BRANDT: Well, I think that one of the most important -- clearly, whenever you can do comparative data, that's better, but what are we interested in here? What we're interested in knowing is, here's a bunch of donors and here's a bunch of recipients of that donor product, and let's see whether or not the donor microbiota has an effect on the recipient to predispose that recipient to any longstanding diseases. I mean, that's the concern.

Anybody, with Phil Tarr's help, and the help of our microbiologists in the world, can take a stool and make it safe for transplant. You just have to make sure that it doesn't have anything that's going to kill you or give you something terrible. I mean, that's relatively easy. What's harder is to say, what's going to happen in 10 years or 15 years? Am I going to develop diabetes when I don't have any family history of diabetes because my best friend, whose stool I used, had diabetes and now my population of bacteria are going to, in some way that we don't quite

understand, facilitate that? Or am I going to get coronary artery disease when my mom and dad lived to 104? Right?

So, I think that these are the issues. And that's what I'm concerned about and I think that would probably save a lot of discussion about speculation as was raised yesterday.

DR. GORMAN: Thank you, Dr. Brandt.

(Applause)

DR. GORMAN: Thank you. Our next speaker will be Dr. Colleen Kelly from the Brown University/Women's Medicine Collaborative, and she'll be talking about FMT for C. Difficile: Overcoming Challenges to Safely Deliver an Effective Therapy.

DR. KELLY: Good morning. So, fecal transplant has been in the headlines a lot lately. I definitely don't miss any of the articles; my mom clips and sends me every newspaper and magazine and buys nine copies of anything I'm quoted in, and definitely some of this media attention is because you can make silly headlines and poop's a little funny and

the treatment sounds kind of weird, but on a more profound level, fecal transplant enables us to use a logical, low-tech, and fairly inexpensive approach to effectively treat a really serious disease, and that's what everybody is so excited about.

So, my objectives this morning are to help us understand FMT for recurrent C. difficile infection, and I'm going to spend a little bit of time on basic mechanisms and evidence support and talk a little bit more in depth about our experience in protocols for administration.

I want to talk about the challenges and obstacles that physicians and researchers face before this can be implemented on a more widespread basis, consider ethical and social issues related to fecal transplant, and, lastly, describe our experience with the IND process and the regulatory hurdles that are faced by those wishing to study or practice FMT.

So, alterations in the gut microbiota have been described in a number of

conditions, both within the GI tract and outside of it, but C. difficile is one of the most basic models of dysbiosis in human disease.

In C. difficile, exposure to antibiotics alters the indigenous flora, permitting colonization by C. dif and proliferation of the organism. It results in a spectrum of disease ranging from asymptomatic carriage to severe, complicated infection. And treatment of this disease, which is caused by antibiotics, has basically been with antibiotics for about the past 50 years, including Metronidazole for mild or moderate disease, Vancomycin for more severe infections or recurrent infections, and in 2011, Fidaxomicin was approved for use in C. difficile, though its role in the treatment algorithm isn't yet well established.

Recurrence is a challenging clinical problem. It occurs in up to 20 percent of patients after initial infection and after someone's suffered one recurrence, they're at greater risk to develop subsequent recurrences

with each episode. These recurrences are often treated with prolonged courses of antibiotics, which, I think somebody pointed out yesterday, perpetuates the dysbiosis, these can be very expensive, and very disabling.

Fecal Microbiota Transplantation is the alternative approach of administering feces from a healthy individual to promote re-colonization with beneficial gut flora. Very simply, animal models and human studies have shown that fecal transplant restores phylodiversity, beneficial anaerobes, and butyrate-producing bacteria. And in the last ten years we've seen a great increase in the incidence and severity of C. dif cases and along with this, diseases that are more difficult to treat and more recurrent disease, and by necessity, I think, we've seen this rapid growth in FMT.

There are over 400 cases now reported in the literature, but arguably the world experience number is in the thousands. A recent systematic review published last

month looking at 11 series of 273 patients was very similar to the results from all of the published series so far. About 90 percent experienced clinical resolution with no reported adverse events.

And we were very happy to see the first randomized control trial published in January demonstrating superiority of duodenal infusions of donor feces over Vancomycin. The results weren't surprising to those of us who perform fecal transplant, it was so effective, again, the study was stopped early and though the group size was small and the follow up wasn't very long, there were no differences in adverse events between these groups.

So, I've been doing colonoscopically delivered fecal transplant for about five years, mostly for recurrent C. difficile infection. I've now treated 101 patients. They range in age from 19 to 92 and the 19-year-old had to take a semester off from her first year of college when she developed C. difficile after Clindamycin for a dental infection. And the 92-year-old drove himself

down from Massachusetts, had an un-sedated sigmoidoscopy so that he could drive himself home, and he plays saxophone in a band, so a very vibrant 92-year-old.

The duration of these peoples' infection has been up to seven years maintained on repeated courses of Vancomycin and all of these patients had relapsed after standard therapies of Metronidazole, repeated tapering courses of Vancomycin, and S. Boulardii and I have also seen many people who failed anything else that you can think to throw at C. dif including Rifaximin, Fidaxomicin, I've had someone who had three courses of IVIG. And my cure rate, similar to everybody's, about 95 percent with one, or in a handful of cases, a second FMT.

And I did have what I believe to be an adverse event. I submitted this and it was accepted as a case report. I had a gentleman in his late 70s who had a very quiescent ulcerative colitis. He had been off all medications for over 20 years. He developed recurrent C. Dif after a skin infection. We

used his wife as a donor. And about ten days after his fecal transplant, he developed some cramping, mucus, and bleeding, that was very reminiscent of his prior problems with ulcerative colitis. We did a sigmoidoscopy and it looked like he was indeed having a flare, both endosmotically and in biopsies. He actually did very well. It was a very transient flare. We gave him some mesalamine, a little dose of steroids, and by his two-week follow up he was fine and his C. dif never recurred.

I follow these patients very closely. Once they've had C. dif and recovered from it, there's kind of a PTSD associated with it and anytime they need antibiotics or anything happens to them, I usually hear about it. So, I do think that I know what's happened to many of these people since I've treated them, and I have had a couple of SAEs. I don't think these are related, but I'm going to put them out there. A lot of these patients are elderly with a lot of co-morbidities, and I had three patients

develop cardiovascular events within four weeks. I had one stroke, one v. fib arrest, the woman had urosepsis, and, lastly, and it was very sad, actually, a gentleman who had very severe heart disease, we did -- he had been in the hospital over and over for C. dif. We did a fecal transplant. He was doing wonderfully. He was able to go outside again and had stayed out of the hospital for four weeks. He actually died on his way to the four-week follow up to see me of a sudden cardiac death.

Recently, I've had one post obstructive pneumonia in a patient with lung cancer and one patient with a recurrent episode of cholangitis, which she had had in the past, and the nice thing about both of those, they were both a couple of weeks after transplant. They received antibiotics for those conditions and their C. dif didn't recur.

I've treated nine patients with inflammatory bowel disease and C. difficile in all of them. We effectively treated the C.

dif with very little effect on the underlying IBD.

And these people are willing to travel. Only about half of the patients that I treat are from Rhode Island, the rest are from surrounding New England states. I've had people come from as far away as Florida. I've received desperate emails from as far away as Hawaii, Italy, Brazil, begging to come because there's absolutely nobody in their country or in their state to do this for them. And I get about ten emails a month now from physicians in institutions who want to develop protocols asking assistance and advice on that.

So, I teamed up with Dr. Brandt to do a randomized control trial to demonstrate efficacy and safety, and our goal was to try to make it the most perfectly designed randomized control trial we could, therefore it's double blind, and we have a sham arm. Patients either receive donor stool via colonoscopy or the sham treatment, which is reinfusion of their own stool.

We're enrolling 48 subjects,

following them for efficacy and safety outcomes. Somebody in the audience said to me yesterday, how are people agreeing to be in this sham arm? They're followed very closely and patients who relapse are put back on Vanco for at least ten days and then they're offered an open-label fecal transplant using donor stool, so everybody gets the good stuff.

I'm very grateful to be working with Alex Khoruts and Mike Sadowsky at the University of Minnesota, who are going to be doing microbiome analysis on our donors and subjects before and after FMT to try to help us with mechanisms.

So, the donor selection, as Larry said, often a partner or immediate family member, but not necessarily. We do use a lot of volunteer donors at our center, some of the staff, some of the residents, medical students. It's important that they've had no antibiotics. My cut off is 90 days, but the longer, the better, and I used to, when I first started doing this, maybe for the first year or two, say, they need to be healthy and

clean living, and I figured people knew what that meant, not bring in some IV drug using cousin or something, but I formalized this now using the AABBDHQ, and for those in the audience not familiar with that, it's administered when people go to donate blood asking questions about all kinds of risk factors for diseases, and we actually exclude patients even -- I have a lovely medical assistant from Germany who didn't come here until the late '80s and she's excluded because of risk factors for a variant of Creutzfeldt-Jakob disease, so it's -- I've also added questions to the AABBDHQ to exclude donors with inflammatory bowel disease, autoimmune disease, all of the things that we've discussed may have a root in the microbiome or things that we just don't know.

And for our study, we also exclude donors with obesity or features of the metabolic syndrome, so you can imagine, it gets pretty hard to find donors. Sometimes for the study I've had to go through three or four people before we found an acceptable

donor.

For pre-procedure testing, Larry went through this, in the past couple of years I have found one donor who was Hepatitis B core antibody positive. I've found a number of donors who were C. dif carriers. This testing has to be done on a strict timeline. HIV testing is done within two weeks of donation. All other testing and the DHQ is done within 30 days, and the donors are also asked to call us and let us know if they have any symptoms of infection between testing and the time of FMT.

The recipients are also tested, and I'm glad I do this because I have picked up somebody who had Hepatitis C and didn't know it. So, the method of processing, it's not as glamorous as the bioreactors, but I was very cheap. It's a plastic spoon, a bottle of saline, you dump about half of it out, six to eight spoonfuls, which is around 40 to 100 grams of stool. We dilute this, no blender, just shake the bottle really good, and very rarely have to filter it through gauze, draw

it up into syringes using a very similar dose because I got my protocol from Larry, and I'm infusing as a colonoscopy or more recently I've been doing it by sigmoidoscopy, lower risk, gets the job done, enables me to still do biopsies and things like that to look for other conditions.

Other methods of administration that have been described and, again, the best route -- and they vary depending on the situation -- people aren't like horses. They won't sit there really nicely while you put an NG tube down. They hate them. Hate them more than colonoscopies, I think, and there was a survey where it was rated the least appealing by patients. That's basically why I don't do it, but a lot of people have demonstrated this is effective. I worry more about aspiration risk, particularly in critically ill patients who may have an (inaudible).

I also think about the ability of these bacteria to make it to where you want them to be, which is in the colon.

Retention enemas are great -- cheap,

easy, anybody can do it, but elderly women, multi (inaudible) people have a really hard time holding an enema for any length of time, so it might require multiple treatments.

Patients are followed very closely. I give them instructions to call me ASAP with any signs of infection or fever or relapse. We do a 24-48 hour phone contact, a one- week phone contact to check in and see how they're doing. I see them all in the office in four weeks and we've added a six-month phone contact, and this is outside the study. The patients in the study are followed much more closely than this.

So, what are the obstacles to implementation? We talk about safety issues because we need more than just, hey, I did 100 cases and nothing really bad happened to anybody. Sources of donor material that are readily available when you need them. Optimal methods of administration need to be defined. And the reimbursement question.

So, is it safe? The previous case series have demonstrated a couple of deaths,

but they appear to be due to serious underlying co-morbidities, not the fecal transplant itself. We've had no published adverse events or infectious complications, but we all know about the under reporting problem, and I have heard anecdotal reports of post-FMT fevers, Rotavirus and Rotavirus transmission, and an aspiration pneumonia in a patient with a severe C. dif infection and an ileus who was given it by NG too.

The risks of infection we can talk about a little bit more coming up. The theoretical risks, I think, is what has everybody a little more concerned talking about transmitting any of these conditions that can have a root in the microbiota.

So, other contraindications, I don't think there's any absolute contraindications, but I don't think any of us who do a lot of fecal transplant would be very comfortable doing somebody who was absolutely neutropenic, I think that would -- I would consider that, maybe, an absolute contraindication. I don't even do a rectal exam on them.

But patients, particularly a lot of IBD patients on anti-TNFs, steroids, have been treated successfully. Patients with more severe levels of immuno-compromise, including those with solid organ transplant recipients and undergoing chemo have also been treated. We're putting together right now a multi-center case series with the fecal transplant working group. It's looking like it's going to be 50 to 60 patients with this kind of history.

And wonder whether patients with underlying liver diseases and ascites are at increased risk for adverse events as well. Dr. Mark Mellow had a nice poster at ACG talking about a double transplant where a gentleman had end stage liver disease and had a bad C. dif infection. The surgeons weren't going to give him his liver transplant. He was able to do a fecal transplant, get him better from that, and then the man was eligible for a liver transplant and ended up living and going on to be discharged from the hospital. That was a nice report.

I think we can optimize safety by benefitting -- balancing risks and benefits. There's nothing we do that is absolutely safe, but we can't have, like, a zero tolerance approach. We have to very carefully balance these risks and benefits and consider the individual patient. I did a patient two weeks ago who was a solid organ transplant recipient on fully immuno-suppression. She had C. dif for a year and a half, over ten courses of Vancomycin, the last time she was in the hospital in January, she'd been in the hospital six weeks because they couldn't get her diarrhea better and she actually had a rectal prolapse during that time, and they were talking about doing a colectomy for her.

We very carefully discussed this, spent about an hour with her and her brother and decided to go forward to do the fecal transplant. It was kind of nail biting and I gave her instructions to take her temperature daily and let me know if anything happened. I couldn't get a hold of her the next day and I was thinking the worst, like, she's in an ICU

somewhere, and she called me back the day after that and said, oh, I'm sorry, I was out on a picnic for my daughter's birthday. I had been going to the bathroom 30 times a day and I hadn't been outside and it was just such a beautiful day and I didn't call you back. I apologize.

I think we can mitigate risks through careful donor selection and screening and certainly clinical trials are going to continue to give us more robust safety data than currently exists.

So, donor identification is a problem. Patients may not have a suitable donor. We do have the volunteer donor pool. Another kind of creative thing that we've been doing by necessity is these tandem fecal transplants so one donor will get screened, maybe, for their family member or for the volunteer, but we'll ask if they don't mind, because there's usually enough to go around, if we can book another fecal transplant patient to follow and get two treatments out of one dose.

I think Dr. Tarr brought up a good point yesterday talking about directed donation being more risky and the issue of donors who might feel coerced and deny risk factors, maybe not admitting -- husband not admitting what he's been doing because his wife needs his stool, you can all imagine these scenarios.

Alex Khoruts is going to talk about his filtered stool, that's frozen and thawed, and he's been having great results with that and it appears effective.

So, the required donor testing is a bit of a problem. It's very expensive. People -- one of the most common questions I get is, well, who pays for the cost of donor screening? We have V codes, so, those cover screening in asymptomatic individuals. And I've had really good luck -- I've put every V code that seems to apply -- screening for parasites, screening for HIV, exposure to this -- and it usually gets covered. Medicare does not cover screening. Other people who might have higher co-pays, people have paid up to

$800 out of pocket for this donor testing.

It's also very complex. Variations between local laboratories, I can't always get every test that I need. The most difficult ones have been ova and parasites, because our hospital no longer runs them in-house, they go down to Quest in Virginia. It's about a two-week turnaround time. So, I have to track the stool down to Virginia and call the people in the O&P room at Quest and beg them to pull it like out of the queue and look at it because I'm on that tight timeline with the HIV testing.

So, it is difficult. The Listeria testing, some labs don't offer it, and the C. difficile on formed stool that we talked about yesterday.

And there is a lack of consensus on this testing, some of the ones -- I'm doing Vibrio testing on people who have never left Rhode Island, Rotavirus in asymptomatic adults, Norovirus when there's not an outbreak in sight, Listeria when the recipients are not immunocompromised and the C. dif carrier, I

actually -- I don't use C. dif carriers as donors, but if you think about it, if you've been in the same house as somebody with a raging C. Difficile infection for six months and you're carrying C. Dif, but you're not sick, you must have something good in there that's protecting you, so maybe those people would be perfectly fine donors.

I think in the future, again, some of Dr. Petrof's "RePOOPulate" material, may be in the future, minimally modified flora, such as that Alex Khoruts has been working on, I think the holy grail are these powdered, encapsulated products that could be easily tested, maybe given first line or earlier, they would be ideal, but I think we're a few years away from these products, also this concept of "microbial ecosystem therapeutics" and manipulating the microbiota to treat a whole host of diseases.

Since we're a bit away from that, we're going to probably be using whole stool for the next couple of years. The best method of administration still needs to be

determined. Some of these case series have suggested lower GI routes may be more effective, but randomized trials are ongoing right now, in addition to our own, looking at fecal transplant be it via enema or frozen by colonoscopy or NGT.

So, reimbursements is very labor intensive. I say it's a labor of love. I could do probably eight colonoscopies in the time it takes for me to set up one fecal transplant. We only are able to charge for office visits and endoscopic procedures because we're operating under an expanded access IND, I can't charge for the fecal transplant itself. Most insurers say nothing, or if they do, they say it's not covered because it's considered investigational and there aren't good controlled studies.

In an attempt to work on this, we developed a CPT code last year to cover the preparation of the donor material. The RVU for this code wasn't accepted and it was given a lesser RVU. I asked somebody what this -- this is about $42, this is what you get, so I

don't really mind that I don't charge for it because it's --

So, ethical and social issues, these are suffering patients. They've failed all available treatments. It had a huge economic impact. I've seen people spent thousands of dollars on Vancomycin and Fidaxomicin and I've seen people lose their jobs, I've seen it affect their mental health, the woman who kind of had a breakdown and was admitted to the psychiatric service because of this.

I was really struggling to figure out how to convey this human impact that's kind of kept me so interested in this and then this morning I got an email from a donor of one of my patients. I did her about a month and a half ago, and this donor, wife of a physician, she came from Albany, but if you don't mind I'm going to just read a couple of excerpts from the email.

"Imagine having frequent diarrhea, out-of-control diarrhea, can't get to the bathroom in time diarrhea and imagine not having any warning. You might be in bed,

eating a meal, taking a walk, going for a ride in the car. Imagine how you feel as you soil yourself, your clothing, your bedding, your home. Imagine how you feel as a family member helps to clean you up.

"Months and months of Vancomycin without significant improvement impacted her outlook, her optimism, her resilience. The year 2012 clearly demonstrated that a lifetime of Vancomycin was no life at all.

And she concludes by saying, "I hope that your work will convince other physicians to get on board, consider this as a sensible option for patients with recurrent and debilitating C. dif."

So, we do have to balance risks and benefits here. These patients need us to treat them, we need to do it safely, and sometimes when these safety risks aren't known at the moment, that can be difficult. But I think an adequate informed consent process, and my informed consent form, now that I'm doing it under the expanded axis IND, it went from a two-page, I thought very concise,

informed consent, to the one that our IRB uses, which is six pages and they initial every page and it's like closing on a house.

But I do detail all of the risks that we know about and ones that we even hypothesize.

And the last ethical issue, and I really don't have time to go into this, and it's not my area of expertise, but this ownership of donor and patient stool, particularly when you have companies that are going to be developing products that are potentially going to be billion dollar products and they need samples from these patients to develop their products. Do the patients release control?

I've been approached by some companies to kind of sell the stool from my patients to them, and it just didn't feel right. Little conflicts of interest there, but we can talk about that more later if anyone's interested.

The social issues, this public perception issue that, really, it works so

well for C. dif, maybe it will work for all of these other things too, and there's a lot floating around online with that. It's pretty easy to give yourself a fecal transplant, and I've seen some crazy stuff. Some people came in to see me about the wife, who was 20 weeks pregnant, and she had ulcerative proctitis, they didn't want to do anything actually conventional for her ulcerative proctitis, they wanted me to do a fecal transplant on her while she was pregnant, and they were treating their child, who was three years old, had ulcerative colitis, with fecal enemas that they had found the protocol online to do themselves using the father's untreated stool, nightly, for eight weeks.

My jaw was like -- I didn't know whether to call child protective services or shake them.

So, access to care is a problem. Really, people are coming from too far away to see me. I think that there should be somebody certainly in every big medical center, a couple of people in each state can handle

this. We do maintain a list and try to regionally direct people to providers to try to help them out there.

And there may be some disparities. I didn't realize this until I was compiling the expected enrollment tables for our grant, but 100 of the 101 patients that I've treated have been white. And that was just kind of -- Rhode Island is a very diverse state, so I don't know if these other patients aren't getting recurrent C. dif or just not getting referred to me.

And then, lastly, this issue of for profit FMT. When you have something that's hard to get and people are desperate, then they'll pay a lot of money for it, and there are plenty of sharks out there that will take their money. I've heard people charging up to $9,000, $10,000 for FMT.

Lastly, and I have to go through this a little quickly because I guess I'm out of time, but my experience with the regulatory environment, I hold two INDs, one for the study and one expanded access IND. When I was

told I had to get these, I had absolutely no idea where to start. There was no one in my institution who could guide me. There's no "IND for Dummies" book. I called CBER. They were helpful in directing me in terms of the process and how long things take, but it was fairly, kind of concrete recommendations.

I was referred to some guidance documents. I read through the 70-page PDFs and I figured out from the pre-IND guidance document that I needed a Type B meeting, but it was like learning another language. I mean, this just isn't something I'm trained to do. I did, fortunately, run into a few regulatory experts who at least taught me the lingo, like refer to them as "the Agency" and use this template so it didn't look -- and I did get a lot of help from my administrative assistant who put everything in really pretty binders and made it look topnotch.

It was a long process. It started in the fall of 2010 when I made my initial inquiry. My pre-IND meeting in December 2012, it wasn't really a meeting, it was like a

scheduled meeting, but I got the answers that I needed.

And then we kind of paused and when we talked to NIDDK and it sounded like we were going to be getting the grant, I went full force to do that May and June of 2012, but I really canceled all my patients for two weeks and I worked two straight weeks, and a lot of time on the weekends, at my desk, like 12-hour days to get that thing done. Hundreds of hours.

My expanded access IND was much quicker. I got that in November when I was informed that it was the best thing to do. That took me two, full, long 14-hour days to prepare that package and it was basically just scrubbing everything about it being a study and changing it into a treatment IND, 30 days until it was active, and it required my local, full IRB application and for me to assemble a safety monitoring board.

So, this is not ideal. Enormous time, administrative requirements, both on my part, but also on FDA's part, and I feel -- I

know Matthew Steele is in the audience back there somewhere, he was wonderful and answered all my questions and was very prompt at getting back to me, but I felt like everybody was just kind of drowning in this.

Few resources to guide physicians and investigators. I've actually -- this is a problem. I mean, FDA is used to dealing with companies and industry and regulatory experts, not, you know, people like us. We can't charge for this expanded access product if it's not under an IND. This is certainly going to impact coverage. And the reporting requirements, the woman who had pneumonia, it took me two and a half hours to write up that SAA. And, again, the local IRB being involved.

So, I think, to maximize access and safety, it must not be an overly burdensome, expensive process. We should be able to share and publish our protocols. I've shared my expanded access IND now with a couple of people and made that easy and I'm thinking of publishing it, I guess, depending on where

things go.

I think it would be great if we could develop a standard operating procedure for donor identification and a consensus donor screening panel that's really well thought out. You know, we're smart people. We should be able to do this. We don't have to get every single crazy test just because we can test for it. There's probably a very logical battery of tests that most labs are capable of doing.

I think the GI and ID societies can be very helpful for education and certification. And lastly, I agree with the idea of a registry. It would provide enormous safety and efficacy data.

So, I'd like to conclude today by saying FMT for recurrent C. dif is logical, simple to perform and appears effective. There are challenges to widespread safe implementation, but they are not insurmountable, and I believe an ethical imperative exists for enabling access to FMT in patients suffering from CDI who have failed

available treatments. And regulation that is not overly burdensome will maximize access and safety.

And this is a picture, it's the nicest thing a patient ever did for me. She was an art student and she sent me this. I have it framed. It's a little poop going in and making happy bacteria in her colon.

So, thank you very much for having me.

(Applause)

DR. GORMAN: Questions for Dr. Kelly?

DR. RAY: Good morning. Arnab Ray, gastroenterologist at Ochsner Clinic in New Orleans. Thank you very much, Colleen, great talk.

Two-part question, very simple questions. In that slide that you had the nine IBD patients that you did who you didn't notice a difference, just curious whether they were Crohn's or UC patients.

DR. KELLY: It's a mix of both.

DR. RAY: Okay.

DR. KELLY: About 50-50.

DR. RAY: Okay, and I'm sure --

DR. KELLY: And most of them had colitis, some colon involvement, the Crohn's patients.

DR. RAY: Okay. And the second part, we've all had the patient who comes in after the dental procedure and got Clindamycin. A lot of these dental procedures are multi part over three or four months. If they develop C. dif after their second or third dental procedure, would you go back and do the -- go straight to the FMT again or would you make them ride the therapeutic merry-go-round first?

DR. KELLY: Are they responding each time to a course of Metronidazole or Vancomycin?

DR. RAY: Well, I mean, like these are usually the patients who, after the Clindamycin, have the third recurrence.

DR. KELLY: So, they get better --

DR. RAY: Right.

DR. KELLY: -- but the next time

they get it again? I'd probably have them -- I mean, as long as they're responding to a finite course of antibiotics, and not in this indefinite Vanco limbo -- but yeah, the dentists love Clindamycin, and the other people, the OB/GYNs, before a C- section or for somebody with Group B Strep. I've seen a lot of (inaudible) C. dif from Clindamycin. I hate Clindamycin. You guys should -- I don't know -- black box Clindamycin.

DR. BRITTON: Rob Britton, Michigan State. So, we've been criticized for our bioreactor work in that we don't have donors come in and donate right in the lab and we get the stool right into an anaerobic chamber within three minutes because of die off of anaerobes. So, I was just curious, obviously, you're probably not working with an anaerobic chamber in the clinic, I was just curious, how long does it take to get the donor stool from the donor and then actually into the recipient, because I think people worry about that maybe more than they should.

DR. KELLY: Absolutely. I think

you're right. It's an excellent question. We mostly schedule these in the morning. I have the donor take a dose of Milk of Magnesia the night before. They're usually able to produce. We give them either one of those little denture cups that you give patients in the hospital to keep their dentures in or we tell them to go to the grocery store and buy a little Rubbermaid and go in it, close it.

I say for them to not freeze it, but I say you can put it on ice. I wasn't always doing that, but more recently I've said, yeah, you can put it on ice. And we usually use it -- you know, let's say they wake up anywhere from five to six, seven in the morning and have a bowel movement. I schedule the cases as late as noon -- so, six, seven, eight hours.

And then in terms of dose, because when I was doing these before the study, I was never weighing the stool, but for the study, of course we're trying to be very precise and weighing it in grams, I was just scooping it out and for one of the study patients who

recurred and had been in the sham arm and was getting the open label, the donor came in with like four little balls of stool, like that big, and it was about -- it was 10 grams, and I was in this panic. Do I do it? Do I make the donor try to give more? I actually texted Alex Khoruts that morning and I said, should I just do it? Should I wait? Should I see if I can get the donor to go more? And he's like, well, just go with it. You know, at least you get some dose response data. And she did great. She did fine.

So, I've done it with as little as ten grams of stool and it's been effective. So, it's very rough methods.

DR. GORMAN: Yes.

DR. YOUNG: Vince Young from the University of Michigan. This question may be not just for you but for anyone who has done the FMT. So, especially with the idea of blending, and I assume this is not pre-equilibrated, i.e. Anaerobic, saline, et cetera. Has anyone looked at how many viable anaerobes are there after you whir it up with

air and do a good aeration in non-equilibrated PBS? Because we've heard a lot about how important the anaerobes are, these difficult to cultivate -- has anyone then gone, found a microbiologist and said, before and after, how many anaerobes are in the feces and how many are there that we're actually giving? Have you done that?

DR. KELLY: I think Alex has, yeah, some viability.

DR. YOUNG: And not PCR, because PCR is not viability, so who is -- who's growing the organisms?

DR. KHORUTS: So, the question is, how do you actually test viability, because even though some people may be very talented microbiologists who can grow this stuff, we are not in that position right now. So, we really can only look at what happens in the patient.

So, I'll go over -- we count the number of bacteria, we do a membrane integrity testing as a sum assay that these microorganisms are viable, but that doesn't

prove they are. The true viability happens in the patient and so we sample the stool and see whether the species that -- by DNA, the microbiome that was put in, is still recoverable.

DR. MCCLANAHAN: Sarah McClanahan, Thomas Memorial Hospital. What are your thoughts on the transplant recipient being on proton pump inhibitors?

DR. KELLY: So --

DR. MCCLANAHAN: Have you ever looked at that?

DR. KELLY: In my patients, I think that I've seen that the people who administer it by the upper GI route do that -- kind of keep bacteria from killed off by the acid, I guess, on the way down. Since I do it by the lower GI route, I don't, and, you know, since proton pump inhibitors have been now, you know, at least reasonably defined as a risk factor for recurrent disease, if someone's on a proton pump inhibitor and they don't have any really great reason to be on a proton pump inhibitor, I usually have they try to stop.

DR. MCCLANAHAN: Yeah, that was my question, so you stop it a certain amount of time before, or --

DR. KELLY: Well, I just -- when they come to see me for the initial consult, I say, why are you on this, and 60 percent of the time they have no idea why, it just got put on during one of their hospitalizations and I kind of assess and I say, well, it doesn't sound like you need to be on this, and we just stop it there.

DR. MCCLANAHAN: Okay.

DR. KAO: John Kao. I'm with the University of Michigan. Colleen, I'm a fan. Thank you for moving this field forward. And so we've had about a year experience with FNT and when we found out that we -- I want to say that I share the same frustration that you had. When we found out that we needed the expanded IND, we had to put our program on hold, and I had to cancel all my cases. And you can imagine what the patients felt at that moment, you know, they had hoped that they can get this, they're hearing that the success

rate is 90 percent, and now they're on hold.

And fortunately I had some really good administrative helping me to try to move the expanded IND and the -- Dr. Steele has been helpful. So, I just want to share that frustration with the group.

DR. KELLY: Absolutely.

DR. KAO: My question to you is, as I move this program forward at Michigan, some of the comments that came down to me was, what do we do when we find a polyp? Is it okay if you take biopsies before we do the transplant? I mean, you mentioned that you do biopsies while -- before you administer them. What's your experience? Is it safe?

DR. KELLY: I routinely biopsy anyone who hasn't yet had a colonoscopy and biopsies to assess for microscopic colitis. In all these patients that I do a colonoscopy, I try to get into the terminal ileum and I do random biopsies in the right and left colon to exclude microscopic colitis.

I guess the polyp question, I guess it depends on the polyp and it depends on the

situation. If I've seen a very little polyp that I can just grab very easily, but I'm not going to be doing like a saline lifted piecemeal polypectomy during their stool transplant, you know, and anything -- I really haven't done any snare polypectomies, but I usually -- and the issue is, you know, from doing this is, once you put the stool in, you don't see anything, so you're not going to see the other polyps. It's not really an adequate screening or surveillance colonoscopy, so my argument is, yeah, I might get that polyp, but there could be three, four more that I didn't see, so in those cases I have them reprep and have a proper colonoscopy, you know, a certain number of months down the line.

And the issue -- and the one thing, because you mentioned this having people on hold feeling, that's how I felt through November, December, January as we were getting this expanded access through, and the one patient, who was one of the SAEs, the lung cancer that progressed and she got a post-obstructive pneumonia, they were waiting

on me. They wanted to take her to surgery and they wanted to do more things because they thought it was a limited stage cancer, but they were very hesitant to do that with her relapsing C. Dif because she would get so sick with the C. dif, and I said, well, you guys can keep her on Vanco and just do what you need to do and we can do her transplant later. But, you know, they were hedging on that, trying to decide what to do.

By the time we were able to do her, it was late January, and then a week and a half later she came in with the post-obstructive pneumonia and then her daughter said, you know, I'm really happy that you did this for us, but I think it was just too late and there's nothing they can really do for her cancer anymore, and she was put in hospice and died.

DR. McDONALD: Cliff McDonald, CDC. One question I have for you is whether you think you're seeing this more in men but now your clinic may be specifically a women's clinic, I realize that. Let me just make one

other comment, because it's very pertinent, and that is the population potentially in need, and I've discussed this with some FDA folks. We don't yet have an official overall burden estimate of C. difficile, but it's in the range of 500,000. We did provide some preliminary numbers from our emerging infections program at the fall IE course at 480,000. We're revising those. The number is a little squishy because it depends a lot on the use of PCR. It's very susceptible to that.

But if you look at that, we get a recurrence rate in that system of not quite 20 percent, it's probably more like 18,000, but to be conservative, 15 percent, that would give you 75,000 cases of recurrent C. difficile a year.

There is an estimate from the literature that the recurrence rate, if you've had a recurrence, is a little higher than 20 percent, in fact, it's 27 percent, but even so, looking at at least 15,000 a year of people who have had multiple recurrences as

defined by three or more overall cases within -- again, that's using the two-month cutoff for recurrences. So, 15,000 population of potential benefit annually.

DR. GORMAN: One last question.

DR. WU: Gary Wu, University of Pennsylvania. Thank you very much for a very thoughtful presentation.

I think informed consent is a really important issue here and I think to a certain degree, you know, acute transmission of pathogens is somewhat straightforward. I'm really interested in understanding a little bit more what you tell your patients about the more hypothetical long-term risks, because, you know, the scientific community is struggling to wrap its head around this issue and it's a very complex thing. So, what do you tell your patients about risk of cardiovascular disease, metabolic syndrome, those types of things?

DR. KELLY: The initial consult visit with them is usually about an hour and during that time, you know, once we determine

that they're a candidate, I give them like a little mini, microbiome lecture. I explain -- you know, I kind of put it in patient terms.

I say, you know, imagine you have a healthy lawn and a few weeds coming up and that's the C. dif, but your lawn has kind of gotten unhealthy and it's coming up all weeds and we want to kind of re-sow a new law, and kind of try to put it in terms they can understand, but I also do say, you know, as we're starting to understand more about these bacteria, we're learning they're really important, they're part of us, we can't live without them, we can't live healthfully without them, and they have all these roles in our immune system and in obesity. And I say, we don't really understand it. We're at the edge of this new era. And I say, because of that, I can't predict that there may -- I don't have a crystal ball to be able to say, 10 years from now, 15 years from now, something you have may or may not be related to something we're doing to you today.

But these people are feeling sick

today and a lot of them are old -- elderly people and they really don't care about what happens to them ten years down the road, they just want -- you know, and so, but I do have that conversation. It's well documented, and ire ally try to give them a lot of detail and really explain, this is considered --

DR. GORMAN: As Dr. Kelly was talking, I was reminded of a quote from Napoleon who said that all important decisions are made with not enough information, and I wondered if she knew now -- if she knew then what she knows now about filing an IND whether it would have ever happened.

And when we talk about informed consents about important decisions, I suspect we all thought we were pretty well informed before we got married and we all thought we were pretty well informed before we had kids, and I think a lot of us have found out that we weren't very informed at all.

I'd like to introduce Dr. Rubin from the University of Chicago, who is going to talk to us about FMT for IBD: Getting from

Point A to Point B.

DR. RUBIN: Good morning, everybody. I'm delighted to present this in what I've been envisioning was a journey, so I was happy when Larry mentioned this as a trip together and you're all co-travelers. It's nice to have a meeting like this, so I want to acknowledge the FDA and the NIH for pulling this together on short timeframe and getting us all together to talk about something we're all interested in.

I could have titled this very simply, "IBD is not C. dif" and I think I would have given you a message that's part of what I'm going to talk about. But people have been very interested in the concept of fecal transplantation in the field of inflammatory bowel disease as early as some of the early reports of using this for other conditions, and I'm going to take you through, recognizing we have a diverse audience, a little bit about IDB and how its condition is currently viewed by our world, and what we can think about in terms of whether or not FMT will be relevant

for that population.

I have no relevant disclosures related to this presentation or the work we're doing in this field.

So, it's estimated that there are currently 1.5 million people in the United States who suffer from Crohn's disease or ulcerative colitis, in Canada, between 500-700,000. It's divided approximately 50 percent ulcerative colitis and 50 percent Crohn's disease, and in some recent studies, it appears that Crohn's disease has been rising. We saw a nice graph that looked at the decline of infectious diseases and the rises of immune mediated or allergic diseases.

And in Asia, there's been quite a distinct and rapid rise of ulcerative colitis reported in Japan, Korea, China, India, and that's of quite great interest in terms of understanding these conditions.

There have been some demographic shifts, in other words, what was seen to be IBD 50 years ago, may not be the same IBD we're seeing now in a variety of different

ways, and that may pose some important questions for us about the role of environment today versus maybe a larger role of genetic disposition earlier. And the long-term outlook of IBD is specifically these are chronic conditions that are lifelong in most patients, without medical cures that are known, surgery is frequently necessary, and there's a variety of other psycho-social and obvious co-morbid factors that go along with these.

Just in one study, this is looking at the Olmsted County population database from Minnesota. You can see what's been tracked in terms of the overall incidents of UC and Crohn's over time. They've reported ulcerative colitis flattening and there's been some other work in the United States that suggests this may be true. Clearly, Crohn's is rising, and when I talk to my colleagues around the country, their observations in their own practices seem to mirror this as well.

We also understand that the number

of people with IBD continues to rise because most people live with this condition as opposed to die from it.

The classification system of IBD has really been largely based on phenotype, meaning, how we see the condition clinically, and for all these years we've been talking about Crohn's disease and ulcerative colitis, with an overlap in the middle of about 10 percent that we would call indeterminate colitis, either there was some feature of their colon that was inflamed that looked a little bit like Crohn's, some family history that confused us, or maybe the patient who's had longstanding colitis and then develops a simple fistula and people are confused about what might be the diagnosis.

The reality, however, is that these are much more heterogeneous diseases and there's a lot of complicating features to all of this.

If you look back at all the different people who have thought and studied and tried to figure out what's causing IBD

from the earliest days and the earliest optimistic reports that someday we're going to figure it out, there's a recurring theme, and the theme has been that people have really thought that IBD must be related to some complicated infection of the bowels, and you can see this emerge in a variety of different reports throughout the ages.

This is extracted from my mentor, Dr. Kirsner's, textbook in which he tried to summarize a lot of the different thoughts and theories about what had been going on with IBD over the years, and I put arrows next to all the different theories and emphasis that's been placed on whether or not this was, in fact, just an infection.

Now, the infectious hypothesis related to IBD is obviously not as straightforward as you might want it to be and the fact that we can treat these conditions, in many cases, with immune suppressive therapy and patients either respond or go into remission and don't get worse, is one important observation that suggests this may

not be as straightforward as we'd like it to be.

Nonetheless, this keeps emerging and it's of great importance.

There have been a variety of theories, as well, about the changing IBD epidemiology. As everyone in this room is aware, the hygiene hypothesis postulates that the environment has become too clean, that our guts are designed to interact with our environment or to be infected or coexist with parasites in some ways and that when we're younger, we have a developmental phase in our immune system that no longer is exposed to the right things to train it to respond properly, and when we become young adults and we do get exposed to something, there's this turned-on immune response in the gut that loses its ability to regulate, and that's what we call IBD.

There persist some infectious hypotheses, whether it's mycobacterium or some unknown organism, and more interest now in potentially viral, or viral and bacterial

coexisting or cofactor type infections.

There have been a variety of theories about the changes in the gut microbiome related to our westernized diet. In fact, that's the prevailing theory in Asia right now. And a variety of different theories that may be just epi-phenomenon related to either the rise of refrigeration, pasteurization.

And if you ask patients in clinic who have IBD, which I do everyday, what do you think caused your IBD, they almost always say stress or the person sitting next to them will say, he or she is too stressed, and then they'll identify some reason for that, although people have tried to study this, and as you understand, it's very complicated.

Ulcerative colitis and Crohn's are both heterogeneous diseases. In UC, we talk about the extent of the disease bearing, in adults especially, 30 percent may just have the rectum involved and another 40 percent will have just the left side of the colon, and another 30 percent, the entire colon.

There's also differences in patterns of behavior. About 5 percent of people with UC will have an acute episode, their biopsies will even show some chronicity and people will call it ulcerative colitis and they'll never have another relapse, yet they're on medication or they're being followed, and at some point in their future they say, I don't know, did I ever really have that, and somebody will scope them, do their biopsies, biopsies come back completely normal, and in retrospect we either say this was a self-limited ulcerative colitis or it was an acute self-limited colitis, which may be the same thing.

Most other patients, however, have a chronic condition that either is reflected by varying patterns of relapses and remissions, or may be related to a very quiet diseases that for reasons we don't always understand, can become fulminant and then doesn't respond to therapy.

There's also some important observations about C. Dif and IBD, but I'm

not going to get into that very much right now.

Now, there are really interesting observations. This is the first endoscopic photo of our conference, I'm proud to put that up there for you, this is what ulcerative colitis looks like in a patient of mine who had left-sided disease, and one of the interesting observations that I wish we understood more, and we still don't, is the distinction between the distal disease being active and that line of demarcation that someone almost took a straightedge and drew a line in the person's colon where above that, the biopsies and everything looks normal. It's a very important observation that would suggest something complex going on, either that the mucosa is different in that location, the blood supply, the lymphatic supply, or maybe even a specific infection that is involving specific portions of the anatomy. But that's an important thing to keep in mind as well about all this.

Crohn's may be considered even more

heterogeneous, not only in location of disease, but also in behavior. We talk about primary inflammatory Crohn's, we talk about penetrating or fibrotic Crohn's, and in fact, we've started to think about a lot of these as overlapping.

The location of the disease in an individual patient tends to be constant, so I always remind my patients that when they read about Crohn's on the Internet, they shouldn't be thinking that tomorrow they're going to wake up with their Crohn's disease everywhere else in their body, because that's what they all think, but rather where it is when they're diagnosed is where it's likely to stay. And there are some challenges to treating Crohn's.

One of them is acknowledging that this is a progressive disorder in many patients, meaning the cumulative damage from inflammation can lead to structural changes and then therefore patients are more likely to need surgery, less likely to respond to therapy. So, we have to keep in mind that when we're thinking about administering a

treatment that we think may be at the core of what may be causing the disease, but there may already be a lot of damage that has occurred, and we talk about this a lot.

These are some of the endoscopic photos of patients with Crohn's disease, and you can appreciate the classic findings of a patchy disease, deeper ulcers, what previously was called "cobblestoning" because of the ulcerations that are adjacent to sort of swollen hypertrophic areas and the disease that can be seen in the rectum in this picture of retroflection.

We also have the very important feature of Crohn's disease that 25 percent of patients may have peri-anal involvement.

So, if you wanted to have a unifying diagnosis for Crohn's disease involving a dysbiosis or some specific infection, you'd like to understand why it would appear so heterogeneous. An alternative explanation, however, is really that Crohn's disease represents many different diseases that we've been labeling the same all these years.

We also have a variety of challenges to medical therapies for IBD that lead to people considering alternative approaches to treatment. We don't have a medical cure. Our current therapies have unpredictable response rates and are not durable. It's not clear which patients should receive which therapies. There's a lot of debate in our field and it seems to change every six months. We have some concerning safety profiles regarding chronic therapy in a young population who's going to have the condition for a lifetime. And we also know our patients are unlikely to stay on their maintenance therapy despite education.

There's also a big issue regarding access, but that's another lecture.

Our simplified theory of the pathogenesis of IBD said, well, a genetically predisposed individual has some exposure to something in the environment and leads to an abnormal or unregulated immune response.

We've started to understand this a little bit clearer by first understanding that

there are some serologic markers that correlate to these different conditions. I point this out specifically to say that we know that people with IBD have leaky bowels and that we understand that they are exposed to antigens and develop some antibody responses, specifically in Crohn's, but you can see this in family members of people with IBD and that these can correlate to something that either is loosely tied to diagnosis or clarification of diagnosis, but may be better associated with prognosis.

And there have been a variety and an explosive amount of information in the genetics of IBD, just further demonstrating how complicated this really is. In this most recent paper in Nature, looking at the (inaudible) studies of IBD in genetics, 163 genes have been confirmed for Crohn's, and you see 110 of which overlap, but of great interest to discussions about potential causes or overlapping physiologies had to do with some of the common pathways that were identified related to infectious diseases or

other immune-mediated conditions.

There is, of course, the observations, as well, about all of these environmental causes in IBD, those that might be related to an altered microflora, like exposure to antibiotics or something in our diet, and those that might be exposed or contribute to an altered mucosal barrier, like infections NSAIDs, smoking, or maybe even stress.

So, what our current understanding is, is that the summation of events that leads to chronic IBD is really genetic polymorphisms, some kind of post-genetic modifications, whether it's epi-genetics or something else, some other external pressures, the colonization with the intestinal flora from childhood or alterations of that over time, and a variety of environmental factors that all come together.

So, I can conclude here by saying that, clearly, IBD is not C. dif but obviously it's a very complicated problem. Nonetheless, there's indirect evidence to suggest the role

of bacteria, or at least the role of antibiotics in the field of IBD. We know that patients who have been exposed to antibiotics or develop a traveler's diarrhea or some type of infection may actually have the onset of their IBD. That's been well described.

We also know that animal models who are susceptible to developing IDB, when raised in germ-free facilities, won't develop their colitis until they are exposed to the organisms.

We have the serologic markers that I shared with you, and then we also know some observations about treatment. If you divert the bowel in Crohn's, about three- quarters of patients will go into remission distally, it turns off the disease. If you treat post-op Crohn's with a primary anastomosis using an antibiotic, it will prevent recurrence, and in fact, there's an elegant study in a few patients where they diverted these patients and took the effluent from the small bowel and squirted it into the colon and they were able to replicate recurrence of the inflammation.

Now, this has been suggested to be related to feeding the bacteria that live in the bowel. That hasn't been completely proven, of course.

The condition called pouchitis that I'll talk about a little bit more is treated effectively with antibiotics and there's been some interest in probiotics, but not very good evidence for it.

Now, studying the microbiome in IBD starts with the most fundamental question, which is, how o you even classify these conditions appropriately? And how do you think about what's going on in these patients? You also have to understand what's happening over time. There's a distinction between remission and those patients who are actively flaring or having relapses.

You have to also understand what your endpoints will be. There's a very big difference in our field between the symptom improvement in many of our patients that's reported in some of our indices, and of course, more objective measures of disease

management like mucosal healing or other serologic markers of inflammation.

We, of course, had the same challenges that have been discussed already in terms of how you might deliver agents, how you standardize interventions, how you discuss safety in the population, and then understanding a little bit more about whether what we're observing in the microbiome with people with IBD is really a cause or an effect or maybe both.

There have been some small studies that have looked at this, and I wanted to point out to you this particular study from 2008, in which patients who had Crohn's disease -- this is NI, not inflamed versus Crohn's disease inflamed compared to ulcerative colitis, not inflamed, ulcerative colitis, inflamed, and then a healthy group. You can see some differences in the e-coli equivalents and beta-actin equivalents that were measured in these and the variability that was observed.

There have also been some studies

that have demonstrated that IBD patients have more variability in their microbiota over time than healthy people, so those who don't have IBD or susceptibility to it seem to bounce back from a variety of insults in their bowel, and those who have IBD tend to have some fluctuation over time or may actually lose control of their microbiota stability over time.

So, this seems to be a very important observation and something that would potentially lend itself to thinking about doing fecal transplantation in a population like this.

I mentioned the pouchitis patient. I'm showing you this diagram for those who don't know what this is. People with ulcerative colitis will need surgery when they have medically refractory disease, or when they develop neoplaysia. The surgery of preference in younger patients is to remove the rectum and colon and to create a new continent reservoir that's connected to the anal canal that's called an Ileo-Anal J pouch.

Now, these patients with IBD who get J pouches will have a risk of developing inflammation that responds directly to antibiotics, which we call pouchitis. Of interest, people who have the same surgical procedure for familial polyposis do not develop pouchitis. So, this is clearly a variant of IBD in people who are otherwise susceptible.

Now, in this interesting study from Israel where they looked at the organisms in the pouch, they found that when the patients did not have pouchitis, they had a specific distribution of organisms favoring the firmicutes, and when they developed the pouchitis and when it became "active"< you can see there was a predominance or at least an increase in predominance of the proteobacteria. Treatment with antibiotics, which is standard of care for pouchitis, led to restoration of that previous pattern, and you can see when the patient had recurrence, it was observed again, the same pattern.

So, this was the first evidence that

tied together what we've been doing, which is treating with antibiotics with some microbiome information that we thought was of great interest.

Now, the thought would be, and this was mentioned yesterday in one of the first lectures about Koch's postulates, that if we actually understood that there was a theory about the specific role of an organism or organisms or the microbiota in the pathogenesis of IBD, it would be really nice to document that, to look for Koch's postulates, which you all know or remember, and then to develop targeted interventions.

However, in our world of IBD, there haven't been very many successful observations of specific organisms. For a long time, and this is a study from the University of Chicago from the 1930s, they were focused on an organism at the time called bacterium necrophorum now called fusobacterium necrophorum and they thought this was the cause of ulcerative colitis. But there were some studies in which they tried to reproduce

what they were observing in these individuals and they couldn't, and that sort of fell out of favor, although it's having some rise of interest in Japan now.

And so what we're left with is the idea that, well, we have a theory, let's skip the middle step and just treat somebody with everything that's in a healthy colon and then figure it out later. And that's a problem in IBD if we're not sure what's going on and we have a great heterogeneous population getting treated with a variety of different agents.

So, I think it's obvious that C. dif and IBD are quite different conditions, and that's one of the first things I say in the many emails I receive from desperate patients every week, that we're enthusiastic, we're interested, but we have to keep in mind that these are very different conditions and that, so far in IBD, we don't have strong evidence to know what we're doing with this.

This table summarizes the case series that have been published related to IBD. After the break, we're going to hear a

bit more about this wonderful pediatric trial, so I'm not going to spend much time talking about that, but you can see some of the early series from Tom Barody, although this includes IBS as well, but Tom has published a nice series of patients in which he has reported complete normalization of histology in some of these patients with UC. He's come to share that he thinks patients with IBD probably need multiple treatments, and he acknowledges, as well, that it's not every patient who is going to respond to this.

My colleague, Severine Vermeire, has looked at patients with medically refractory Crohn's, which we might argue is the wrong patient population to try and look at this in, with limited success and no good strong outcomes.

This is Tom's study from 2003 looking at these six patients where his follow up of significance in some of these patients showed complete normal histology, so this certainly drives some of our patients' interest in this field and wanting to get

involved and come to us for fecal transplants.

So, who would you include if you were going to design an FMT study in IBD and you wanted to study this further? Should it be UC? Should it be Crohn's? Adults? Kids? Colitis? Ileitis? You see the complicated features that make this very difficult for us.

How severe should their disease be? Should they be in an active flare or should they be actually in remission when you decide to do this? Should it be someone who's newly diagnosed or someone who has longstanding disease? And there's a variety of other factors related to therapies that worry us. Patients on concomitant immune therapies, even though we've heard anecdotally at this meeting seem to do well with those who have been receiving FMT for C. dif and have had organ transplants or IBD or other things. We still have some concerns about what might be happening in somebody who has a mucosa that's been injured or ulcerated and is on some therapies and then we're introducing an entire other host's microbiome.

Stacy Kahn, who has really been leading a lot of this work at our institution, has been working with me and did this nice focus group study initially with our patients with UC, so acknowledging this is an IBD population at a referral center, but they all, as you might already know because you're sitting in this room, thought this was natural, they thought it must be safe. Even patients who were in stable remission from our clinics who were part of this evaluation told us they would rather do this than be on their medicines, and I think that we all understand that.

The focus groups led to a survey instrument that we designed and then just published, and this gave us some guidance as to who should be the donor, or at least who the patients want their donor to be, and surprisingly, a large number of our patients didn't say they needed a directed donor, they would trust the doctor to help them understand that, which is of interest, and there are a variety of other concerns that we could talk

about later.

Now, there's a variety of different concerns that we have regarding protection of human subjects and how this could go forward in our field, and I think it applies to C. Dif as well.

My general philosophy has been that desperation is not an acceptable recruitment strategy and I think most in here would agree with that, but desperation in the absence of clinical efficacy benefit that we know of, especially in IBD, is a big problem, so that's another distinction from C. Dif.

Neither is lack of insurance, and our institution doesn't allow us to recruit anyone without insurance anyway.

Clinical trials of FMT require safeguards, and we've been saying that all along, and we also think that donor protection is of interest, and I was happy to see Colleen mention that.

So, we actually had an ethics conference just on this topic: who should be our donors? And what was brought up is that

in organ transplantation with living donors, they have an opt-out. If the donor, behind a closed door, tells one of the screeners that they really don't want to donate their kidney or part of their liver to this individual family member or whomever, the opt-out is we walk out of the room and we say, it's not a good match, we've done our tests or evaluations, and we don't tell the reason.

In stool, or at least directed donors with stool, the concept is they ask someone, they show up, they want just your stool, and nobody really thinks more about it, and so our ethics board really brought up that there wasn't an opt-out for donors.

After a lot of discussion, we also decided for that reason, among the others that have been raised here, that anonymous donors was probably better. Treating this like blood transfusions and storing donors, and that's why I'm very interested in Alex's presentation later and understanding more about this, but from a cost containment point of view as well, especially for study design, having a single

or a couple donors that you've screened and then can continue to use is a nice thing.

We've heard a bit about regulatory issues and both from our IRB locally, the FDA, who actually have been very easy to work with, but a very challenging process, and then a variety of other local agencies, we had a lot of discussion as well with our infection control group, our ethics group separate from the IRB, and our P&T committee.

So, here's what happened at the University of Chicago. So, we submitted our IRB in October 2011 proposing to do this in ulcerative colitis patients. And they came back and said, we're giving you conditional approval, but you need an IND. And we said, oh, we had no idea. Are you sure? And they said, we're sure. And we said, okay. We called the FDA and they said, yes, that's what you should do.

So, the process then began and we started to submit our pre-IND, and I want to thank Colleen and Larry for sharing their hard work for us, but we modified for IBD. We

received the initial response. We worked with a very helpful person at our institution who has some experience with this, and then we submitted our formal 206-page IND in January.

While this was all going on, we had to withdraw our original IRB submission because it was expiring, they wouldn't sit on it any longer, and they told us, just resubmit it after you get your IND or when you're close.

So, we submitted our response to the suggested changes and then we got some additional suggestions from the FDA from a different reviewer, which were helpful, but a lot of extra work. So then we just submitted our final 168-page response to the most recent IND request. Simultaneously, we've gone back to our IRB and we had our other conferences at our institution to make sure this was all going to make sense.

So, we've been working hard to try and get this going.

We're going to study this in ulcerative colitis, and I have a particular

interest in people who have milder disease and either newly diagnosed or failing 5-ASAs only. I don't think we should be doing this yet on people who are on more potent immunosuppressive, not only because of safety concerns, but I think then we're selecting out a group of patients that may be more refractory, and I'm not even sure I understand yet what the immunosuppressive therapies do to the microbiome in these individuals anyway.

We have translational endpoints in this study, which we're calling a Phase I trial, that include looking at the microbiota of the donors and the recipients and we'll be exploring that carefully with our colleague Gene Chang at our institution. And then we have a variety of things built in for ethics and safety, and Stacy just got a grant to look at tolerability as a separate issue as well.

So, rather than go into all that right now, I think I'll just summarize, because we'll have time to talk about any other questions. The concept of modulating fecal microbiota in IBD is not new at all and

there's lots of indirect evidence that bacteria or some combination thereof play a role in IBD, or at least antibiotics can be used to treat parts of it.

However, we have to be careful as we move forward with this for a variety of reasons. This is clearly not the same as C. dif, and I would encourage all of you who are getting inquiries about doing this in IBD patients to be mindful of that and to communicate that.

I do think that this is worth studying and the key is really to be very careful about which patients we include and who they are and what their disease type is and we should not be thinking about just doing this in all IBD and mixing things up because we're going to get very confusing results and we won't be able to move the field forward.

I want to spend a minute to acknowledge the many, many people. It really does take a village to do something like this. First and foremost, Stacy Kahn, who's one of our pediatric faculty and is here at this

meeting, Gene Chang at our institution, a variety of people from my group who have helped us with all this including Dylan Rodriguez, who maintains an FMT LISTSERV, so anyone here who's not on our LISTSERV but would like to be included in that, for those group emails that go out occasionally and people can communicate back and forth, we're delighted to add you. Just give me your email address before the end of the meeting today. Our infectious disease colleagues, very importantly, Allison Buanamici, who helped us with our IND work, at the FDA we're grateful fro Matthew and Katie, and then a variety of other folks around the country, in particular around the world, Tom, Larry, and Colleen.

And with that, I'll conclude and look forward to your questions. Thank you.

(Applause)

DR. GORMAN: Questions for Dr. Rubin.

DR. KHORUTS: Alex Khoruts from Minnesota. One of the many differences between C. dif and IBD is that the C. Dif

patients, at least the multiply recurrent type, are carpet-bombed with antibiotics for six months plus. By the time that's done, most of the attacks are gone and you have very limited diversity left. So, you put in the material and then you see this rapid normalization of ecology, if you will.

In contrast, the IBD patients, while they may have somewhat diminished diversity, it's nowhere near that. So, in your protocol, are you planning to pretreat them, precondition them? How do you decide? Do you just do it -- just put in some stuff or antibiotics, what kind, and for how long?

DR. RUBIN: Excellent question. So, part of understanding the difference between IBD and C. dif does happen to do with modifying or understanding what the baseline micriobiota profile is in these individuals.

In our patients with IBD, they're not going to be specifically pretreated the way you're asking. I don't know whether that will guide us further or not. Obviously, we need to know more about whether that's

necessary. So, in other words, do you eradicate the organisms in the bowel before you try to give something new? We've considered doing some antibiotic therapy on the way to that, but we're still sorting that out.

Do you have a recommendation, Alex?

DR. KHORUTS: Of course, it's speculative and I think it's totally fair to try. It's the simplest, you know, you could argue for whatever, but my guess is it's going to be a diversity of protocols will need to be tested and one can, you know, say in ulcerative colitis, perhaps, your literature suggested, aminoglycosides were somewhat helpful in the short term, so perhaps they're targeting something important, or maybe not.

I think that's going to be part of a rationale for multiple trials and trying to explain it in different ways.

DR. RUBIN: Well, I can tell you for sure, we won't give them Clindamycin. But your point is very well taken. I think it's an important question.

John?

DR. KAO: David, great talk. John Kao from University of Michigan and, David, I just want to thank you for getting the FMT group together. I think you really should be applauded for your effort, which culminated to a meeting like this, and thank you for letting us know about the requirement for an IND so that now we're trying to be compliant.

The question I have for you is, you know, we've seen some case series from Borody that FMT will work for IBD, but we've also heard from Colleen that in her series, her experience for a C. dif patient that also has UC. It did improve their C. dif but not their UC. So, in your mind, what do you think is the difference? Have you had a chance to look at the differences? Is it the duration of treatment, number of treatments? Is it patient selection? What's your hunch going forward before you even start your trials?

DR. RUBIN: Well, I was very interested in Colleen's case report because this is, of course, one of our fears is that

people with IBD will get worse, not better, and that's certainly something we have to keep in mind, and that issue has not been raised or needed in the C. dif discussion so far.

I'll tell you, and I do have permission to mention this, but I didn't have a slide, in press is a case series from Amsterdam of five severe UC patients and they did not have a clinical response and a couple of them actually got worse.

So, we do have to keep in mind who these patients are, and my theory has to do with how I designed our study or how Stacy and I talked about this, which is, if we take people who are sicker and on these other therapies, we're going to be in trouble.

Colleen's case stands out unique because this individual was in complete remission when she looked at his bowel and had been on no therapy for 20 years, so you almost wonder what type of UC that might be. So, I'd put that one aside and I would just say, we should really start with patients where we clearly know what they have, where their

disease severity is less than the patient who really just should go to surgery, and look at those individuals first and then move from there. That's the best I can say.

Larry?

DR. BRANDT: Yeah, I have an experience now of about 25 patients with inflammatory bowel disease that I treated, and these patients are not treated as C. dif patients, they're treated by an arbitrary protocol in which I give them a colonoscopic infusion of stool in the typical fashion and then I have them and teach them how to give themselves a squeeze enema of 60ccs of stool and I have them do that every day for a week, every other day for two weeks, once a week for four weeks, every other week for eight weeks, and then monthly as maintenance.

Disease patients -- I treated several different types of patients. Most of the patients were patients who had severe ulcerative colitis defined as requiring immunosuppressives when the patients didn't want to take immunosuppressives, and therefore

they came to me as an alternative, or patients who were ready to go to surgery but didn't want to be operated on and came to me as an alterative, and patients who were on immunosuppressives and biologics and weren't responding to them. And I've had short-term and long-term patients.

And what I've noticed is, as you sit, this is a very disparate group, patients respond very, very differently, I absolutely agree with narrowing the field so you treat a consistent group. I think that the patients who responded the best are the ones who have the disease for the shorter period of time and who had it clearly precipitated by an infection or by C. difficile and I have cured a small number of those patients, both clinically and histologically. But I also have made very stable and very healthy some patients at the far end of the spectrum.

I had one particular case that I'll share with everybody and then I'll stop talking, about a young man with Crohn's disease who jejunoileitis, and he had this

disease many years and was one of the patients who self-treated -- put in a nasogastric tube every night to nourish himself because he couldn't eat. And he did this for many years when he was a young man -- a teenager.

And now I see him at age 27 and he starts not to do well again, and he was on a variety of agents and he wanted me to talk to him about fecal transplant.

So, I said to him, well, you're so used to this tube, why don't I put down a nasal jejunal tube in you, and for those of you who don't know, it's a tube that goes through the nose and let's say halfway down the intestine, and I used a special tube that doesn't come out, it's anchored down there. And I had him self infuse stool every night before he went to sleep. And he did it every day for two weeks. I figured if it didn't work after two weeks, it's not going to work, and every day he kept very careful notes on this. Didn't do anything.

Now, that's an n of one. You can't get much less than an n of one, but it was a

very instructive case because what it said is, you know, this doesn't work on everybody, and number two, you ought to be more selective in choosing who you should do this on, and I think that's what you're talking about today and I think you should be commended for that.

DR. RUBIN: Well, the points that you made very nicely are the duration of his disease was long, and the location of his disease was small bowel. And we haven't even talked about small bowel and microbiota today or yesterday, so there's a difference in our considerations and that's really what my point is. So, thank you.

DR. WU: Gary Wu from University of Pennsylvania. Thank you very much, David, for your presentation. You know, there are a lot of associations between the gut microbiome and human disease, but actually the only evidence for cause and effect relationships for most of these diseases processes have been demonstrated on animal models and one of the biggest challenges for scientists over the next decade or two is to determine how much of

what we understand in animal models is relevant to human disease.

So, in that respect, I mean, I think FMT in carefully consented patients with all the safeguards that you obviously have gone through are very important in terms of proving cause and effect relationships in human subjects similar to what has been demonstrated in clostridium difficile colitis. So, I'm very interested in understanding, in your clinical study, how long will you be following your patients after transplantation? And I presume that you'll be collecting stool samples for analysis on a regular basis, but I'm wondering how far out will you be monitoring these patients?

DR. RUBIN: Well, so, Stacy, was it six months? Or how far are we going to continue to follow the individuals?

MS. KAHN: Six months.

DR. RUBIN: Yeah, so, the original study is its design is six months. Obviously, we'll have interest in following longer if we need to. We will -- we have a number, I have

the schema, but I hid it because of time, but we have a number of time points where we're not going to -- not only going to measure stool, we also are going to continue to measure fecal calprotectin, a variety of serologic markers. We're going to try to collect more than just symptomatic improvement, which we know is not sufficient to really give us the data we need for this.

So, I think it is important, as you said. My concern about our study, to be transparent, is that I'm not sure a single colonoscopy, as we've designed it similar to what's done for C. dif, is the right thing to do for IBD, although I would counter that by just saying that because we're doing mild ulcerative colitis, I think that it's an unproven hypothesis. We need to start somewhere, so that's why this is a Phase I, in a way. We're going to look at safety and a variety of other factors, we're going to sort of get our ducks in a row, and then we'll go from there.

DR. WU: Yeah, as you know, I mean,

whatever you find will be very interesting because, again, it could be that the microbiota is dysbiotic simply because of the inflammatory process and whatever you put in just becomes dysbiotic in a short period of time, but I think the longitudinal aspect of your study is going to be very important.

DR. RUBIN: Thank you.

DR. GORMAN: Thank you, Dr. Rubin. In the interest of time and to give everybody an intellectual break and a chance to talk to their colleagues, I'm sure Dr. Rubin would be willing to answer questions not at the podium.

Could we reconvene at 10:45?

(Applause)

(Recess)

DR. GORMAN: If we take our seats and become quiet, we can have lunch. Was that good? All right, troops, I'm going to take back everything nice I said about the FDA if the FDA contingent doesn't sit down. I still see two FDA members standing. Okay.

Thank you very much. We'll continue this morning's session with a presentation

from Sachin Kunde, and since I come from Brooklyn, we would pronounce this the Helen DeVos -- but I suspect it's "Devois" -- Children's Hospital, and he will be presenting on "Preparing for Regulatory Challenges: Experiences of the Pediatric FMT Trial".

DR. KUNDE: Good morning, everyone. My name is Sachin Kunde. I'm a pediatric gastroenterologist and I'll be talking about experience from a recent pediatric fecal transplant trial that we just completed.

The study was funded through Helen DeVos Hospital Foundation and I do not have any other disclosures.

So, what we have here is we think we have a treasure, but we can't use it. We can't use it because there are hurtles, and my goal today is to stimulate a healthy discussion among ourselves and as well as try to get some answers from FDA to help clinicians offer this, and we will do this by sharing my experience that we had during this clinical trial.

So, Dr. Rubin just set the stage for

this. We know that FMT is efficacious in C. difficile infection by a recently published trial, and potentially it may be efficacious in inflammatory bowel disease and it may be a future consideration for other diseases as well.

We also know, and that's why we are here, is it's been classified as a biologic. When used to mitigate a human condition, it is classified as a drug and it will require an IND if you use it in human subjects if you intend to use to treat a condition.

So, let's look at ongoing FMT trials that are ongoing at this point. And there's a lot of interest in C. Difficile infection, also colitis, Crohn's disease, and type II diabetes mellitus, but I would like to point out that only two of them are pediatric trials, which is still encouraging, at least people are thinking about using this therapy for children because they also suffer from these diseases.

Mass General is conducting a Phase I study and also Seattle Children's is

conducting another Phase I study looking at children with inflammatory bowel disease.

So, if we look at literature, and I will just briefly mention this, the recent review of different case reports looked at patients who received FMT in inflammatory bowel disease, and 26 percent of patients (inaudible) lower (inaudible), only 7 received upper GI route, and they showed 76 percent patients -- there was reduction in symptoms, 76 percent patients decreased IBD medications, and 62 percent patients claimed remission, but this was with or without C. difficile, but if you look at the subgroup of those patients, 18 of them had only inflammatory bowel disease without recurrent C. difficile infection. And 72 percent had reported resolution of symptoms.

If we look at some important case series that have been done so far, and if you look at the outcome in the last column, you will see there is a clear difference depending on the route of administration. Although there is no prospective study and not clearly

studied in IBD, enema or lower GI route of administration seem to be more effective than upper GI route of administration, although probably the patients that they were selected for upper GI route administration may not be ideal.

So, why it's important to study IBD in children and fecal transplant in children, because 700,000 people in the United States have ulcerative colitis and one in four are diagnosed during their childhood. So, they have -- this is a lifelong condition that they're suffering starting in the beginning of their life.

Only limited data is available if we look at children with IBD looking at FMT, and this is only case report -- two case reports, actually, published by the same group, and the only mention was that the enrolled patients starting at age 11, but we don't know the outcome specific to pediatrics in those case reports.

So, we recently conducted a study, which was a Phase I study looking at safety,

tolerability, and clinical response after FMT in children and young adults with ulcerative colitis. The study is recently accepted for publication at The Journal of Pediatric Gastroenterology. We enrolled ten patients, age ranging 7 to 21 years, and we were only looking at clinical outcomes at that time along with safety and tolerability data.

We prepared fresh fecal material from related donors and most of them were their mom or dad or a sibling. We preformed fecal enemas everyday for five days. We aimed to instill eight ounces of enema, but we were expecting them to hold at least two ounces.

All of the patients were negative of C. difficile infection and they had mild to moderate ulcerative colitis based upon the PUCAI scoring.

So, we started off with getting an IRB, which was in fall of 2011. We got an IND in early 2012, and the study was completed in ten months.

So, this was a study design. In week one, the first week, subjects and donors

who are enrolled and the consents were opt-in. Donor screening took place in the same week. And the baseline PUCAI score was calculated.

In the second week of intervention, of course they received fecal enemas for five days, and every day we were monitoring the adverse events.

From week three to six, which is four weeks after fecal transplantation, we had weekly PUCAI score monitoring, as well as we monitored adverse events weekly.

So, these were some of the adverse events that we saw, and they probably closely correlate with The New England Journal paper, except the one which is fever, which is a significant one, but almost all the adverse events were easily manageable and expected by patients -- bloating, abdominal pain and cramping, diarrhea, blood in stool, fatigue, and interestingly, two patients had fever. One of the patients had fever only on the first day and didn't have any fever for the rest of the four days. The other patient, who was a 20-year-old female, who developed fever

for first day and the second day, she would develop fever within three to four hours after fecal transplantation, which meant she was at home, and within next three to four hours, the fever will disappear. So, by the time she will wake up in the morning, she would be completely fine.

So, when I saw this pattern -- and that's why we call this probably related to FMT and not necessarily possible, so it's probably more related to FMT installation. I gave this patient an antipyretic and antihistamine, just simple Tylenol/Benadryl within 15 minutes after fecal transplantation on day number three, four, five, and I was able to suppress the fever.

So, there might be some systemic short-term immune response, which is probably manageable, like as if you have an infusion reaction. And that fever -- the response of fever has been shown in previous case reports as well without signs of sepsis.

So, the patients, even though they were children, we were very pleased with the

tolerance that -- the amount of fecal enema that they were able to hold. Only one in ten subject was not able to hold any fecal enema, and that was probably related to his anxiety and he never had fecal enema or enemas before, and this patient was an 18-year-old adult.

The average tolerated enema volume was 5.5 ounces, that's 165 mL, and the average retention time ranged between 3 hours to 24 hours. So, on average it was 10 hours per patient.

And we think the possible factors that can influence the tolerability of fecal enemas, of course, previous experience with enema, disease location if the patients have more symptoms of proctitis or distal disease, and of course, anxiety of a child, and most importantly, parents, do play a lot of role because these patients and families were traveling to us, out of Michigan, even from Canada, and when they come here, I mean, all the family members are sitting in the room and the child is getting enema, and if they are not able to hold it, the expectation from

family members is really high, and that actually precipitates the intolerance.

We also looked at clinical response. So, in this graph, on Y-axis, you have PUCAI score -- higher the score, the worse is the disease, and on X-axis you have weeks in duration.

Week one we had enrollment, week two we performed fecal transplantation, and week three to six, four weeks of follow. As you can see, immediately after the fecal transplantation, at third week, there was a dramatic response in most of the patients. So, seven of the nine, 78 percent, had clinical response within one week, which was defined as decrease in PUCAI score by 15 points. Six out of nine, 67 percent were able to maintain this clinical response by the end of the study at one month, and 33 percent of patients claimed remission based upon PUCAI score going down to zero within one week after fecal transplant, and they all maintained that remission by the end of the study.

So, when we compared the PUCAI score

before and after, there was significant improvement after fecal transplantation at one month after FMT compared to their baseline score.

So, we are concluding that fecal enemas were feasible and well-tolerated by children with ulcerative colitis. Adverse events were acceptable, self-limiting, and manageable for the subjects. There were no serious adverse events noted. And FMT indicated possible efficacy in the treatment of ulcerative colitis.

So, how did we achieve this? I think, of course, we had a team approach from the beginning and we anticipated a lot of hurtles on the way. The most important player in 2011 when we conceptualized the study was IRB. At that time, I was not personally aware that FDA needs to be involved in this process because we were not aware about this being a biologic.

So, we are going to -- I'm going to discuss a few points, which will be controversial and that's the point of this

discussion is to whether these are important or not.

So, when should the IRB be involved? Of course, if it's a research study, you have to have IRB approval, and that's what we did, but moving forward, if it's a non- research study and if you are only using FMT as an intention to treat on clinical basis, whether it's for C. difficile infection or IBD, should you have IRB approval or should you get your IRB involved? And an answer may be yes, but that may be debatable. Because, of course, we're not -- we're using a drug, which is not approved, we're considering this as a biologic. There are limited data available, and we are requiring to get an IND. So, your local IRB may want to be involved in this process to oversee the use of this biologic.

So, if you are planning for your IRB application and you haven't started it or you're in the middle of this process, I would recommend addressing every safety concern that you can imagine. Donor screening, of course, there's great guidelines available in Clinical

Gastro. Route of administrations, the safety data -- I mean, it's not prospective, but whatever retrospective studies we have are out there. Radiation safety would be important if you are considering putting an ND tube or nasojejunal tube, and that's something you need to address with your local IRB.

If you are preparing and freezing the material, and Dr. Khoruts will address this, and you're thinking about adding glycerol, make sure you address this concern because IRB members are not physicians and they may not be aware of the literature out there, so you need to provide them as much data and evidence as you can. Glycerol is classified as generally recognized as safe substance by FDA and there is a lot of data available on their website.

Make sure you have data-safety monitoring committee established, at least you should have an infectious disease physician and a gastroenterologist, if possible, on the data-safety monitoring committee. And you should be ready to address the adverse event,

what should be the course of action of you have a patient developing fever or worsening of symptoms?

The most important thing I can -- if you can take home -- is try to get a study coordinator if you don't have one already because there's -- it's unimaginable how much time you have to spend doing all this paperwork, as Dr. Rubin just mentioned. They can help you with patient visits and hopefully with administration of FMT, but ultimately, it may boil down to you, post-FMT follow up, calls, and of course, communicating between FDA and IRB for different applications and regulatory support. They can be really, really helpful.

So, what are the special considerations if you are planning to use this in children? Of course, they are a vulnerable population, so IRB is going to be very careful about what type of patients you enroll. Make sure you have accents in place along with the consents for the children. Privacy concern for -- like any other donor screening or

recipient, sometimes children don't want their siblings to know that they received fecal transplantation or their friends to know that they received fecal transplantation. I had a few patients who wanted their siblings to go out of the room or not talk to them about this fecal transplantation. So, these can be very simple, but important for a child.

Anxiety is really important around this issue because, as I just mentioned, when all the family members are sitting in the room and child is -- they want to hold in as much as possible or as long as possible, they sometimes don't communicate with you and you can have really big problem in the room itself dealing with family dynamics.

So, we used to have child life support where they provided audio-visual aids, reading material, while the fecal transplantation was going on to divert their thought process while they were getting the enema.

You should have probably a consultation visit, as Dr. Kelly mentioned,

and spending at least half an hour to one hour discussing the consent, donor history questionnaire, and different reading materials that may be part of your booklet.

I think it's important that you provide this donor history questionnaire really beforehand and not at the time of enrollment because they get a chance to look over and if they don't want to be a donor, one of the parents or any other family member, they can make that decision and not be embarrassed at the time of enrollment to find out that they cannot be a donor.

Who should be the donor for a child? It's an important question. For our study we utilized adult donors of more than 18 years of age, but the data -- we know that fecal microbiome does change -- has a lot of diversity within first three to four years of life and by four years of life it starts resembling an adult fecal microbiome, so it may be appropriate to utilize an adult donor for a pediatric patient as long as they are more than four or five years of age, but

again, a controversial topic that can be discussed further.

So, I was very happy with my IRB progress and I thought I was really doing a great job. I got IRB approval and I was ready to start the clinical trial, but suddenly one day they called me and said, you need to stop because you need an IND. And I was shocked. I couldn't believe because I never thought I would have to deal with FDA, never in my life, and I was just probably six months out of the training at that time, but I recovered and followed their guidelines. I just educated myself.

And what I have found in the last one and a half years is that it's a challenge, but they are helping you. So, I really want to commend FDA, CBER, and specifically Matt Steele for being there for every step. And it could have been a very silly question that I email him, but I get a prompt response. So, really, thank you for the support that you've been providing for this unique therapy.

So, the way I started with IND was a

pre-IND meeting, because we didn't believe it was a drug and biologic at that time, but probably you don't need pre-IND meeting at this point because we already know, but if you need any guidance how to get at FDA, there is a great website they have, a CBER website, and there's a guidance for industry document on the website.

There are three types of INDs that you should probably know. One is a research IND, which means if you're conducting a prospective study and using this as a research tool, then you need to get a research IND, which is probably more extensive.

Emergency use IND is, for example, if you don't have any IND at this point but you are seeing a patient who emergently needs a fecal transplant for C. difficile infection probably. You can get it within two days -- two to three days, but remember, you also have to complete all that paperwork within the next two to three weeks, so there is no way out of the paperwork.

There is something called treatment

access or expanded access IND, which probably most of you would like to use. It's essentially, you're not doing research and you're not using it emergently, but you want to have it in your hand if in case you need it to treat a patient. And that treatment access -- treatment or expanded access IND has probably not so many stringent guidelines as much as you have -- or inclusion/exclusion criteria as much as you have for a research IND.

IND sponsor is a term which means who holds this IND, who is responsible, finally, to monitor the -- or oversee this IND? It can be your institution or it can be yourself, an investigator, and I would recommend that you as an investigator should hold an IND because it gives you a lot of leverage in the future.

We perform donor screening at that time recommended by FDA. We utilized donor health history questionnaire that is generally -- there is a joint form of DHQ, Donor Health Questionnaire that is approved by American

Association of Blood Banks and FDA, that's available on both their websites. Screening protocol is widely available and it's no different than any other study or recommended by Clinical Gastro.

One of the obstacles or hurtle that we had was stool culture because probably we were one of the first IND holders at that time. We were questioned, although our lab was federally approved and, of course, universal standard methods to take stool -- organisms -- pathogens -- we were asked to perform something called a spiking experiment at that time, which means can you tell us the sensitivity of specificity of these seven organisms at your institution. And no data was available at that time, so we applied for a separate grant to find out the sensitivity and specificity and revalidate our data.

And the three main organisms that are not commonly done routinely at your lab, probably, are Vibrio, Listeria, and Yersinia, and that can create a big problem when you are doing stool cultures. And hopefully we will

have better clarity from FDA if this is something you need to do for every IND holder.

We monitor adverse events based upon CTCAE, which is Common Terminology Criteria for Adverse Events. That's a very handy criteria. It's available on National Cancer Institute website, which was recently updated.

The grading of adverse events was done using Guidance for Industry that was published by FDA during the vaccine preventive clinical trials.

Also, one thing that has transpired through our conversation with FDA is that -- should you allow this to happen at home? Can you recommend somebody to do this at home? And the answer that we received was no became it is -- you don't know the adverse events that will happen at home. So, that's something you will have -- we'll have to discuss further.

So, what should be your role? I think your role is a complex role as a liaison between two regulatory bodies, between IRB and FDA, and in my mind, I always was told by my

IRB director, and I agree with that, is you have to have -- treat them equally in the sense if you have a modification to any documents with your IRB, make that modification with FDA and vice versa, because if one institution says one thing, the other one is not going to trump that decision, probably not, so there's no point in going back and forth, you just have to modify the other part based upon what the other one recommended, which can be really challenging.

The other role -- the most important role you should have is PI oversight. When you document all these things, detail that -- I can't emphasize the importance of documentation, all the patient communication, symptom logs, your discussion during enrollment, during treatment, after the treatment, everything should have detailed documentation. Making sure the data safety monitoring committee meetings, you have points taken at that meeting, and all this needs to be reported to FDA every year. So, you have to be aware about that, there is annual

reporting required once you have an IND.

The other important thing that my IRB keeps telling is, be ready. So, hopefully it never happens to any one of us, but we have heard about the stories and so you have to be ready in the sense, if you do all these steps of documentation and you show that PI oversight is there, I don't think we have to worry about this as long as you follow the guidelines.

But what if you unintentionally miss something? What would be the consequences in that setting? So, that will be something that we should discuss.

What I think there will be challenge in pediatric FMT is, historically we have been waiting for adult safety and efficacy trials before moving on to children and that creates a long gap between adult and pediatric studies, although children are probably equally effected by these diseases, and that creates a prolonged period of off-label use, and we really hope to avoid this in this setting because we have to treat children and

adults equally at this time, although we probably should be more safer, but we should allow these trials to continue in pediatric population.

So, here are my questions. Of course, we have to have a standardized donor screening guideline, that is number one because discussing with other IND holders it's transparent that not all the screening guidelines are equal. Should we have different guidelines for clinical setting versus research setting, C. dif v. IBD, if you have universal donor, individual, family member donor, fresh sample versus frozen sample? Should we have different screening guidelines? In my mind, probably not, but if it -- if that's what is being thought at FDA level, we need to know that.

When we have different -- now, from here on, probably we'll have different IND holders and communicating adverse events with each IND sponsor would be really important and that, again, goes down to establishing a registry so that everyone is educated about

it.

When we have -- now, of course, some of us will want to do research on this, of course, moving forward the funding is not increasing, so what will happen when you have different IND holders trying to answer the same scientific question? So, it's critically important that we establish some sort of collaborative effort. So, one of the initiatives that we have done so far as a pediatric gastroenterology few centers in the nation have together -- informally have created pediatric FMT workgroup. And of these eight centers, I think four of them already have IND along with us, so it helps us -- we arrange meetings every couple of months and discuss each others' experience and progress at the center, troubleshoot regulatory issues and learn from each other, and that gives us basis for future multicenter studies if we have to do in future.

So, in summary, applicability of fecal transplant in various conditions is different and, of course, IBD is not going to

be as straightforward simple like C. difficile infection, but there is some data and there is some potential that we need to carefully study further. We have to, first of all, find out (inaudible) patient population. We don't have efficacy data available, whether it can be used an induction medication or a maintenance medication. We don't know the route of administration, dosing, and frequency. And, of course, mechanism of action is not known at this point, although we are working towards that.

And, of course, we need to consolidate our efforts to achieve all this.

I would like to thank my team here. Luckily I have two study coordinators who are always dealing with these regulatory issues. Chris West is looking for -- always keeping tabs on different grants, which we can apply, Sue is Director for Clinical Laboratory, really great help to let me set up this whole therapy dance and then did the microbiology work that was recommended by FDA on spiking experiments. And Denise Roe is our IRB

director and a great communicator between FDA and me.

With this, I conclude my talk. Thank you.

(Applause)

DR. GORMAN: Any questions for Dr. Kunde?

DR. BRANT: Just -- that was a very nice presentation. You explored a lot of things. Thank you.

When people give enemas, there are two ways to give enemas, one is by self-administered or doctor- administered squeeze bottle, the other is with an enema bag. I assume you used enema bag?

DR. KUNDE: No, I used squeeze enemas. The way we did it was we had two ounces, four bottles. We will put them in (inaudible) position with hips elevated. We'll give them left lateral position enema. One two-ounce enema every 15 minutes, so once you give it, I will rotate them, and when they feel comfortable and when they say I'm ready for the next one, we will proceed with the

next one.

So, the tolerance was told by -- was defined by the patient. Even if he was feeling urgency or if he perceived that he or she is not going to hold an enema, we would stop at that time.

DR. BRANDT: Great. I would urge the audience to be aware that when they use enema bags, the recommended distance over the hips is 18 inches. I've had many patients who have held -- put the enema bag on the top of the shower or a coat hook on the door, and that increases the risk of perforation significantly. So, if you're going to do this, keep it relatively low, but I like the way you did it. Thank you.

DR. KUNDE: Thank you.

DR. KELLY: Colleen Kelly. Great presentation. You really did a good job of conveying the IRB/IND, all of the necessary things. I just have a question. The follow up period for your study, it looked like four to six weeks?

DR. KUNDE: So, for the primary

endpoints -- or, not primary, but the clinical endpoints we looked at four weeks after fecal transplantation, but we are required by FDA to follow them for six months to look for adverse events and, you know, other things. So, we are making phone calls every month to each of these patients and none of them had any serious adverse events. One of the patients actually had hospitalization two months after fecal transplantation, which was not related to -- she had gastroenteritis at that time. We did report that to FDA. And the other patient actually, if we go back to slide if we can, the one which there was a flare up of -- there was one patient who flared -- had increase in their UC symptom within two or three weeks after fecal transplantation, so that probably talks to your patient similar to that, but he showed initial response. Before we started this fecal transplant, he was flaring up. So, I don't know if it helped him and five days were not enough for him, the amount was not enough, but, again, it can be a flare or it can be a side effect of FMT.

DR. KELLY: A follow up to that. These patients, are they off all other IBD therapies at this point?

DR. KUNDE: No, we continued all IBD therapies. We did not do antibiotic pre-treatment, we did not give them any cleanouts to avoid confounding. So, they just came in. We made sure they're not -- they have their exclusion criteria -- they are not severe disease or they are not on any biologics, they were all excluded. And, you know, we just continued their therapy.

And whether they will -- because three patients went in remission, we let their primary gastroenterologist decide whether they want to get off medications at that point.

DR. GRAHAM: As we know, as we've heard, IBD and C. dif are different. And in IBD one expects a 30 to 40 percent placebo response at any trial. So, why no control group?

DR. KUNDE: Because it's a preliminary study and I -- we didn't have funding at that time to conduct all this. So,

specifically, we were just putting the first step in this field, and that's a valid point, and that's what we had to do looking at -- and this is open-label, so there is going to be a lot of criticism about this and it's valid, but moving forward I think that will be the --

DR. GRAHAM: But the interpretation is always going to be questioned --

DR. KUNDE: Yes.

DR. GRAHAM: -- because of the large placebo response even with biologics or everything else we've used until -- I mean, it's always been said your first step should not be into the mud.

DR. KUNDE: Thank you.

DR. VERSALOVIC: So, age of the donors, what is the age range of your donors? And, of course, we know currently with microbiome research that age is certainly a key factor in effecting bacterial composition in the gut. We've been considering dropping the age into the young adult range to get closer for adolescents, but how are you approaching this?

DR. KUNDE: So, the age range in our population for donors was 18 to 50 and we didn't want to use pediatric donors for pediatric patients just because we didn't think it was ethical at that time because donor -- production of stool by donor is a challenging task, on time, on demand. So, we -- I agree with you and probably younger the age group will be probably better at that time.

DR. GORMAN: Please identify yourself before asking a question.

DR. LOUIE: Yes, it's Tom Louie from Calgary. Just a question about fever. You had a couple of patients with fever, so as a safety precaution, were blood cultures done? And do you recommend that as part of a protocol?

DR. KUNDE: So, both these patients had fecal transplant in the evening around 5:00 or 6:00 o'clock after the clinic, because you don't want anyone in the clinic at that time. So, they went home and they essentially recorded that in their diary, but they didn't

call us at that time.

By the time they came back the next day, everything was resolved, so we didn't feel the need at that time to do a culture. But moving forward, we should be doing blood culture, at least CRP monitoring, to see a systematic inflammatory response. Yes, that should be one of the --

DR. LOUIE: A follow up questions.

DR. KUNDE: Yea.

DR. RUBIN: So, regarding the fever, though, was there anything in particular about those patients regarding severity of their colitis or the height of their PUCAI or the medicines they were on?

DR. KUNDE: No. One patient who had -- one patient had fever just for one day and it was mild, so I think looking back it can be just a subjective fever by the patient and it was not documented how high was it. But the other patient who had fever everyday was going as high as 102 degrees and she had pancolonic disease and she had a PUCAI of 50. So, still a moderate disease.

So, I did not see -- and the other one who had fever only for one day had mild disease with a PUCAI of 20. So, I did not see any correlation with disease activity or severity, even endoscopy, because all of these patients had endoscopy within six months of FMT, clinical based, and all of them had active disease.

We didn't actually look at the MAYO score or anything to correlate with fever.

DR. RUBIN: So, fever and an elevated CRP was reported in a couple of the European cases as well.

DR. KUNDE: Yes. But none of them documented sepsis or culture.

DR. RUBIN: No.

DR. GORMAN: One last question.

DR. SAUK: Yes, Jenny Sauk from MGH. I had a quick question. The patient that had the fever, was it the one that also had worsening disease?

DR. KUNDE: No.

DR. SAUK: No, that wasn't the one?

DR. KUNDE: No. No.

DR. SAUK: And then the second question I have is, you do have some long-term follow up on these patients. How do they do over the long-term with their ulcerative colitis?

DR. KUNDE: So, some of them have finished their six-month follow up, and the three patients who went in remission, two of them are still in remission and one of them had antibiotic for ear infection. So, he had a recurrence of the disease.

The patients who improved at one month, about half of them have increased symptoms again, maybe two or three months later, so I would say --

DR. SAUK: So, would you consider a repeat therapy for those patients that responded? I'm just curious.

DR. KUNDE: I would consider, but it's not part of the study yet, so again, it's an open question and, yeah, but we cannot offer this at that --

(Applause)

DR. GORMAN: I suspect our last

speaker for this morning needs no introduction since everybody calls him by his first name. I thought originally that was because his last name was hard to pronounce, but that's not the case, so the last speaker, Alex Khoruts from the University of Minnesota speaking on the Standardization of Fecal Microbiota Transplantation.

DR. KHORUTS: All right. Well, I thank the organizers, as well, for putting this together, hoping for some clarity and guidance as we conclude this today.

I'll talk about my clinical experience and some science that we've done that hopefully will be helpful.

I have some disclosures. I'm an advisor to CIPAC, one of the start up companies that is trying to commercialize full-spectrum microbiota for FMT. I have received funding from NIH as well as my own institution, not enough, for studies of gut microbiota following FMT.

So, these are some of the challenges that have been mentioned already. Donor

selection. Clearly concerns were brought up about possible long-term consequences as well as short-term concerns about infection. When we started doing this, this was -- all of these difficulties that were brought up were clearly evident. I was actually reading the microbiota literature getting all excited about the field and was completely unhappy with the kind of donors that people were brining in. We had diabetes and gastric bypass and this and that, but that was the standard at the time.

What kind of things do we screen for and test for? How the screening is done, felt from the beginning -- actually, it's a fairly intense project or process, I felt we need to have a physical exam and history separate from the recipient, and do all the testing as was mentioned, not -- if the donor doesn't pass, not to tell the patient why that is, and try to keep that separate. That ties in with lack of reimbursement as well, a fairly intense effort that is not paid for.

Practical considerations were also

brought up just now. Yes, when we started, this was an afternoon -- still is -- an afternoon affair. We wanted all the other patients to leave because there are aesthetic considerations in others and labor intensive, and there is the inspiration aspect of when the material is going to arrive and we're pacing back and forth and the nurses are all ready and the material is not there. And that can take hours.

And we spend a lot of time trembling in our chairs about, how is the FDA and why was this regulated and what should we have in place, because clear guidance is only emerging.

This was our early technology, not unlike what was presented. I'll say that our patients often believe, and the industry promotes, this concept that good bacteria look something like yogurt. That's not true. You can never make yogurt out of these, but we did use the blender. With the first case, I learned that it's critical to have the O-ring on the blender. And also, a barrier is still

recommended in case the O-ring doesn't function well.

There are some particles that get in the way to drop in the syringes, so you need some sort of a strainer to get started. And this does involve various emotions, as well as courage and determination, all that, that I'm not showing here.

These were already shown; this was our first patient. This lady was 61 years old. That's how I got started. She came in with eight-month history of recurrent C. dif. She's been in and out of the hospital. She's gone through all the antibiotics. And I felt this is the university and she has no other place to go. She lost about 40 pounds of weight. She was living in her diapers, having a bowel movement every 15 minutes, 24 hours a day, in a wheelchair.

And it took me another seven months to try all my antibiotic attempts and talk to our ethics people and they say, just go ahead, you have to save this person's life. And I said, can I study her stool? You should study

her stool. Okay, so that's what we did.

So, the first, that was TRFLP assay, that's all we had money for, which is not that expensive, but it gives you kind of a barcode what's there, and that's the patient one week before the procedure, this is kind of a washout on the day of procedure with the colonoscopy prep. That was her husband of 40 plus years. They married young. And this is Bacteroidetes band. And that's the patient two weeks later. And that actually was the first demonstration that we had engraphment, even though our -- who is there exactly is very sketchy by this. We just pluck out the names of colonies. It's not very comprehensive, but the barcode looks about the same, and that was one month later.

And there were some replicants, so that was the end of one demonstration of engraphment and somehow this became, quickly, the dogma that's what happens. And that's how it felt. And I think all of us in this room -- physicians, scientists -- have gone into our respective fields to make a difference,

perhaps to save a life here and there, and this is what it was. And I think there's hundreds of lives that have been saved by people here, and it is an incredible feeling, but one can't go on this feeling for long because there are those issues of going forward are not trivial.

And so, as we've gone through our first ten patients, I was actually quite challenged with the whole process and thought that this has to be streamlined and standardized. And this was an evolving process. It didn't happen overnight, but these were the three main objectives that we had.

First, as I said, I was not particularly content or happy with the kinds of donors that the patients were able to bring in, and I thought, we should take responsibility of that. It really should be possible to establish a volunteer program that we can screen and be satisfied with whatever criteria that we think scientifically are reasonable.

There should be a way to standardize the preparation. This was mentioned, you just try to get it, sometimes you get a little pellet, sometimes it's a big production of some loose material, or whatever. How is it done? There's many steps that can be introduced and you would like to know that you're actually giving at least comparable doses with each -- to start the standardization.

And the part of donation -- it's not like donating blood. There is -- it's a human being involved. It's not always available. It would be easier to be able to somehow freeze the stuff and be able to use it on demand.

And also when you have a number of patients to do, that becomes more practical that you can go to your freezer and pull out your samples or your doses.

These were some of the criteria -- it's not exhaustive, but this is what we published in supplementary data of our paper in 2011. We were thinking in broad

categories. There's an infectious risk. Obviously, there are systemic infections like HIV and hepatitis, but also there are enteric infections one thinks about, and so there's two parts to this, one is a history and physical exam, extensive questionnaire, just like blood donors, as well as laboratory testing.

Obviously for this, it doesn't stop there. At this point in time, I thought it was at least probably or possible that every GI co-morbidity or problem may somehow involve microbiota and we would want to exclude anybody with any GI problems, be it IBS, inflammatory bowel disease, GI cancer, constipation, diarrhea, et cetera. I felt that if patients were using probiotics for something that was a red flag or a yellow flag. If they're doing it to make themselves feel better, I don't feel particularly good about that donor. If they just believe it's good for general health and they have absolutely no issues that may be different.

On physical exam, we look for

metabolic syndrome markers. We also -- another thing to worry about is immunologic, autoimmune considerations, neuro-developmental disorders, et cetera. This is not an exhaustive list. We do some metabolic screening and just look for some autoimmunity.

The testing is performed in a certified laboratory with FDA approved test kits.

So, we published this in 2012, total of 43 patients of this emerging experience. We're somewhere around 120, 150, somewhere in there. It just keeps growing. And the results are about the same, so I didn't replicate it.

So, we started with ten donors, ten individual patient-identified donors, those are the first ten procedures. Then it moved on to a more standardized volunteer material, fresh, and then it happened that sometimes we couldn't get fresh, so we reached for the freezer and it worked fine, and so we accumulated some experience with that.

This is a hardcore patient group, so

about half of them -- (inaudible) here, on average they had about a year of recurrent C. dif and the range is pretty broad from maybe six months to multiple years. It wasn't on here, but later I had a patient who had something like 12 years of recurrent infections.

The mean number of relapses, about six, and they have the predictors of recurrent disease, so about half of them were hospitalized as a sign of severe infection, which is one of the predictors.

About half, while they're being for C. difficile, they're also getting some interim non-C. difficile antibiotics. And about half were on PPIs. There's renal insufficiency another risk factor, et cetera.

We did have about a third in this cohort, about a third had concurrent IBD and we know that C. difficile is a problem in this population, it's more prevalent.

The success rate here is with first application, so we -- seven out of ten initially, but it kind of settled at 90

percent or so. And the failures were offered a second time, and up until this morning, last night, we were at 100 percent, just had one failure the second time around.

There were non-IBD and IBD patients. As you might expect, the non-IBD are somewhat older, but severity, number of hospitalizations, relapses, duration are not that different. There is a big more diverticulosis, perhaps that's related to recurrence in some way, in the IBD population.

Notably, we did not see that treating IBD patients with concurrent C. difficile, somehow flared their IBD activity. Most of them, the IBD got better and the simplest explanation in my mind is that we cleared the C. difficile problem, and that's why we saw some improvement, but there could be more interesting results.

So, obviously, it doesn't stop there. So, we have to move forward. In working with the FDA I think we've made our protocol of screening and testing even more rigorous. We're now moving material

production in a different facility that is registered, certified, and there it will be done under GMP manufacturing conditions.

And we are standardizing, or already have done that, standardized the dosing, so we count the number of bacteria and do an integrity by membrane integrity assay. And what it looks like now is very similar to what you might get at a platelet transfusion. We have little compartments here so we can store the donor sample for future testing or if anything goes wrong, we can go back. It's bar coded, so we have traceability all along the process, from the moment of donation through manufacturing, in the laboratory, and then the product that goes in the patient so we can always link all of those steps should anything go wrong.

These are some of the results, actually, this is with frozen material. These are three individual patients, we recently published that. The first column is the donor material, frozen donor material, we're just looking at DNA. As you might expect, we're

seeing -- it's phylum level, there is Bacteroidetes and there is Firmicutes.

The little red band is proteobacteria, e. coli (inaudible) that clinicians are familiar with. But -- and that's what they often think stool is made of. Obviously, it's only a minority, but as was mentioned by Eric Pamer earlier, there is, in patients, although his patients are somewhat different, but this theme is similar, there is major expansion of proteobacteria in this case. They completely dominate the microbiome. Oftentimes it's a single species that just takes over.

Bacteroidetes, they're not gone in this patient, but they appear to be virtually completely eliminated in the majority that we've looked at.

And then three days after the procedure, which is, in our case, colonoscopic, usually three days is when we have the first bowel movement that we can count on collecting. It looks virtually identical to that of the donor. And that

persists.

In this third patient here, it was kind of interesting, around day 28 -- this is, of course, retrospective -- but around 28, there is some expansion of proteobacteria and then there is a bigger expansion, and what happened here is a bladder infection, and actually the antibiotic was initiated a little bit after this expansion was noted. Perhaps there is some connection there. It's an anecdote. However, it may be, none of these have had C. Difficile recurrence. This patient did not normalize within the three months that we studied her afterwards, after that episode of getting bacterium and having her UTI.

The problem of UTIs in C. difficile is actually one of my biggest headaches, is some of these patients have been on chronic antibiotics for so long and perhaps the expansion of these proteobacteria has played a role in starting up other recurrent infections, such as recurrent UTIs and they've seeded the bladder and now it becomes a

separate problem.

And in this group of patients it's very challenging because you may try to do a fecal transplant in them, but they may still have their bladder infection two weeks later, and I've certainly seen that.

A little bit more microbial data. This is PCA plots. The X-axis separates the majority of the difference, about 50 percent or so, while the Y-axis is pretty minor. Anyway, you see that each particular time point -- there's two donors here, one is a triangle, another is a circle. There is fluctuation, there's like Brownian motion in place, but there's -- every particular day is going to be slightly different.

Our patients, before the procedure, are in a completely different part of the plot and afterwards, they just join this group.

If we look at diversity, this is sustained, so they start as (inaudible) mentioned already, as anticipated by whatever diversity index you measure, markedly reduced microbial diversity. This is where the donor

is. And that's where they quickly stabilize.

We've done a little more kinetic study. So, we've sampled their fecal material everyday for a month and then repeat it a little later. So, before -- this is a three-dimensional PCA plot now -- before the procedure, the microbial communities exist in a -- you could say a different part of the universe, somewhere in Andromeda. The donor is the green dot here, and then each of the four recipients is a different color dot. Three of these actually received freshly prepared material, one is frozen, and I'll summarize this in a little movie. So, they start out there, the procedure happened, and then they oscillate around where the donor is.

And so that's the donor. This is each one of the individual patients. So, they're still individuals. We don't know why that is so. It's likely that there's some residual micro-organisms that separate them, but also they have different diets, they're different hosts, they have different physical characteristics, et cetera. They're

distinguishable.

Next, we thought, and I continue to think, of the gut microbiota as playing this integral role in human physiology. So, it's been shown in germ-free animals that -- comparing germ-free and non germ-free -- that about 10 percent of all detectable metabolites in systemic circulation vary in concentration by at least 50 percent due to activity of gut microbes.

We know there's multiple roles they play in energy metabolism, instruction of the immune system, potential roles in behavior regulation, neurologic development, drug metabolism, interplay between microbial and host metabolism of hormones and everything else you can think of.

So, as we were doing this, I thought, we're kind of doing transplant procedure of an organ-like tissue like structure that is going to have metabolic effects, and we should study some metabolites. So, we looked at urine. The urine is one of the simple sites to sample metabolites. It

averages things out. It also is a particular site, which your body does not want.

However that may be, we can once again, doing this statistical plot analysis, separate before and after transplantation. The metabolites are different before and after. And then we can look at which ones are increased, for example. And we're still analyzing this. This is purely an example. But one example here is p-cresol, which is a tyrosine metabolite, exclusively microbial product, and it is completely absent -- this was like 18 patients -- it was completely absent in all but one of the recipients.

And then after the procedure you see it rises up and it stays up, so it's kind of a marker of engraftment and perhaps it does a lot of important things. So, we know that sulfation of p-cresol that happens in the liver interacts extensively with all sulfation reactions there. It's been shown in Tylenol metabolism, for example.

Another big one is bile acids. We study them in fecal material as well as urine.

Here I'm just showing urine. I think this is mechanistically very important because bile acids play very well defined roles in lifecycle of C. difficile, some of them, as was mentioned, are germinators. They promote much like fertilizer on spores, and others are inhibitors.

So, I wanted to touch, in a few minutes, on the reality of FMT in the community. I spend about an hour and a half every day answering emails from patients telling me their very heart wrenching stories, and many of them say, I'm just doing this. I just need a few tips. So, there is an anxiety that's built in there. That's not how they want to be doing it. They would prefer to have medical guidance, and then I'm kind of walking a tightrope. I don't really want to be involved in becoming their doctor, just occasionally I say, that was really stupid.

There's limited access. Actually, so a story on that, a patient emailed that she was living in New Mexico, there's absolutely no way she could find anybody to do this for

her, so she decided to do it. This is after the fact, and she made up her own protocol.

So, she felt two donors is better than one. So, she got one from a neighbor and one from her son's mother- in-law, mixed them together, did self enemas, then she emailed. Didn't work. What went wrong? So, well, did you use like water? I don't know, maybe there's some chloride in your water. Maybe it killed everything off. So, she inquired about some sources of saline, for example, you can get that -- trying to, again say, I'm not really advising you here, but that probably is a factor.

So, a couple months later she emails again. I did it again, this time using one donor, but and C. dif is gone, but I had diarrhea again and I've got parasites.

There are many who have limited access, who are truly legitimate patients. Just like Colleen, I get people that come from far away, but many can't make it. There are unorthodox practices, both in material preparation, probably, but also how the

material is administered. I had a funny email from a physician who said, yeah, he does this all the time with NG and he just sends people with an NG in place at home, and he's done it to this couple and just told them to do it daily for a month.

And his only question is, he doesn't understand why they have abdominal pain.

There are things like -- as was mentioned earlier, not so long ago there were problems with endoscopy and transmission of H. phylori and hepatitis C and whatever, and I'm sure there is a wide range of how the material is prepared, what criteria are used for screening, processing, and what quality control is being used.

There is clearly emergence -- we've entered a different age. I think every physician in this group is -- that I've met, is one of the most extraordinary individuals, is the ideal physician who simply wants to help people, have all done it at great sacrifice to our salaries and whatever, but the reward is our patients.

This is a different age now. There are predatory practices already. I had an email from a patient a couple weeks ago in Wisconsin who said her mother is just laying on the sofa with recurrent C. dif, moaning, groaning, thinks she's dying. I don't think she's going to be able to make it anywhere to drive more than an hour, but she quickly found somebody within an hour, it's just $10,000 out of pocket.

And of course, all of this is happening without any data collection.

So, that's a thought I thought I would throw out. We do have a model, perhaps, that can be borrowed or built on or slightly modified -- blood banking. There could be standardized facilities where the material is produced. We have a way of distributing, tracing, tracking all these steps that can be centralized, coordinated, and inspected. So, I would pose this question -- I'm not -- I don't know, these numbers just confuse me or whatever, but that's in working with more competent people they thought, you know, this

is kind of an interesting template.

So, the fecal microbiota could be regarded as tissue-like, and transplantation of donated feces from a healthy donor to a patient is comparable to using other human tissue transplantation to replace or repair defective tissue. I understand the hesitation of this human equivalence here, but it is part of our bodies, and if the FDA regulated stool transplant materials using these tissue regulations as a template, how would it look? So, I think this is about how it would look. We would have stringent regulatory guidelines for donating and processing fecal materials, any facility preparing these materials would have to be registered for FMT. The FDA could inspect any of these facilities. And we'd have, once again, same idea, register all the FMT recipients so at least we can collect the data and study it going forward.

This is our skeleton team. This is a very collaborative work. Mike Sadowsky is our microbial ecologist, who has been studying soil and Mississippi river and now thought

this was the greatest thing yet. Matt Hamilton has a sign of number one and number two business. He is responsible for standardization and most material preparation. Alexa is leading forward with more mechanistic studies. Chi Chen is our metabolimics collaborator.

And we had collaborations from outside as well. Rob Knight's group helped us set up this movie thing. Oleg Pally from Wright State University, the comparison of 16-S sequencing, technology versus chip array and the results came about the same.

And grant support, and this completely would not be possible without donors, wonderful nurses, and referring physicians.

That's all I have.

(Applause)

DR. GORMAN: It's always a tough balance between the needs of the many and the needs of the few. We're going to choose the needs of the many now. It has a fringe benefit of making sure that we all stay until

the end of the program to be able to ask Alex all our questions.

So, we're going to dismiss for lunch at this time and get back here at 1:10 -- 1:00, 1:00, 1:00! See you then.

(Recess)

DR. STIBITZ: Okay. Thank you everybody. And it's my pleasure to call to session this final session of the workshop, and the intent of this session was to try and look forward a bit in terms of -- and to address regulatory considerations, which I've sensed there may be some. So, even if not, I think we should go ahead and at least try.

So, since a number of people are leaving to try and catch planes and so forth, time is even more important than in previous sessions, so we're going to really try and keep to the schedule and remember any time that we might run over, it will just be taking away time from the roast -- I mean, the panel discussion.

So, also before starting, I just wanted to use this opportunity, again because

departure may be a bit chaotic, to thank some of the people involved in putting this workshop together, and first would be my co-chair Melody Mills, who has provided great knowledge as well as insight and enthusiasm, and without her this workshop would not have been nearly as good. (Applause) And also the rest of the planning committee, which included Theresa Finn, Douglas Pratt, Matt Steele, whom some of you know, apparently, and Paula Agger. So, thanks to them as well.

Also wanted to thank Chris Nguen and Irene Carroll, who many of you dealt with for registration, who have been manning the desk outside, and for many, many logistical points.

Also to our colleagues here at Lister Hill, our AV person Patch Seibert and Melissa Hush.

And then, finally, some of you will have dealt with these folks, the folks in our office, who took on, in the absence of any other personnel assistance, all the travel for our people -- of course, NIH traveled some people also -- and they were Diane Morris and

Rasheeda Hutchinson. So, thanks to all of them.

Okay. So, this session is meant to be looking forward some and to address regulatory considerations, and I think in both regards, our next speaker's talk will be very germane. This is Johan Bakken from Minnesota and he is, at least, a household name to us due to his part in drafting the guidelines that we generally direct people to for FMT. So, Dr. Bakken?

DR. BAKKEN: Thank you. I, too, would like to give my thanks to the FDA for putting together this really stimulating conference, and specifically to Scott for -- I also wanted to interject that the consensus document that you made reference to was certainly not my product alone, it was the hard work of 13 individuals, multiple conference calls, and I just happened to be the first number in the output.

So, anyway, we all put in a lot of effort with it and hope that it is a useful document.

As you heard from many stimulating talks, particularly today, from the clinician's point of view, at least, I think we all share a common goal, and that is to resolve recurrent C. difficile infection, but we have many different styles and ways to accomplish this goal. And so, what I hope to do today is to share with you a little bit of the landscape of providers of FMT in the ID community, at least, in North America.

And what I will share with you in a few minutes is the results of a survey that we conducted last fall. I'll give just a very quick review of the history of FMT and give you my subjective map of North America, based on personal contact with providers of FMT where you might find treatment centers.

The survey will specifically address when survey respondents felt that it was appropriate to begin or consider FMT, how survey respondents have screened the potential stool donors, just quickly talk about the installation practices, and the estimated success rate as we have recorded it or

perceived it in North America, and talk briefly about complications, and round off with a short review of providers in different countries, particularly in Northern Europe, and see how they do it there.

So, I did a PubMed search on various search terms, and I think you can see that fecal transplantation therapy is a popular item, although not as popular as fecal biotherapy, which is not as encompassing, but there is a lot of activity in the literature, and this slide here illustrates, basically, what has happened since Eisenman treated the four patients in 1958, and as you can see, there was a fairly quite period up until the last three years where the bulk of published reports and case series have appeared in the literature.

The blue bars indicate the number of cases who have been treated, whereas the red bars indicate the number of patients who have achieved a durable cure with FMT. And you can't help but be impressed. I think that there is very close correspondence between

case number and success rate, and that holds true even in the last three years.

So, the route of installation, based on 41 published reports, starting with Eisenman in 1958, is that two-thirds of the installations happen via the lower route, either through enema or colonoscopy installation, whereas the upper gastrointestinal tract, be it the nasogastric tube, nasoduodenal tube, gastroscope, or even the G-tube, feeding tube accounts for about 30 percent of the case reports.

We now have rounded 700 published cases and this is what has been published in English speaking literature, at least, with an average success rate of 90 percent, somewhat higher when the installation happens via the lower intestinal tract than when it happens from the top. And as other speakers have pointed out, I think it's a simple (inaudible) that it is a reflection of the volume that is instilled because it's a little more concerning to instill a large volume through the -- into the duodenum with the possible

risk of aspiration.

This subjective map is a reflection of people I've had contact with in various states and if there are individuals in the audience who is doing FMTs whose state is not represented, I apologize for that, but I would like to hear from you so that I can expand my map so that we have a good sense of where patients may be referred because I get emails or phone calls at least once a week, usually more than once a week, and they come from diverse locations and it becomes a matter of trying to refer patients to the closest treatment center.

So, the survey we did was done through the Emerging Infectious Disease Network, which is a web service available to adult and pediatric ID practitioners. This particular survey was sent to adult ID practitioners in the U.S. and Canada, and we sent the survey out electronically by email once and with a repeat in three weeks if we didn't have a response.

The survey was conducted in

September and concluded in the middle of October last year and we feel that we have a fairly representative segment of the adult ID community in that the response rate was 51 percent.

Not all respondents answered every question, so there's a variable respondent rate depending on what the question that was asked, but 80 percent of those that were asked about FMT, to be considered for recurrent C. difficile infection, 80 percent were favorable and they indicated that they would consider it.

There were 9 percent of respondents that would not consider FMT under any circumstance and the only explanation that was given as a footnote was that 5 percent of respondents reported that they were unable to administer FMT because of unwillingness on the part of the patient and whether we can say that 95 percent of the patients otherwise were receptive to the idea, such as Dr. Brandt indicated in his presentation earlier, I think is probably true because in our hands, in

Duluth, we have not met any patient who was unwilling to have the treatment again.

And by the time they qualify or come to the point where they need treatment, they almost beg us to proceed.

So, 29 percent of respondents indicated that they already had FMT programs instituted at their particular institution and another 25 percent indicated that they were in the process of establishing an FMT program.

Most of those that were asked indicated that they would consider using FMT as intervention for recurrent C. Dif infection after the second, or in particular, after the third relapse, but there was a smattering of responses, and "other" includes days other than -- or further than eight days, some people would do it very early. But the median value here is 2.4 days -- or relapses, excuse me.

The majority of respondents, roughly 75 percent indicated that they had had to deal with at least one relapsing episode, but there were a few individuals who had taken care of

as many as 25 patients or more all having had relapsing C. dif, so based on this survey, at least, it appears that recurrent C. difficile infection is a common problem, frequently seen in the practice of infectious disease physicians.

Almost everyone indicated that the donor of the FMT was a family member or household member. What we in Duluth, at least, fondly have called bed or table contacts, so it reflects intimate behavior or very close behavior, and the majority of the patients we have taken care of in Duluth, and many of the patients in this survey, is a spouse supporting the idea that spouses share everything, including their microbes.

And whether a spouse is the most appropriate donor source for stool based on efficacy may be one argument, but it seems that it's a very good reason to prefer a spouse at least as a risk reducing potential for transmissible agent.

The consensus document reviewed many of the factors that previous speakers had

talked about, how to eliminate or exclude a donor based on either chronic infectious autoimmune conditions, previous antibiotic treatment in the recent past, chronic immunosuppressive or antineoplastic therapy, risk behavior or history of IVDU, inflammatory bowel disease, malignant bowel disease, history of major GI surgery, and detection of a transmissible infectious agent after the donor screening results are in.

So, the FDA has made recommendations about when it is appropriate to screen donors of human tissue, and in this situation it's not human tissue, but it parallels more maybe the screening procedures that are enacted for blood transfusions or for blood donors for transfusion purposes. So, if there's a risk of transmission of an infectious agent to the patient or to the operator or to other handlers of the tissue, if there is potential for threatening or fatal disease, and if there are in place testing methods that can be utilized to detect infectious agents, then screening is recommended.

So, in the consensus document, we went through what we have published in the past, our group has published in the past, and it is a consensus document because not all recommendations had 100 percent unanimous support. Everyone agreed that C. difficile toxin testing should be done and likewise routine bacterial culture for enteric pathogens should be done. But there was mixed feelings about whether or not everyone should be tested for ova and parasites, both with antigen testing and with microscopic evaluation of stool in the absence of any significant travel history. The same would be acid-fast stain for Cyclospora and Isospora. In my personal practice I've never seen either. And Helicobacter pylori was mentioned as one thing to -- or discussed as one entity to test for. That has not been the practice we had followed in Duluth before and I am unaware of any transmission reports of Helicobacter to recipients, at least as defined in the literature.

On the blood testing side of the

donor, HIV testing, of course, hepatitis A, IGM antibody testing, and hepatitis C antibody testing as well as surface antigen for hepatitis B was a unanimous recommendation, but there were some mixed feelings about whether or not finding hepatitis C core antibodies or hepatitis B surface antibodies is conveying a risk for transmission in someone who's otherwise defined as healthy.

And we have, in Duluth, done RPR looking for evidence of syphilis, but we have not tested for FTA unless the RPR is positive, and so whether or not both RPR and FTA is strictly indicated, we couldn't totally agree on, but we put it in as a consensus.

So, this is what providers around the U.S. and Canada are doing. We were a little surprised to find that six providers don't test for anything, but those that did subject the donor to screening tests, 75 percent or so tested both for HIV, for hepatitis B surface antigen, hepatitis C antibody screen, IgM, hepatitis A, C. difficile toxin, and enteric pathogens. And

then there was a lower report of testing with RPR and particularly what we have not recommended in the consensus document, CMV.

So, the results of donor screening has potential disadvantages and advantages, and obviously the potential advantage of screening is that you reduce or eliminate, perhaps, the risk of transmission of an infectious agent. But it brings me back to the argument for preferring a spouse or an intimate partner in a longstanding relationship, thinking that partners share everything.

The potential disadvantages may be apparent in the setting of severe disease or maybe with a hypervirulent strain, and it may eliminate the donor where there is only one donor potential. And up until now, the fact that the recipient, typically a Medicare age patient on fixed income has to bear the cost of the screening can be a substantial barrier.

The 149 respondents have said that they either had first hand's on experience with FMT or had been involved in caring for

patients that had FMT performed by someone else in their practice. We found that 72 percent of those that were queried responded positively, and spouse and life partner, as already stated, served as the donor for almost every sample except for three respondents that had used frozen stool.

No one seems to use stool substitute or synthetic stool, as Michael Tvede in Denmark or as Petrov in Canada. The volume of the fecal slurry typically was higher, but a deficiency in our survey was that we didn't ask the respondents to stratify the volume that they used in regards to the route of installation, whether it was by colonoscopy, enema, or ND tube.

The success rate was uniformly estimated to be very good, at least 80 percent or higher for 75 percent of the respondents. There were two respondents that stated that one patient had failed and so accounting for a very low success rate, but the majority of those that had been treated, enjoyed durable cure.

I did my ID training in Norway, and so I had a lot of experience -- literature experience, at least, by the time I came to the U.S., and so I still have a lot of contacts in the infectious disease community in Northern Europe, and so I sent a query to representatives in Norway, Sweden, Denmark, Finland, and Holland, Els van Nood, who I've known for some time, and this represents about 25 million people, not a very big population worldwide -- or on a world basis, but they already have a substantial number of treatment centers, it's hard to get exact data, but in the country of Norway, five million people, more than 20 treatment centers.

And the interesting thing was that routine screening of the donor is not performed in Scandinavia, at least. It is in Finland and it is in Holland, and the preferred sources of stool varied a little bit from country to country. In Norway, they take any healthy donor, family member or unrelated. In Sweden, they prefer family members. In Denmark, they use synthetic stool. They still

use Tvede's cocktail from 1989 published in Lancet, consisting of ten separate isolates, and until this day, they have done at least 200 treatments and there is a multicenter study using the same cocktail involving Norway, Sweden, and Denmark, as we're speaking.

Makila in Finland, has done most of the treatments in Finland, more than 150 cases have been treated, he estimates, countrywide, and in Holland, there are eight centers and roughly 150 patients or more have been treated as well.

And in either case, there has not been a reported adverse effect in the literature or to their knowledge, those that I have corresponded with.

What has been reported, like in van Nood's article, in the review that Gough did, and a recent article from Scandinavia by Sofi, the most common "adverse effect" if you can call it that, was failure to resolve the infection. One patient developed peritonitis after colonoscopy done in one center in

Norway. I think peritonitis is not unheard of or uncommon in colonoscopy done for a variety of other reasons in CDI. Irritable bowel syndrome seemed to be experienced for some time after the transplant. In van Nood's study it was called mild enteritis and there was one patient in Scandinavia that had an upper GI bleeding after an upper GI tract installation.

But in general, there is a paucity of adverse effects in the published literature at least.

So, the conclusions of this survey, and of literature in general is that the raw material stool is in virtually an unlimited quantities and it's cheap. And that FMT today is by far the most effective therapy at resolving recurrent episodes of CDI, far more efficient or effective, I should say, than any other alternative therapy.

It's easy to perform, it can be done virtually everywhere. There is not clarity in the literature about whether or not there is a strong need to screen the potential donor,

particularly if one adheres to a spouse, and the experience of, perhaps, as many as 2,000 patients now based on the anecdotal experience in Scandinavia and maybe here in the audience as well, who have treated far more than they have published. So, the published literature to date would suggest that FMT is safe, it's cost effective, and the patient satisfaction rates are very high, as evidenced by Dr. Brandt's talk.

So, with that, I'll conclude and take any questions.

(Applause)

DR. STIBITZ: There's one.

DR. KELLY: Hi. Colleen Kelly from Brown. I just wanted to comment on the syphilis testing because --

DR. BAKKEN: On the what?

DR. KELLY: The syphilis testing. So, shortly after we finished the guidelines, I added the FTA antibody because -- really not knowing what I was doing. I said, well, I was on this working group and I checked that box. The fist patient I did that in had a false

positive FTA antibody and negative RPR. It resulted in a call from the health department, because that was reported to our Department of Health, completely panicking this donor and a lot of explaining to her, and then having to get a second Treponemal Based test.

DR. BAKKEN: Right.

DR. KELLY: So, I just kind of wanted to point out those issues with syphilis testing.

DR. BAKKEN: Well, the syphilis testing is sort of a moving target. Typically, the RPR is the test that correlates with activity and the FTA, you could think of as PPD, once you're positive, you're going to remain positive for life, and so you base your clinical decision making in the setting of a positive FTA, what the RPR is, and for someone who's been adequately treated or has had a lot of years between the active infection, which may have burned out, will have a low or absent RPR.

So, in the setting of someone who has a positive FTA and has undergone treatment

for syphilis in the past, and has a negative RPR, you wouldn't do anything.

DR. KELLY: I guess -- is there a lot of false positives with the FTAs?

DR. BAKKEN: Pardon?

DR. KELLY: The false positive rates with the FTAs?

DR. BAKKEN: There is a false positive rate.

DR. KUNDE: What do you think about EBV testing? Because we, for our Phase I study, we required to do IGM antibodies --

DR. BAKKEN: What kind of antibodies?

DR. KUNDE: EBV VCIGM.

DR. BAKKEN: Oh.

DR. KUNDE: And I think that was the most common one that eliminated donors. Is EBV antigen required?

DR. BAKKEN: Well, there may be a difference between pediatric patient populations and adults, attesting to the fact that in my practice, at least, seeing pediatric cases is very unusual, that is,

pediatric cases with CDI, perhaps explained by the fact that we are not a transplant center other than fecal transplants, but not a transplant center in the traditional setting with organ transplantation, which is done elsewhere in Minnesota.

And adults will -- that are otherwise defined as normal hosts, will have resolved their EBV infection, and so finding positive antibodies would be difficult to incriminate if the individual otherwise has been defined by health questionnaire and by the way they appear as healthy.

DR. KUNDE: Is EBV transmitted to stool? That's the question.

DR. BAKKEN: I don't think it is. I don't know the answer for certain, but I don't think EBV is transmitted through stool.

DR. KUNDE: Thank you.

DR. STIBITZ: One more question.

DR. RUBIN: Could I comment about the EBV thing?

DR. STIBITZ: Sure.

DR. RUBIN: It may not be

transmitted through stool normally, but we have to worry about people who are bleeding or who have colitis, and it may be a different transmission that way. So, we have to think about that.

DR. BAKKEN: Sure, but, again, I need to get back to the fact that it's the donor we're talking about and the donor from the get-go is an individual who is otherwise healthy. And so EBV is a self-limited infection in normal hosts.

DR. RUBIN: Yes.

DR. BAKKEN: And even though the virus stays in your body for life.

DR. RUBIN: That's a valid point. Thank you.

DR. KHORUTS: I think I was in the camp that supported the RPR and part of the reason was not so much the infection, but in part it was, but in part it's cross-reactivity, and a poor test of autoimmunity. There's a lot of lupus false positive that would -- kind of a surrogate market that another test that might be useful for that

reason, but obviously the donors go through informed consent as well and they deserve their time to -- false positives can happen and we have to be prepared to deal with that.

DR. STIBITZ: Okay. Our next speaker is Dr. Herbert DuPont from University of Texas Health Science Center, and he is going to tell us about his efforts towards developing a treatment.

DR. DuPONT: Thank you very much for the invitation to participate as the timing of this meeting is perfect for us because we're just beginning to develop whatever is needed to establish a bacteriotherapy or fecal microbiology treatment facility.

Dr. Jiang -- Zhi-Dong Jiang and I, are developing the requirements and looking at what is needed to establish a new center. And neither of us have conflicts to report that relate to this program.

We'll talk about the growing problem of C. dif related deaths in hospitalized patients, briefly talk about principles of CDI therapy, and I will describe my first

experience with fecal transplantation in 1970. My guess is that I did this before anyone else in this room, maybe somebody will say they did it before 1970.

I want to show you a survey of Houston physicians as we plan the development of a center in our city, and then I'll describe, briefly, where we are with the development of a new program.

This is a study done by one of our pharmacists at our University Hospital and looked at death certificates in Texas and whether C. dif was listed as a contributing or as the cause of death, and what we can see is this rise that occurred in the early 2000 mirrors the data from the CDC on the incidents of C. dif increase in this country.

These are hospitalized patients. This curve, which is also rising, is nursing home patients with C. dif associated mortality, and we have outpatients and other groups there.

We have continued this study through 2011 looking both at Texas death certificates

and also data from national death certificates, and this curve continues to rise beyond the point that we see right there.

So, C. dif is a major cause of death in this country and it needs to be -- this needs to be -- this increase in mortality needs to be dealt with.

Now, this is an editorial I wrote in The New England Journal of Medicine following the evaluation of Fidaxomicin, and in that article I indicate that there are three ways to treat C. dif, one is inhibit the vegetative forms of the organism, the other is to preserve or reestablish the gut flora, the third is to facilitate the development of an immune response to the toxins. And each of these are relevant, and as we see recurrent disease, the second one of these becomes much, much more important.

Now, with regard to recurrent C. dif infection, the objective of the first recurrence is certainly inhibition of vegetative C. dif cells and prolonged antibiotic therapy is needed. I have been

pushing for trying to do studies with longer duration of initial therapy of C. dif. The other spore forming infection that most of us in infectious diseases know well about is Anthrax. We give two months of therapy of antibiotics for Anthrax infection.

Here we have an infection, a spore forming infection, we give ten days of treatment and we have a 25 percent recurrence rate. What's wrong with this story? Don't we need to give longer initial therapy with the first bout of disease? I have no question in my mind we do.

With the second recurrence of disease, the enhanced colonization resistance, a reestablishment of flora is the most important factor and antibiotics play a relatively minor role, we believe, at that time.

Now, with regard to what we call bacteriotherapy, as we mentioned, the treatment of choice for second or third is fecal transplantation. I believe that, obviously, and we're all focused at this

meeting, that the primary mechanism of this treatment is to improve the anaerobic microflora of the gut, increasing the Bacteroidetes and Firmicutes in the colon of the infected patient.

But I believe that inappropriate attention is also being given to metabolites and other compounds found in the GI tract in healthy people. Organic volatile fatty acids appear to be important. One study has looked at intestinal alkaline phosphatates and demonstrated taking alkaline phosphatates from the intestine. It reverses the microbial alterations in experimental C. dif infection and normalizes the gut flora.

So, focusing on the bacteria is appropriate, but we must also consider other components within the fecal transplant environment and what we are providing that's deficient in these patients.

Now, I want to describe my first exposure with transplantation. I was a young assistant professor of infectious diseases at the University of Maryland in 1970. I had an

elderly man that I was caring for who developed severe antibiotic-associated colitis and renal failure after his surgery. He failed to respond to oral Vancomycin. It's interesting that Wendell Hall, some years earlier, in 1966, and a young physician working with him, Dr. Khan, at the Minneapolis VA, demonstrated that oral Vancomycin was the treatment of choice for what we called staph enterocolitis at that time.

So, I was using oral Vancomycin. Now, this is four years before Tedesco described Clindamycin colitis, and seven years before John Bartlett demonstrated that Clostridium difficile was involved in this problem.

Because of the report of Eiseman, et al, in 1958, I proposed we do a fecal transplantation. At that time, we had no IRB. Research was much more efficient in those days. And what was available to me was the chairs of the department, the different departments at the University of Maryland. So, I presented this case to the chairs at

their executive council and said I wanted to give this fecal material to this dying patient, and they responded that they supported it and the chief of surgery said, "I'll get you the stool you need from an elective surgical patient on the floor who is perfectly healthy."

No more screening was discussed at that point. And so I was given the stool and the individual from the chair of surgery at the University of Maryland. We used a Waring blender. We administered by retention enema. And it was a dramatic response in this patient.

Now, why have I not appeared in any of these presentations that we've had here? (Laughter.) Now, I want to indicate that this was not published. Why was it not published? Well, I thought it was great and I certainly would like to publish it. I ran to do a little more research on the donor. Turns out, the donor was in for an elective cholecystectomy, but the donor was a woman who was a typhoid carrier. We had infused 11

logs/per gram of stool of salmonella typhi into the rectum of my patient.

Now, the colon is a pretty resistant organ and no typhoid fever occurred, so maybe that's the most important part of my scientific experiment, you don't get typhoid from the rectum.

Anyway, it was a very interesting response, and that was when I first became interested in this field.

Now, in 2012, Dr. Jiang sent a questionnaire out to -- and by the way, we started a major C. dif program in Houston in 2002. I had been working on infectious diarrhea globally on four continents and we decided in 2002 we ought to do something in the U.S. and we began to focus on C. dif.

A questionnaire was sent out in 2012 to all gastroenterologists, infectious disease physicians to see if there was interest in us establishing a fecal transplant center. We used the Harris County roster of physicians, mailed to 264 ID or GI doctors with a stamped return envelope.

What we found is that a little over a third of the physicians responded to the questionnaire, 56 gastroenterologists, 33 ID MDs and if we look in blue, whether a center is needed and whether they would refer patients to the center in Houston, you can see the response was favorable.

We published this in Clinical Infectious Disease Journal. Now, I don't know if you all look when you see a publication and you look on the first sheet, when was the paper submitted and when was it accepted. It's extremely interesting data.

Fred Zar's study showing that Vancomycin was better for severe disease than mild disease, if you look at the date difference between submission and acceptance was two weeks. This could not have been reviewed, and so our paper had a similar experience.

So, Sherri Gorback liked both of these papers and so it went on very, very quickly.

Anyway, we're starting a study --

we'd like to start a study. We haven't done anything yet. We were waiting for this meeting and we will wait for our discussions with the FDA, but we plan to do the transplantation in two university hospitals in the world's largest medical center, the Texas Medical Center, St. Luke's Episcopal Hospital, which will soon be St. Luke's Health System, has a new owner, and Memorial Hermann Hospital with more than 1,300 combined beds.

Interestingly, our protocol has been accepted and approved by the University of Texas IRB. We will make amendments to it. It is not the final protocol, but it is approved by the IRB.

We are thinking -- were thinking before this meeting, I'll tell you -- it's past tense -- we were thinking of either recurrent C. dif or inflammatory bowel disease. We are now changing our mind after this important meeting.

We thought for the first 40 patients we would administer the fecal suspension via colonoscope. This has been the mode of

treatment that's been successful and it's easier for reimbursement to follow that route.

We're working with payers to try to identify codes that will help the reimbursement, but like others presenting in the last day and a half, this is a challenge.

Once the protocol is finalized, it will be registered with the FDA and we'll enter a dialogue with the FDA.

The criteria for patient selection, three or more bouts of CDI in outpatients, two or more in inpatients without other explanation for diarrhea and a fecal positive test for C. dif toxin on two or more of the bouts of CDI with the last positive test within the lat 90 days of transplantation.

Subjects will either take a course of oral Vancomycin or Fidaxomicin, a full course, ending two to four days before transplant, at which time they will receive a colonoscopy prep and undergo transplantation.

The donors, we're working with the blood bank at St. Luke's Hospital and we will have professional donors or non-family donors

is what we're postulating at the present time.

We're working with the blood bank. We may use their apheresis patients who come in on a regular basis who are interested in this program. We will screen the donors in two ways, one is their stools will go to Dr. Jiang and her CAP/ CLIA certified enterics laboratory and she will look for all pathogens that could be spread by the fecal/oral route.

The blood bank at our hospital will do the other screening and it will fit in with exactly their program of screening, the same pathogens that they look for and it's a bundle payment of $70 for the screening using our blood bank for the non-enteric screening.

We will follow our donors, as well as the recipients, for -- the length of time will be discussed with the FDA, but we will follow them long enough and be able to trace back and look for recurrent or adverse experiences with the population.

Like many talking this past day and a half, we would like to move towards frozen donor stool aliquats to help with the

standardization of the donor material.

We see, much like the literature has shown, that we would need to give approximately 50 grams or more of stool. This, often, is a dose related success rate. More is better than less. We will take it to the hospital microbiology lab and then transport it two blocks away to the Center for Infectious Diseases for Dr. Jiang and her laboratory. She will filter it through coffee filters, and as I had experience with that already, and then we will give a daily questionnaire to the recipients.

We will collect stools from the recipients minus four days, one day, before transplantation, day zero, the day of transplantation, day seven, fourteen, and thirty, and frozen for future studies. With recurrence we will then use a second donor to administer a second transplant or at least make that available to the recipients.

We are using a stomacher rather than a blender for developing the material that's filtered and think that that's probably easier

to work with in the laboratory.

My conclusions is that -- and, by the way, this is our C. dif team at St. Luke's Hospital, which includes the head of the Infection Control Department for the hospital, the director of the laboratory, there's Dr. Jiang, there's me, assistant professor of infectious diseases Hun Mo Ku at Baylor College of Medicine, Kevin Gary, a professor of pharmacy at the University of Houston, Todd Lascow, the director of the microlab at the hospital.

The hospital is entirely behind this program. The University of Texas Health Science System is completely behind this program. And we are serious about engaging in this and trying to figure out what's going on.

We don't see fecal transplantation as a long-term medical therapy. I feel quite certain that 10 years, 20 years from now, this will be of historical importance only. We'll absolutely at that time know what we're dealing with and what fecal samples are providing and we can move on to something, not

only more aesthetic, but more efficacious. Thank you.

(Applause)

DR. RAMESH: (Off mic.) -- so, we have been transplanting for past several years without even doing HTLV testing. So, that's one, and second is, in case you have a false positive, what is the mechanism for contacting donors and -- like post-screening counseling and how do you plan to achieve that and any guidance on that.

DR. STIBITZ: Excuse me, could you please repeat the first question? You weren't on the mic.

DR. RAMESH: The first question is, HTLV screening and the second question is counseling, if anybody is false positive or true positive.

DR. DuPONT: Well, my first comment is that I don't care about false positives. I'll exclude the stool. We should have -- we're going to have a pool of donors and anybody with any kind of positive, false or not false positive, is an exclusion as far as

I'm concerned.

The other thing is we're going to screen the donors two weeks -- within two weeks before the transplantation and hopefully we won't find a cause for concern to educate the recipients, we will have ruled those out before we actually make the transplantation.

DR. RAMESH: No, sir, the question is, counseling for the donors in case they are positive.

DR. DuPONT: Oh, very good. The donors, if they're positive, we will do exactly what our blood bank does currently and that is to inform them, not their doctor, inform them of the positive result and offer to be involved in counseling, giving them advice, or talking to their physician.

DR. HAYS: Did I understand you correctly that you're going to have the donor specimen brought to the hospital, taken to the laboratory, then sent to the processing laboratory, then back to the pharmacy for distribution to the endoscopy lab?

DR. DuPONT: That's correct, and

keep in mind that those are two blocks apart.

DR. HAYS: So, I wonder, in terms of time, is that -- I'm just trying to understand how you could get all of that done within six hours. Is that likely?

DR. DuPONT: I think so. It's probably no more complicated to move between, essentially, the two places where we're going to be working than it would be from one area of the hospital to another area of a hospital.

We've already had some experience with this, at least in donors and screening donors. We haven't given stool to recipients yet, but we believe we can do it.

DR. STIBITZ: I was very interested in your observation that your typhoid carrier did not appear to have transferred disease to the recipient. Do you have anymore thoughts about that? I mean, I find that very interesting and a little surprising.

DR. DuPONT: Well, there's two comments about that, a comment that I would have made yesterday morning and now a comment since I talked to Dr. Brandt some hours after

I arrived here. My early comment is, you don't get typhoid fever from the rectum, you get it from the small bowel and Peyer's patches. Dr. Brandt informed me that occasionally organisms in the lower GI tract can actually cross the ileocecal valve and reach the distal small bowel. So, even so, I think it probably is not common to be able to acquire typhoid that way.

But Shigella, you know, other agents I can see transmitted that way nicely.

DR. STIBITZ: All right. Thank you very much.

(Applause)

DR. STIBITZ: And we're doing really wonderfully on time. So, our next speaker is Lee Jones, the CEO of -- should I call it a start up?

MS. JONES: It's a start up.

DR. STIBITZ: Called Rebiotix, and they're seeking to develop a business around this.

MS. JONES: Well, good afternoon, everybody. I would like to thank our sponsors

here for inviting me to participate in this meeting and thank all of you for still being awake this late on a Friday afternoon after a two-day intensive program.

I was pretty honored to be able to speak today and as I was getting prepared for this meeting I got a call from a former employee of mine who, after seeing another fecal transplant article in the press, called me and said, hey, I saw this article about feces and, weirdly, I thought of you. I'm not sure I appreciated the word association, but I do appreciate being part of this program.

For the last couple days we've heard some -- about the wonderful science behind the human microbiome and how it can influence our health. I'm going to take a slightly different path and for the next few minutes talk about harnessing the power of the human microbiome and how we can make that widely available through a commercialized prescription product.

So, my name is Lee Jones. I'm the founder, president, and CEO of Rebiotix. I

have greater than 30 years of experience commercializing regulated medical products primarily on the medical device side. I've worked at small companies, large companies, and academia.

We founded Rebiotix in 2011 with the idea that we could develop treatments for hard-to-treat gastrointestinal diseases using the human microbiome, starting out with using a derivative of fecal transplants.

It's been quite an interesting adventure and it's been one of the most fun things I've worked on in my career.

When I first heard about fecal transplants I thought it was the stupidest thing I'd ever heard, I couldn't believe that anybody actually did that, but the more I got engaged and more I understood what the potential of the therapy was, the more excited I got. So, I partnered with another person and we decided to take a look at what the potential business opportunity would be.

So, we evaluated a number of factors, and for those of you who have never

started a business before, this is a typical thing that a businessperson would look at. We asked ourselves, is there an unmet medical need? Is there something out there that we can solve that nobody else is able to do today? How many patients are there? How big is this market? What are the alternative treatments, not just today, but what do we see coming in the future? What are the regulatory requirements? And those were important because they would give us an idea of the time and cost to gain market approval. Who would pay for this if we got it done? And in the case of fecal transplants, what other applications were there besides Clostridium difficile?

And what we found is that there was an unmet need that, you know, patients who get Clostridium difficile disease have some options, but those people that have recurrent disease have very little option because there's more C. dif patients, there's more recurrent patients, so the number of patients were growing.

These patients were very expensive to treat -- the first initial hospitalization, then multiple treatments of expensive antibiotics, plus the influence on their own lifestyle. Antibiotic treatments had limitations. Fecal transplant -- now, understand, this was in 2011 -- was promising, but seldom used. The regulatory requirements were unknown, so we had a tough time exactly predicting how hard it was going to be to get to market and we did see that there were potential applications besides recurrent C. dif.

Now, for the last couple days we've heard about all the kind of good news/bad news challenges with FMT. From our perspective, here's what we saw: There was over 50 years of positive anecdotal clinical evidence that suggested it worked. Now, from my perspective, having been in this industry for a long time, it's pretty rare to find a therapy that you already know has a good chance of working. The bad news is that there was no regulatory classification. We didn't

know if it was a tissue transplant or a cellular therapeutic or a drug. So, we knew it was going to take a new regulatory paradigm.

The good news is that, you know, I had spent quite a bit of time as part of Rebiotix going through an exhaustive literature search, just like many of you have, and there were few reported adverse events. But in those same papers, it was really clear that there was no standardization whatsoever. There was no standard in donor screening, I think the closest that we came to seeing that was through the FMT workshop that we've talked about today. But even they weren't associated with a major medical organization. They're pretty much a standalone group. There were no manufacturing standard methods, materials, volumes, dosing, or delivery methods. So, as a result, it was really unknown safety and efficacy.

Now, the good news is that fecal material is cheap and available, as we've all known, but the bad news is that means that

anybody can do fecal transplants. I mean, as we've heard earlier this session, you can go online, you can find recipes for do-it-yourself, they sell do-it-yourself kits, there's colonic health retreats, and they're pretty pricy, they're in the $8,000 range, and a whole group of physicians are doing a bunch of different things, as we've known, and from my experience, having worked in industries where you have technology that can overrun -- you know, in this case it's a little bit unusual because the technology is available to everybody, so anybody can do it -- a few disasters could really damage this promising therapy.

And finally, the really bad news, and we've heard a lot about that today, is that everyone who performs FMT today has to be their own manufacturer. You have to find and screen donors, you have to collect the stool on demand, you have to process the fecal material, and while it's not so bad, I haven't heard anybody who says, yes, give me that as a job, I can hardly wait to do that on a daily

basis. And it must be done for each and every patient.

And what all this -- and today, I guess, the overlay that was new to me was the regulatory aspect. You know, I, as an industry person, live with regulations all the time, so to me this was just normal, but to hear that now you, as individual physicians, have to go through a similar regulatory process that I, as an industry person, has to do, all it really does is, at the end of the day, delays what you really want to do, which is treat your sick patients.

So, at Rebiotix, we're solving the problems of FMT by creating a ready-to-use, off-the-shelf product that can be ordered as needed, and conducting rigorous clinical studies to demonstrate the safety and efficacy of treatments for patients who have failed standard treatments for CDI.

Now, we wanted to be able to claim a therapeutic benefit for our product. If all we cared about was making money like the evil corporate empires everybody always blames

people to be, we would just say, here, eat this, it has a health benefit, and we'd be selling product on the grocery store shelves today.

We think we have a serious product for a serious disease, and as a result, wanted to have a product labeled for therapy for that disease, and the only way I know how to do that is to go through the FDA. The challenge here was that we didn't know how to do that. Between my partner and I, we hired six different regulatory consultants and we got six different answers, anything from it's a tissue transplant, you know, it's just like a blood donation, no big deal, you should be able to get this done, to this is a biologic drug and I'd stake my career on this.

So, we did like many of you did, we went to the source and said, all right, we want this to be designated as tissue transplant, because we thought that was the most appropriate thing, and that was in March of last year. In August of last year, we had a notification that the product did not meet

the criteria for tissue transplant primarily because, in the letter we got, because it was not human tissue that was being transplanted. The decision that we received was that it was going to be reviewed by the Office of Vaccine Research and Review at the Center for Biologics Evaluation and Research and it was going to be a drug, a biologic drug.

Now, for us, did it really matter? The answer was no because the most important thing to me was to know what I was supposed to do next. You know, if it was a tissue transplant, we had to worry about tissue regulations and quality systems and a whole series of infrastructure that's maybe different than what you'd do for a drug. So, for us, getting this kind of decision was really the most important thing, then I could go forward and develop the rest of my company around -- to meet these regulations and requirements.

So, in December of 2012, we had our pre-IND meeting. We submitted our IND for a Phase II study of our new drug, RBX2660, which

is a microbiota suspension, and right now we're waiting to know when to start the clinical study, we're in the process of enrolling centers.

You know, as I mentioned earlier, you know, I have a significant background in commercializing regulated products, and as a result, you know, I know that regulations and quality standards have a very important role to play. They do two major things for all of us, they protect the patient, and because they do that, they protect the industry. This is one of those things that if it runs amuck and has a disaster, it's going to be hard to recover from because people will lose faith that this is something that could be helpful.

On the other hand, balance must be struck between the risk and benefit. When we put this company together, we saw that it was a very small risk for a very large benefit. So, we're pretty excited about moving forward with this technology.

When we began drug product development, we had some assumptions. One was

that live microbe delivery was important and a requirement. The second assumption was that the number and diversity of microbes that we delivered to the patient should be a reasonable match to raw, human stool because we know that raw, human stool works, and our third assumption was that if we did one and two, we could be reasonably assured that our product would work once we got it to the clinical study.

We moved on to the most challenging part of the whole thing, which was what we called the Chemistry, Manufacturing, Controls. We had to characterize the raw material, we had to develop the manufacturing processing, evaluate storage methods and shelf life, develop the delivery kit, and establish the quality release specifications.

For industry, our standards are a little bit higher than a physician-sponsored IND. Our IND was over 1,500 pages, just to give you an idea, so it took us -- our collective company, a month of solid writing to put all this -- not to mention all the data

that we had to generate. So, my heart goes out to you because we had a team. I can't imagine trying to do that all by myself and trying to make -- you know, learn the rules as I went.

Our goal was to deliver a consistent quality product to the customer each and every time, and the product had to be easy to use in routine clinical practice. I can tell you from what I've heard today and the other people that I've talked to that have done FMT in their practice, it's not routine, it's not easy to use. You have to find the donor, you have to process the material, et cetera, et cetera. We didn't want anybody to have to go through any of that.

It was easy to say, in actual experience, this was not an easy task to accomplish. It's taken over a year and $2 million of our investment so far to develop a product that's ready for commercial clinical study. The bulk of our work involved characterizing the human stool, which was, you know, typically variable input material, and

discovering what affected its properties.

So, I have to tell you that every time I hear -- I've been at a number of conferences over the last year, if somebody stands up and says, "this is going to be really cheap because stool is really cheap," I can say that this will be economical, because the donor screening and all the payment for that is already incorporated. There's no manufacturing. Once we deliver a product, all that stuff goes away for the physician, but it's not going to be free.

So, what's next? The next step is to conduct the clinical studies. We have a product and it's a ready-to-use enema format. We chose enema because as we went through the literature search, we believed that the enema procedure generated the least number of procedure related complications compared to colonoscopy and nasogastric tube or nasojejunal tube. And it's easy for just about anybody to perform.

The indication is recurrent Clostridium difficile- associated diarrhea.

The Phase II study is an open label, non-randomized safety study. If we are successful with the Phase II, then we'll move on to a randomized, multi- centered, double-blinded, placebo-controlled study for safety and efficacy.

So, looking to the future, we think that other indications and delivery methods are going to come to the forefront. We've heard some of the discussion today, the challenge with being in the regulatory process, it's likely that our product won't be coming out until sometime -- if everything works well -- 2015. So, I have a hunch that the science and a lot of the experiments you people are doing will have generated a lot of -- a lot more information than we have today.

The products are going to evolve as the science evolves, I truly believe that. What we're seeing today is a product in its most crude form. And then maybe someday it will be used to treat a broad spectrum of other non-GI conditions.

So, in order to realize this future,

you know, I believe that we need a new terminology. In that same literature search that I went back through, I just started listing how this has been referred to. I think everybody's sort of struggling with the same thing. You can see there's, you know, stool bacterial flora replacement, FMT, fecal infusion, bacteriotherapy, et cetera, et cetera, and last but not least, my favorite, rePOOPulate. You get the picture, and it's not pretty.

I had a chance while I was doing this, again, thinking that this is sort of the crude start -- get started product. What other products are out there today that we commonly use that started the same way? And I found a few. I'd be curious to know how your patients would react if you said to them, "Here, this injection of slaughterhouse pig pancreas juice is going to help your diabetes", or "swallow this pregnant mar urine preparation. It's going to help your hot flashes." Or, finally, you know, if you have cancer, "I can treat it with this yew bark

extract." Some people might appreciate that, but most people probably wouldn't as they're concerned about their disease.

I have a hunch that your patients would feel the same way about this as I felt about hearing fecal transplant for the first time.

So, I would say that sometimes it's best not to be too literal. And here's what I would propose. Drop the word "fecal". It's too limiting. We heard yesterday a skin microbiota process were replacing some microbiota helped those diseases. I think, you know, the NIH Human Microbiome Project, they tested 18 different microbial populations on healthy humans. So, I think that "fecal" really narrows the field down too much. I think it's repellent, and while I have -- you know, my colleagues and I have a great time at the office making jokes, as many of you I'm sure do, we really think this is a serious topic and needs to be presented that way and the word "fecal" just doesn't bring that to mind.

So, I propose Microbiota Restoration Therapy. I'm sure there's other proposals that would work just as well, but this is the one that I would suggest.

So, in summary, FMT has potential, but it also has challenges. We're solving the problems of FMT by providing and developing a commercialized, standardized, ready-to-use product. Regulations and quality standards can protect this dynamic industry. And better terminology, such as MRT, is needed if we're going to move forward.

So, in conclusion, I think the future of MRT is exciting and it's up to us to make it a reality. Thank you.

(Applause)

MS. JONES: Any questions?

DR. RAMESH: Mayur Ramesh. Center for Infectious Disease. So, obviously, we are trying to create or replicate human flora, which you've already done, it seems like, so the ultimate probiotic, as people have touted it. So, in the -- FDA does not regulate the probiotic industry, that I know of, and I may

be wrong in this, such as, say, over-the-counter kefir procures.

MS. JONES: Right.

DR. RAMESH: And kefir products are definitely much more, and they carry a far more number of bacteria than the conventional probiotics that are available. So, obviously, yours is a very standardized kefir product, if I may call it, and so, why is it that we are having this meeting on FDA regulation?

MS. JONES: Because part of it, and again, this is from my industrial background, it all depends on the claim that you want to be able to say that your product does for you. If you go to the -- look at the kefir products, they can't say, "drink this and it cures C. dif infection". The only way you can get that is by demonstrating the proof of your claim through your standard clinical studies and generating the data.

If I didn't want to make that claim, I wouldn't necessarily be here and we wouldn't necessarily have to have this meeting. So, it's more about how you want to project that

product and what you say that it can do. And that's it.

Any other questions?

MR. ROEHR: Yeah, what has the FDA asked you to do in terms of -- I'm sorry, Bob Roehr -- what has the FDA asked you to do in terms of long-term follow up, either in the Phase II or in anticipating and trying to work out a Phase III?

MS. JONES: Because of the long-term disease concerns, you mean? Is that the --

MR. ROEHR: In terms of long-term follow up of the patients who receive it, you know, are there any -- are they doing it on the same basis as an antibiotic, which has generally been short-term, or are they looking for longer?

MS. JONES: Well, the clinical studies are based on the disease. So, recurrent C. dif in the context of MRT is an acute disease, it's not a chronic disease. So, the endpoint of the study is determining the symptom relief, let's put it that way, so in our case for the Phase II study, it would

be the elimination of recurrent diarrhea or diarrhea related recurrent Clostridium difficile disease, so CDAD.

So, at the cessation of the diarrhea and having it not recur for 60 days, that would be the endpoint. The safety, for the Phase II, is six month follow up.

DR. CASSELS: Fred Cassels, DMID. Am I to understand that the product is human stool and that it's based on individual donors and individual material, and then along those lines, what release criteria are going to be established for that material, reproducibility from sample to sample, things along those lines?

MS. JONES: Yes, there are.

DR. CASSELS: Sort of GNP related --

MS. JONES: Yeah, we've developed those and there are release criteria that we measure. There isn't a standard to say what they have to be, so we base our standards on what we would find in raw, human stool.

DR. GRAHAM: David Graham, Houston. I think your name is not going to make it.

Throughout this meeting, people have brought their mothers up, and I think that's the key, and that in real life, people are going to always ask your mother, what do you do? And it's got to be a name that they can say, it makes sense, and they don't have to ask, what does that mean? To your word, they would say to the mother, what does she really do? And she says, well, I do, transplants.

MS. JONES: Are you talking about the MRT?

DR. GRAHAM: Yeah.

MS. JONES: That's not --

DR. GRAHAM: So, it's got to have a cute name that the mothers can say and everybody will either say, fine, or not have to ask what does it really mean.

MS. JONES: I'm thinking that the MRT really is an industry wide concept for what we're trying to accomplish as a group.

DR. GRAHAM: I think it's a bad name for a commercial product.

MS. JONES: It's not a commercial product name. That's not our product name at

all. Yeah, instead of saying "fecal microbiota transplant", take the word "fecal" out and substitute it with something else, because it's too -- the word "fecal" itself, is the wrong word to have. That's certainly not the product name. The product name won't be assigned until after the clinical studies are completed. It's not going to be anything like that. It's going to be a drug name.

DR. GRAHAM: There's a book about constipation entitled, "Inner Hygiene". I think that's the direction that we want to go.

MS. JONES: Dr. Rubin.

DR. RUBIN: David Rubin. Thanks for your presentation. It was excellent. A comment and then a question. So, my comment is that, at least in our survey and focus groups with ulcerative colitis patients, and I would predict similarly for people with recurrent C. dif, they're happy to call it anything as long as it's working. So, for them, the fecal doesn't turn them off. I think it's important to think about it for future applications and I don't have a problem

with that proposal.

But my question for you is, I recognize a lot of this is proprietary, but can you share anything about your product and how it's stable or what -- how it may or may not be similar to some of the things we've been chatting about during this meeting?

MS. JONES: Well, for this first iteration, it's an enema, prepackaged so that there's no mixing or thawing or anything. We do keep it frozen at our facility. Right now we have, at minimum, six-month stability data.

We test a variety of attributes about the fecal material -- microbes, diversity, similar to some things that you've been talking about. We make sure that it has a minimum criteria of those types of things so that each patient will always get a standardized dose.

So, what we've done over the last year, we had to develop the test, that was pretty tricky because most people -- and I've asked people, I went to a number of meetings and asked people, how do you determine what's

alive and what's dead and consistently and over time? So, that was a hard question, because if you do the 16SRNA testing, you get a bunch of genes, but that's whatever you happen to have that day, including what you ate that day.

So, somebody told me, well, if it's in there and you see it, it was alive at one time. But my thing was more about what can I recover and how long can it last and so, again, it is proprietary, we've spent a great deal of effort trying to figure out how to do that, and we're pretty happy with the results. That's all I can say.

Any other questions?

DR. KUNDE: How many donors do you have?

MS. JONES: You know, roughly about five at this point in time, because the number of patients that we have to do for the Phase II study are so small. Now, one thing I can say is that we don't do exactly the same type of screening. We do the screening, but then we have to quarantine the material until we do

another screening. So, we never release something from any donor until that donor has passed a second health test. So, we have an ongoing relationship with these donors, an ongoing -- we do somewhat similar, we do -- use the blood questionnaire every time they donate and we do a number of other regular screening and testing criteria.

So, we have, like I said, a pretty tight relationship with these people to make sure that what's going in is pretty safe. We don't pool any samples and we don't pool between donors.

DR. KUNDE: Do they produce the stool on-site or at home or --

MS. JONES: Mostly at home. It's fairly hard to get the donors to, on a regular basis -- because it's not a regular thing. Sometimes it could be in the middle of the night, sometimes in the morning.

DR. BRANDT: Larry Brandt, New York. It's such an interesting and complicated situation because you have five people, those five people are not the same everyday.

MS. JONES: You're right.

DR. BRANDT: We don't know that their stool is the same everyday. If they change what they eat, it could influence the stool. You say we don't know if it's alive or dead. I'm not sure that it has to be alive or dead. We don't know what percentage of what we put in is dead, so the living versus dead is -- so, it's your product consistency that I think is a thing that's making me think about it the most. One of your donors dies, now you need another donor. Well, now your product is going to change. And I don't know whether you're mixing the five donors together and getting an aggregate or whether you're doing it separately, but now you have a new donor, what do you -- that's going to change the whole population of your product.

MS. JONES: But I challenge you to say that's exactly what you're doing. I mean, every single person who does an individual donor one-to-one has the same challenge. So, I don't know that I'm convinced that anybody knows exactly what's supposed to be in there

and what ratio. What I can say is based on the literature and what I've heard in the last couple of days is that by taking a raw, human stool and processing it and putting that in a recurrent C. dif patient, you have a pretty good outcome.

DR. BRANDT: Yeah. The one thing I do know is that nobody knows anything.

MS. JONES: Yeah, that's true. I mean, I think -- and we're in the same situation. And like I mentioned, you know, I'll base this on my experience, there's very few things that I've worked on that stay the same from one year to the next. I mean, I've been, a lot of times, particularly in the device industry, because it's a little easier to see, you know, I'll open my drawer after a couple of years, pull out the stuff that I used two years before, and laugh and think, how could I have thought to use that in a human being, because today it's smaller, sleeker, cleaner.

I think, just like a lot of people have said here, this is the worst we're ever

going to see because the science is going to evolve, we're going to know which microbes make a difference, or not, alive or dead, or not, I mean, we made an assumption that live mattered because, you know, we're thinking microbial replacement. That might not even be true, but we don't know any better today.

So, what I anticipate is that, just like the doctor right before me, this isn't going to be the one and only ever therapy, that we're going to start here, get something out there for people to use that's standardized, that's easy to use, that we can track, and watch the data occur.

This is so different than anything else I've ever worked on because normally, you know, if you're a device company, you control the material, right? Or if you're a drug company, small molecule, you own that and you dole it out in little bits and pieces so the science is really controlled.

Here, it's like you took a fire hose and said, all right, anybody who wants to do it, do it this way. So, you know, we're

trying to catch up as fast as we can and watch the developments and make sure that whatever we come out with is the best we know how to do at the time, and then put that in the context that we can't change anything through the regulatory process. Once it's settled, it's settled.

So, I anticipate there's going to be a number of evolutions of our product as well as the other companies that are here that are looking at the same thing.

So, the work that you're doing and everybody else is doing here that either you try it on an IBD, or you try it on this, or you try this dose, or that dose, all that information, as you publish it, I see. So, I can start getting an understanding of what your needs are or what the patients needs are, how do I need to look at my things to get them to help you? Because at the end of the day, if my stuff doesn't work for you and your patients, I have no business.

So, we all kind of have the same goal in mind. Like I said, for me it's

important that this product serves a need and the unmet need here for the first case is recurrent C. dif because those people just have such miserable lives, and I think I can make a business out of this, I can help you, as well as your patients, and me.

DR. KHORUTS: How are you reimbursing your donors, if at all? And I ask because -- for the question that they're bringing in their material. How is that GMP? Who is supervising the bathroom? How do you know they're not bringing somebody else's stool, especially if you might be paying them?

MS. JONES: First of all, we don't pay them for the very reason we don't want to create a conflict. People are very well known to us. So, the likelihood that they're going to cheat -- there's really no incentive for them to cheat. They could. They sign a statement saying that this is their stool and they sign a consent form, a legal document, to be participating with us. So, we don't have a fail-safe, fail-proof, but then I would suggest that nobody else here does either.

Unless you're sitting in the bathroom with that person when they're actually having a stool, because they take it out -- they either bring it from their home or they stick it in the little door -- how do you know -- you're assuming, just like we are, that once it gets in that container, that it's what it is. And so, you know, the risk was pretty minimal.

Any other questions?

DR. RAMESH: Does the IND have to be modified or changed if the donor changes? Or what is the -- I mean, obviously, I should be asking the question to FDA.

MS. JONES: No, our IND, it's more related to not -- it's not donor-specific, it's product. So, if we change our manufacturing method, we change our storage method, we change our delivery method, we change our labeling, our packaging, we change, you know, something in the clinical study or the informed consent, that's what requires a change on the IND part, not the donors.

Any other questions?

DR. STIBITZ: Thank you.

(Applause)

DR. STIBITZ: Okay, so we're ready for a break, and before we break I just wanted to say one thing. As I was sitting here after giving my thanks to people involved in putting this workshop together, I realized I had left out one of the most important, and so Sheila Dreher-Lesnick has been a huge help. She works with me. She's closest to me, so that's probably why I didn't think of her, but Sheila. (Applause) So, we are actually a wee bit ahead of time. Be back here at 3:15. Thank you. Okay, everybody, hold it. We have a query for the audience. It has been suggested that since a lot of people have to leave, that we might want to move up the beginning of the next session to 3:00 o'clock. All opposed? Okay, 3:00 o'clock. See you there.

(Recess)

DR. STIBITZ: So, we're coming to the culmination of this workshop and it's my pleasure to introduce our next speaker, Dr. Jay Slater, who is the Division Director of

Bacterial, Parasitic, and Allergenic Products, who is tasked, at least in part, together with our sister division, DVRPA, in regulating FMT. So, here's Jay.

DR. SLATER: Thank you very much. And actually since we're close to the end and we're thanking people, aside from thanking the organizers, I actually would like to thank all of you, both speakers and other participants. It was always our intention to try to learn as much as we could about what was going on in the community, and I certainly think that we have done that, and I think we've had a very good discussion, which I hope is just beginning.

My job is to give you some of the regulatory perspective. Some of this is going to seem clearly redundant in view of the fact that we've touched on this a whole bunch of times already.

So, in my talk -- actually, could we leave the lights up? Would that be against the rules? Is everybody okay with that? It's just that time of day. I don't want to hear

the soft sound of snoring.

(Laughter)

DR. SLATER: And this is a regulatory talk, so that's always --

(Laughter)

DR. SLATER: I'm going to talk about why the FDA regulates fecal microbiota for transplantation. When is an IND application required? What's included in an IND application? What the FMT research needs are? And how we think the FDA can help achieve them?

Why does the FDA regulate fecal microbiota for transplantation? This is the only slide of mine that seems to have been malformed somehow, but it's too wordy anyway, so that's okay.

These are the statutory definitions of drugs and biologics. This is not in the regulations and it wasn't made up in any of our guidance documents. This is actually authored by Congress. And drugs are "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of

disease, and articles (other than foods) that are intended to affect the structure and function of the body of man or other animals." And biological products are defined as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product --" I know you were all waiting to see where fecal material fit in -- "or analogous product, applicable to the prevention, treatment, or cure of a disease or condition in human beings."

And although I suspect not everyone in the room agrees with this, after much deliberation, FDA determined that fecal microbiota, when used to cure, mitigate, treat, or prevent a disease, fecal microbiota for transplantation meets the definition of a drug and a biological product.

So, given that, when is an IND required? Well, if the fecal microbiota are being used to cure, treat, mitigate, or prevent a disease or condition, it is considered an unapproved, new drug, for which

an Investigational New Drug application or IND is required.

So, fecal microbiota for transplantation meets the definition of a biologic or drug. When it's being use to do this, it's an unapproved drug and it needs to be done under IND.

So, what is an IND? We throw around these words, and it's worth taking a step back. This is an Investigational New Drug Application. And if an IND is, in effect, if you've submitted an IND application and it's been accepted for an Investigational New Drug, it exempts the Investigational New Drug from premarketing approval requirements. In other words, it doesn't have to be licensed. It can be used in that study.

And furthermore, it allows the Investigational New Drug to be lawfully shipped across state lines for the purpose of conducting a clinical study of that Investigational New Drug.

By the way, just in case you were wondering, an IND is not necessary to conduct

a non-clinical study. INDs only are related to studies in humans.

Again, I suspect for most of you in the audience, this is old news, just bear with us, but there are three phases to an IND study, these are the phases of product development under IND. Phase I is predominantly focused on safety and on dose ranging, and typically Phase I studies include tens of subjects.

Phase II, after you've completed the Phase I, focuses on safety and early evidence of effectiveness, and usually involves several hundred study subjects. Phase III, safety, effectiveness, typically several thousand subjects. And for the most part, FMT studies are in Phase I, and it's important to point out that these are the phases of product development under IND, but IND rules apply even when you're not planning on developing a product, in other words, if you're just studying fecal transplant and you're not planning on going ahead to make some commercial product, you would have to do them

under IND, and typically, depending on the scope of your trial that you were you conducting, it would be usually a Phase I or a Phase II trial.

So, what are our objectives when we perform review of IND applications? And first and foremost, regardless of the phase of the study, our emphasis is on the safety and rights of the study subjects. That's the first and foremost concern that we have. When you move on to Phase II and III, we are also interested in assuring that the quality of the scientific evaluation is adequate to permit an evaluation of the effectiveness and the overall safety.

You've heard from several speakers how hard it is to submit an IND, but I have to tell you, I've really talked a lot of people through this and like most painful experiences that are dreaded, looking back on them is much better than looking forward to them, and, you know, it's definitely something that's hard, it's hard for a reason, and it's very doable.

But what are the contents? You have

to have a general investigative plan. If the sponsor and the investigator are not the same person or if it's a multi- center trial, you need to have an investigator's brochure. You need to have manufacturing and product information, you have to provide all available non-clinical pharmacology and toxicology data to support that it is safe to initiate studies in humans, you have to have a summary of any previous human experience, and you have to give information on the clinical protocols that you're going to be following and investigator information.

The amount of information that must be submitted in an IND depends on such factors as the novelty of the drug, the extent to which it's been studied previously, the known and suspected risks, and the development phase of the drug. So, bringing this to fecal microbiota for transplantation, the developmental phases are often going to be fairly early, but we actually have a lot written about what our suspected risks are and so that may actually add to the complexity of

some of these.

The central focus of the initial submission should be on the general investigational plan and the protocols for specific human studies.

In general, the protocols for Phase I trials can be less detailed and more flexible than protocols for Phase II and III trials. Phase I protocol should be directed primarily at providing an outline of the investigation, an estimate of the number of patients to be involved, a description of safety exclusions, and a description of the dosing plan. It should specify and detail only those elements of the study that are critical to safety.

So, more on the content of the protocol itself. Clearly, clear statement of the objectives and the purpose of the study, the names and addresses and qualifications, including a CV, of the investigator, sub investigators, names and addresses of the research facilities, and the name and the address of the IRB.

Patient inclusion and exclusion criteria are very important. The study design, the dose and duration of exposure, descriptions of observations and measurements, descriptions of the clinical procedures to monitor the effects of the drug and to minimize risk, and individual and study stopping rules.

This is the only abbreviation that I think I failed to spell out. CMC stands for Chemistry, Manufacturing, and Controls. So, what are the Chemistry, Manufacturing, Control information that we need to know in a Phase I trial? It's "a section describing the composition, manufacture, control of the drug substance and the drug product. The emphasis in an initial Phase I submission should generally be placed on the identification and control of the raw materials and the new drug substance."

Phase II, Phase II clinical studies, controlled clinical studies conducted to provide preliminary evidence of effectiveness. By the time you get to Phase II, these are

typically randomized, well controlled, and very closely monitored for safety. Up to several hundred patients. The entry criteria are actually less restrictive than in Phase I and they reflect the target population that you're aiming for overall.

So, now getting specific about FMT and the IND review, what are the things that we're looking for in terms of the clinical review for FMT submissions? We're looking at the study design, that it be well described and that there are procedures built in to minimize bias and risks. Again, patient inclusion and exclusion criteria are very important, the number of patients that you're expecting, procedures to limit transfer of pathogens, we've talked about this from the very beginning of our presentations yesterday, donor screening procedures, product testing, procedures for administration, quantity of product to be administered, frequency of administration, monitoring and reporting of adverse events, and patient outcomes, monitoring for treatment effects.

Now, the CMC, the Chemistry, Manufacturing, and Controls for FMT submissions focuses on the manufacturing process, what's the process for donation and storage, for instance, if it's fresh or frozen, method of preparation, the addition of saline or stabilizers, the quality of the ingredients that are used, tests to characterize the materials, and the storage conditions.

But obviously there are challenges for product characterization with fecal microbiota. Defining the "product" is obviously non-trivial and it's been a topic of discussion both yesterday and today. What's the active ingredient? What are the potency? What is the stability of this product?

Defining the manufacturing process, consistency of manufacture, this is another way of saying that this is a complex biological product and it's hard to figure out how you're going to define the CMC of the product. But what I want to emphasize is that we, as the FDA, have experience with this.

Complex product characterization challenges have been overcome in the past. People have made references to issues that have to do with blood, human cells, tissues, and cellular or tissue-based products, products that arguably are as complicated, in some cases, more complicated than a fecal transplant material, and these have been overcome.

So, I think this is not a barrier, this is just yet one more thing that makes these challenging submissions to deal with.

I want to spend just two slides talking about expanded access. This is another kind of IND, and, again, many of you in the room are familiar with this already. It's not an approach that we're encouraging, for reasons that I think will be clear in the next slide, but it is an approach that exists and has been used.

The aim of expanded access to investigational drugs for treatment use is to facilitate the availability of an investigational drug to patients with serious diseases or conditions when there is no

comparable or satisfactory alternative therapy.

The aim is not to obtain safety or effectiveness data from adequate and well-controlled trials to support approval.

So, what are the criteria from the regulations? In order to accept this, the FDA first of all has to determine that the patients have a serious or immediately life threatening disease or condition for which there is no comparable or satisfactory alternative therapy, and I think we can probably agree in this room that patients with recurrent C. dif colitis arguably fall into that category.

The FDA needs to agree with the investigator that the potential benefits justify the potential risks in the context of the disease or condition being treated.

And finally, the FDA has to determine that providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support

marketing approval of the expanded use or otherwise compromise potential development of the expanded access use.

So, one of the concerns that the regulations tell the FDA it has to address in approving expanded use is that by approving expanded use, we're not somehow jeopardizing other studies that are really being done as trials to demonstrate the effectiveness of the therapy in doing so, and that, I think, is something that the scientific and medical community needs to keep in mind about this expanded use route. It's there, it exists, but it's really not something that is optimal for moving the field forward.

There are some additional criteria, if you want to be in the intermediate size of tens to hundreds of study subjects for expanded use. There has to be good evidence of safety and at least preliminary evidence of effectiveness, but all of these other characteristics need to be met.

So, in three or four slides to just summarize what the FMT research needs are, and

I think if I were writing this slide down I probably would add some things to it based on what we've learned the last couple of days, but let's just go with what we wrote before.

Where are we now? There's published data and studies that are very encouraging for the treatment of refractory C. dif colitis. That's clear. What's needed is adequate and well-controlled trials to evaluate the therapeutic potential, the full therapeutic potential, of FMT for the treatment of C. dif colitis and especially for other diseases. And what would be ideal would be to identify the key microbes in the fecal material responsible for the beneficial effects leading to efficacious, defined products targeted for specific diseases.

We obviously need to understand the human gut microbiota in health and disease states. We need a good assessment of the risks of manipulation of the microbiota to the recipient. Early pre-clinical and clinical studies suggest that perturbations in the gut microbiome can have profound effects on health

and disease, and these effects may be beneficial or harmful, they may appear short-term or long-term, and they may extend far beyond the gut.

We need to have investigations of which components of the stool are responsible for the therapeutic effects and what are ht potential longer-term effects of transferred microbiota on the recipient. This is clearly an inadequate list, but it's a start.

What are the potential long-term effects of alterations in the gut microbiome? Obviously, immune status, nutritional status, autoimmune status, wound repair and fibrosis, cognition and mood, cancer risk, and others. And we've heard about some of the others in these sessions.

This is the problem, and again, this has been pointed out repeatedly by several of our speakers today: All of the evidence that has been presented suggests that the gut microbiome and manipulating the gut microbiome is a powerful method that can have long reaching and very subtle effects. It's going

to be a difficult scientific and clinical problem to work out long-term. That said, as has been said repeatedly, this is a very low-tech procedure with a CPT code.

The how-to guide appeared in MedScape about six weeks ago, I don't know how many of you have read it. I learned a great deal from it. I think it was extremely well done. I learned things about FMT that I hadn't know before.

That said, it's a how-to guide. This was emailed out to a lot of doctors. And it walks you right through the procedure very easily.

So, I think we've heard this concern from several of our speakers that we have a situation in which we have a subtle, challenging, powerful problem in our hands, and we have a very large number of people who are doing this off the grid.

So, clearly we all have an interest long-term in controlled clinical studies of FMT. These will enhance progress in FMT research by assuring appropriate entry and

exclusion criteria, clearly defined endpoints, subject safety, good records of treatment protocol, patient demographics, medical histories, oversight and input on the design and conduct of trials by fellow healthcare providers, scientists and ethicists, appropriate and consistent product characterization, and arguably, most important, good analyzable, interpretable data regarding the outcomes and the adverse events.

This whole part of the talk was -- if I were just going to condense this whole part of the talk, the first part of the talk was to tell you, well, you know, the FDA has determined that fecal microbiota is a biologic and therefore it needs to be under IND and there are good reasons for that. The second part of the talk is really to try to convince you that even if we were waffling on the edge and weren't sure, it would be in the scientific and medical community's interest to have the FDA actively involved in this process because having the FDA involved will assure that at least most of the people that are

getting this will be getting this treatment in a way that we can actually look back and figure out what's the best way to do it. Okay? That's not the reason the FDA is doing it. The reason the FDA is doing it is because it's a biologic, but FDA will continue to work with the medical and scientific communities to ensure patient safety and medical progress.

So, in summary, FMT used to treat, prevent, cure -- I forgot mitigate, oh, lord -- or mitigate a disease, meets the regulatory definition of a drug or a biological product, and IND is required when FMT is an unapproved new drug. Early phase IND focuses on safety. Evaluation of FMT presents some unique challenges, but they're just challenges, they're not barriers. We can do this.

Future clinical and lab research is important for the development of this therapy and controlled clinical trials will help advance the science and assure patient safety.

Any questions?

(Applause)

DR. STIBITZ: What happened to the

lights? So, I think what we decided to just form the panel up front for the panel discussion, and we can start the questions at that point, if that's okay with everybody. So, would the speakers from today please come down and have a seat?

Okay, I don't think there's going to be any problem generating questions, but I just made a few notes to throw out some ideas that we might want to consider. And I forgot my glasses.

AUDIENCE: They're on your head.

(Laughter)

DR. STIBITZ: Oh, thank you. I'm not that old. So, one of the concepts that's come up repeatedly today is that of a registry, and I think there seems to be a great deal of support for that and some questions, which seems to me that we would need to address are, what -- i.e. What information would such a registry capture? Who would run it? And, very importantly, who would fund it?

Standardization is also something

that's come up repeatedly. This is -- there seems to be a clear need for a standardized protocol for treatment, for standardization of the material, and this involves issues such as identification of donors, donor screening, and testing of stool material, and also, perhaps, standardization of follow up procedures, what kind of data do we feel it's important to recover?

And then there's the involvement of the FDA, and I believe there's a feeling that there needs to be some clarification of individual investigators' regulatory responsibilities, and also perhaps a feeling that the IND process is too cumbersome.

So, take it away.

DR. RUBIN: Could I ask Jay a question? Your lecture was very helpful. Could you clarify for me -- and forgive me if this is just a very novice question -- the distinction between an expanded access IND and compassionate use?

DR. SLATER: They're different. Expanded -- the real intention of expanded

access is for -- it was original intention, as my understanding and my colleagues, please kick in before I -- oh, are you going to answer the question for me?

MS. FINN: No, Jay. This is Theresa Finn in the Office of Vaccines, FDA. So, by "compassionate use", do you mean emergency use?

DR. RUBIN: It could be considered that, yeah.

MS. FINN: Yeah, okay. Emergency use is considered part of expanded access and the criteria in that situation is that, you know, Jay put on his slide "Intermediate Access Use" and there was an additional requirement, which was, one was for safety and the other was for preliminary evidence of effectiveness.

In the case of emergency access -- emergency use, it's done on the context of a patient and a physician, and the physician and the patient have to determine, in the context of that person's disease, it would be a good idea to give this particular therapy, and I

think that's what you mean in this situation.

DR. RUBIN: Thank you.

DR. SLATER: Yeah, that's a great question. I would guess, until corrected otherwise, that the answer is, yes.

COURT REPORTED: Could you repeat the question, please? He was not on the microphone.

DR. SLATER: Oh, I'm sorry. The question was, does everything that I said about fecal microbiota for transplantation being a biologic apply even if this is an auto-transplant, in other words, if somebody has banked their own stool, or saved their own still before some aggressive treatment, to be re-instilled, and again, anytime you ask anyone from the FDA to make a judgment in public on one foot, they will -- if they're aware enough, they'll say, you can't really take this home, but honestly, as an individual, I don't see why it wouldn't be. I don't see it as -- the fundamental feature here is isn't transplant, the fundamental feature here is, what is this substance? The

process of harvesting fecal microbiota from a person for future use is not our normal disposition of fecal microbiota, which is somewhat easier and less regulated.

So, I would argue that it would be.

DR. McDONALD: It sounds like you have concurrence back here?

DR. SLATER: Yes. I was looking at you, but I --

MS. GRUBER: This is Marion Gruber, Office of Vaccines. I would like to make an additional comment here because we've discussed that very example, actually, with our colleagues in the Office of Cellular and Gene Therapy because, you know, there are also numerous therapies where you take the tissue or the cells from the same patient, you then manipulate it and infuse it back, for instance, you know, so the question then, I was told, you know, is it an IND or is it not an IND, s it considered a drug or not, also depends on how the material, the tissue, the cells are manipulated. So, if it's minimally manipulated, maybe it's not an IND. But the

threshold is very, very low. So, I mean, it's almost like the minute you take it out of the body, give it back, it's already manipulated. And so I think you can make the same parallel assumption here.

I mean, you don't give, you know, this fecal material directly. There are manipulations that even if you look at the same patient. So, I would, from this perspective, or these considerations would also lead me to believe, it would be under an IND. Yeah.

DR. McDONALD: This leads me to a second question -- I think I might be on now -- and that is, do you have -- one issue that comes up here is congruence, congruence across the agency, specifically congruence between CBER and CDER. Four out of five people in the United States receive an antibiotic each year, profound perturbation in the microbiota.

Now, especially when you say that persons own microbiota becomes a drug, you remove the idea of any infectious agent, you're talking about a change in the

microbiota, and yet CDER is not at the same place as you are. There is not yet -- in fact, I think we had a question from a major pharmaceutical company yesterday, and that is, what should be the criteria for new drug development with regard to the microbiome? As far as I'm aware, I was just on an advisory committee within a year ago, there wasn't any framework yet, and it was actually a very important drug that was going to be used in possibly a large proportion of the U.S. population. And most antibiotics are, and yet they don't have that same level because I think you're expressing concern about -- especially in that last answer -- perturbations to the microbiota, and yet they're being done every day by FDA approved products.

So, I just want to bring that up, and this is an issue that I think the Agency has to grapple with. If it's good for Peter, it has to be good for Paul. And I'm especially concerned about that at the CDC with antibiotic resistance, the tremendous

perturbations, the microbiota that are occurring everyday, and this hesitancy about those. And I think appropriately so.

And if you've heard, it may be that antibiotics are doing some of those profound things you're talking about and yet I don't know if that other Center is quite at the same level or we are quite as a whole society ready to fully use the same level of precaution across the board.

I hope I -- maybe I lost you on that last part, but I think it's around congruence, it's around the fact that perturbation is occurring regularly, and yet you're showing a lot of concern about that, especially when you apply it to someone's own microbiota, because that's the only thing you could be concerned about there, is really just the changes in the relative populations. These are all organisms that they should have had previously.

DR. STIBITZ: Melody has a comment.

DR. MILLS: So, I just have a question, and maybe Eric Pamer, whom I see is in the back, can address this, but after a

bone marrow transplant, is it really the same person in terms of the immune response? Is it really their own microbiota at that point?

DR. PAMER: This conversation is a little disconcerting to me because we had thought that a reintroduction of the patient's own microbiota following transplant probably wouldn't require an IND because patients who, for example, bank blood or blood products aren't -- those are not regulated by the FDA, I understand, if it's their own blood product that's being re-infused.

So, if one does need to do an IND for this, I guess one question that I have, is this going to get easier now that the pioneers who are all sitting up there at the front have INDs, some at various stages? It should, I would think at this point, be, for new investigators in the field, more straightforward to get this through. Would that be a correct assumption?

DR. SLATER: I think it is fair to assume that it should get easier, but the way that it would get easier is maybe not the way

that you're thinking it would get easier. In other words, I do think that as -- in all seriousness -- I mean, I think, as more and more people are doing this, it would seem to me that the scientific community will have, itself, good evidence of what the issues were, what the hurdles were that the FDA put up, both in terms of the clinical studies, the designs of the clinical studies, product handling and product characterization.

It seems to me that there's a reasonable amount of information sharing that could go on among scientists who are doing like types of studies that should make this go much easier and quicker, certainly, in other investigational fields that discovered, all of the sudden, that they had to do these studies under IND.

The example that comes to mind is sub-segmental bronchial challenges with allergens and other provocations, which, you know, about a decade ago, all of the sudden, the investigators were told they needed to do this under IND because of certain events that

occurred.

It was a very rough couple of years, but since that time, these have become much more routine, not necessarily because the FDA has made the path much easier, but because the scientists learned what worked and how to put these studies together in a way that would work. And certainly, getting studies submitted to the Agency that are better at the get-go and assure patient safety and have all of the elements that we would be looking for that I tried to describe, will make life easier, not only for the investigators, but also for the reviewers.

DR. PAMER: I guess one question that I have is, if one, for example, submits an IND where the production follows very closely or identically one that you have already approved, is this like an NIH grant going in where a new panel of reviewers will go over it and something that's been previously rated as fine could be rated as improper? Or are you going to put in place acceptable ways of preparing fecal transplant

material and -- so that won't be re-scrutinized and that it won't have to be reinvented with each IND application?

DR. SLATER: So, there are two answers to your question. First of all, the community of reviewers that reviews these is distressingly small. It's a group of people that do these reviews. It's not going to be necessarily the same person, but these are people that talk to each other and that meet and discuss what the standards and criteria are. So, to that degree, this is much better than the situation with the NIH study section, in which you could have people from -- with all different biases involved. That's unlikely to happen in this situation.

That said, don't deprive us of the opportunity to learn as we go along, and just because we thought that something was okay one or two or three years ago, we may have, in the interim, our reviewers may have, in the interim, learned things that concern us more. So, don't necessarily expect that something that sailed three years ago -- that you

negotiated three years ago, will necessarily sail today.

We are all learning here, that's one of the reasons that we were interested in cosponsoring this workshop, and we will continue to learn. So, we will change our reviews as time goes on.

DR. STIBITZ: I think Dr. Brandt is next.

DR. BRAND: So, Jay, I have a personal problem that I think is shared by a lot of us on the panel. We all get a lot of calls each week, emails, calls, asking us, how do you do a fecal transplant, what's your protocol, will you share it with us, and so forth. And I usually go through the advice that I go through.

But now I'm struck by the fact that the FDA wants an IND to be done, and yet, the FDA has not publically announced or set forth any kind of public message that they do want this, and therefore, just like you send out a black box warning, that from this moment on, all of you who are performing fecal

transplants should know that this procedure requires an IND. And therefore, if you continue to do it without an IND -- and you said you weren't a lawyer the other day, so, I'm still going to use the same word, "legal", but you're violating a law, let's say, and therefore some punition could come down.

If any kind of legal action happens because a bad result is obtained by that procedure, and the physician did not have an IND, was therefore using an unapproved biologic or unapproved drug, there's little in the way of defense for that person.

So, should I be telling them that? I don't think so. I think it's really the FDA's job to do that and I want your opinion on that.

DR. SLATER: Well, independent of the second part, that it should be the FDA's job to announce it, and you know, I think you certainly could tell them that you have learned this.

DR. BRANDT: I'm not a shy person. I have told them.

DR. SLATER: I've figured that out. I guess what you're asking is, how does the FDA disseminate information about IND requirements? Is that what you're asking?

DR. BRANDT: No. I'm really asking -- I'm really asking why the FDA, in view of the fact that it's well recognized that this is an increasingly performed procedure, and yet one that requires an IND, as we currently understand it, why you have not -- the FDA, not you personally -- why the FDA has not just come out and said, listen, guys, you can't do this anymore. That's basically what it is, because now there are a lot of people that are doing it who are being placed at greater risk than they are -- than they should be placed at because the FDA has not told them what they should be doing.

DR. GRUBER: I have a very short comment, answer to that. My name is Marion Gruber. I'm with Office of Vaccines.

This is exactly why we're having this public workshop, to get the word out there that, you know, if these products, this

material is used -- again, the regulatory language -- to treat, cure, mitigate, or prevent a disease, then it is considered a drug and/or biologic and it requires an IND. This is the first step, if you want, that we come out publically and discuss it with the scientific community and the many other stakeholders. I mean, obviously, we're transcribing this workshop. We have to start somewhere.

I mean, I think Dr. Midthun gave some introductory remarks yesterday. This is nothing that we have -- I mean, I've been with vaccines, I don't know, for the last 20 years or so -- this really wasn't, you know, on our radar screen until a couple of years ago when investigators, IRBs, really contacted the FDA and asked us about it, and we had a lot of internal discussions with our attorneys, and I will tell you, many of us in the review divisions struggle with the same issues that you have been presenting us with over the last couple of days.

Is it really feasible to ask a

medical doctor, an investigator, to put an IND together? You know, for a company who has its regulatory staff, well, they have persons hired to do that and they put it together, but if I'm a doctor who wants to treat these desperately ill people, should I be doing this in addition? We have struggled with that question too. We even have struggled with the question and had long discussions with our attorneys, should we regulate this? Is this practice of medicine? We give this a lot of thought and attention internally, to the point where we say, okay, now we have to come out and we have a public workshop, we will hear the concerns to take into consideration and really define, what is the regulatory path? What is really reasonable? Is it reasonable to ask an individual investigator to do clinical, randomized, well-controlled studies? Or is it something that even -- and I'll throw this out here -- NIH could undertake?

Is it -- how do we look at, you know, protocols? Could there be one protocol where treating physicians could be the

individual investigators in order to alleviate these problems? Or should we even think very differently, and Jay mentioned that we've had other challenging regulatory -- challenging products, the blood, cell therapy, (inaudible), cord blood, and we found ways to move that forward.

So, I found it very interesting when you told us this morning about the idea that there is a banking facility that could be inspected by the FDA. It could, you know, transfer material to the different hospitals. So, it's a different kind of regulation then all licensure pathways.

I think these are many, many different ideas that we've heard today, that we've already internally discussed, but that we need to take into consideration now to further discuss it internally.

So, I think, again, this public workshop is the first step to -- was the first step to get the message out, you know, there is a regulatory component, how are we going to do this in the future, what everybody else can

contribute is something that we need to discuss further.

DR. BRANDT: Let me just end by saying, thank you.

DR. KELLY: So, all of this may not matter -- well, I won't say all of this -- the individual doctors using fresh or frozen stool, a couple of years from now, I think -- I mean, there's at least three companies in this room who are developing a product that may be ready before the results from our study are even out, but how much data would the FDA want on efficacy and safety before approving FMT, in the form that we're doing it, as a drug? I'm going to guess that our randomized control trial of 48 patients and following them for six months is probably not enough, but let's say there was a multi-center trial with a couple of hundred patients followed for a couple of years. Would that be enough that you would lift the IND requirement and say, using this protocol, any doctor can do it and we don't need to be involved?

DR. SLATER: You're going to hate

the answer, and the answer is, I can't answer that. I mean, I think that the review of clinical trials is something that is intense, detail-oriented, and data-driven. And so, for me to answer theoretically what the numbers would be, would really not -- it would not be a real answer, even if I gave it, so -- sorry?

DR. KELLY: Again, I just think ideally, I think what we're all going towards is some kind of a standardized product that's easy and safe and studies can be duplicated and results are more consistent, and I think that that's probably going to happen through industry rather than magic fairies coming down and giving us money to do it. So, okay.

DR. BRITTON: So, Rob Britton, Michigan State. So, one of the questions that dovetails off that, and maybe this is for Lee and Alex, people who are trying to standardize this, is Jay mentioned that potency is something you need to be able to measure, so of course when you're taking individual fecal samples out of patients and a few hours later putting them into somebody else, you really

don't have time to do that, but with a banked product you have the opportunity to measure things, and coming from the probiotic field where we often don't say what disease we're treating, all they every do is say, okay, they're alive, not really sure what that really means, but you guys, I think, have the opportunity to go further maybe showing that you can cure C. dif in vitro. What are the effects on the immune system through either a cell culture organoid model? Are there any effects on gut hormone release, GLP1, serotonin?

So, I'm just curious if any of you who are actually going down this road have thought about what targets you're going to try to target so you can tell the FDA, this is what my product does time after time after time?

MS. JONES: Are you asking me?

DR. BRITTON: Any of you.

MS. JONES: Obviously, we have thought about that, maybe not to the degree that you're talking about, because we're

looking for a clinical outcome, so -- and this is a discussion that's kind of underway, but the clinical outcome that gets measured goes back to what got put in. If the outcome isn't what we expected, then the potency of the product wasn't adequate. So, it's kind of a chicken and the egg thing. We have to get something out there to test before we can tell whether the potency was appropriate and our measurement of the potency was appropriate.

So, we're waiting to see to get these studies done to be able to put a number on that.

DR. STIBITZ: Let's go up to the top.

MR. SHENTAG: Yes. Hi. Jerry Shentag, University of Buffalo. I'm just wondering about the statistics, which are usually what one would have to determine the number of patients in a trial, of the type that, for instance, you're doing in Rhode Island, and if you think about that as a placebo-controlled trial with superiority over placebo and placebo being the person's own

stool, you know, given back to them, probably that's pretty close to a parachute study as I've ever seen, and the end that you'd need to show statistical superiority, probably somewhere around ten patients, simply because it's nearly 100 percent effective with the different stool and with their own stool it's nearly zero, at least you've probably got some better estimates of that.

But using those estimates would come up with your population size for superiority and if superiority is the standard over placebo in this particular product, I wouldn't think this would be a tough regulatory decision to get FMT approved. And maybe you would have some comment on that without, you know, doing anything other than defaulting to the statisticians opinion here, but I think I know what that's going to be based on the numbers.

Not to press you for anything like that, but this isn't one of those thousands and thousands of patients type trials if it's superiority, and I think it is.

DR. KELLY: So, our study is actually overpowered a bit because it's 48 patients.

MR. SHENTAG: Yes, your study is overpowered.

DR. KELLY: And 48 patients will give, I think, very, very good efficacy data. My guess is that for the safety data they would want many more, and we're only following patients out for six months and we've all talked about needing longer-term safety data. So, maybe -- I'm just guessing that maybe the problem isn't the question of efficacy, it's the question of safety that's going to kind of keep all of this a little slower than I want.

DR. STIBITZ: Let's go over here.

MS. LOKHORST: It seems to me that -- my name is Denise Lokhorst and it seems to me that a regulatory pathway -- one regulatory pathway has already been considered and that's a BLA based on Lee Jones' talk, and she wants to have the product out, she said, by 2015.

So, a couple questions. What are the requirements to get a BLA? And are you

requiring stuff like investigate which components of stool are responsible? I mean, that -- are you going to require all that in order for her to receive approval? And that might be a long-term undertaking.

And then, again, if a product like Lee's is approved, that would solve individual investigators having to have their own IND because they could simply buy it from Ms. Jones' company and then use it in clinical practice. But I guess my question is, what are the requirements for a BLA? Because, clearly, a -- this has been discussed within the Agency, and a pathway has been sort of determined.

DR. SLATER: Well, so, the question is just, what are the requirements for a BLA approval?

MS. LOKHORST: Yeah, and are you going to require -- you said --

DR. SLATER: For her product?

MS. LOKHORST: Well, for any -- not for her product, but for any product. I mean, there are other companies -- there are other

companies out here using synthetic stool, but you specifically said that FMT research needs identify the key microbe in fecal material, investigate which components of stool are responsible. I mean, that might take years in order to figure out, and would you hold up a BLA approval just to get that?

DR. SLATER: So, I'm sorry, because I realize now that there were a number of places that my presentation was probably confusing. That was the slide in which I was listing what the FMT research needs are, that was not a list of what's required for licensure of a product.

That was where I was trying to convince you that in terms of making real progress in the science of studying this very important field, there were a lot of questions that needed to be resolved and that what was going to interfere with this was the large flux of patients into the hands of people who were not collecting any entry or exit information on what they were doing and weren't collecting the data, that we were

going to actually lose the opportunity to learn those important lessons.

But that was not a discussion of what licensure requirements were going to be, and I'm sorry if that was confusing.

DR. STIBITZ: Dr. Eisenstein.

DR. EISENSTEIN: Thank you. Barry Eisenstein, Cubist. Coming from the world of CDER, where my company interacts, we deal with antibiotics and we understand the process pretty well for antibiotics. That said, there are a number of indications that cannot be easily analyzed, like meningitis is an example, osteomyelitis is another one, where there hasn't been a new antibiotic approved for that indication for over 25 years, yet drugs are being used off- label. And I've heard Dr. Janet Woodcock, the head of CDER, say explicitly that it's not the job of the FDA to regulate the practice of medicine, so there's no intent to get in the way of physicians being able to prescribe antibiotics for, say, meningitis, when the patient is obviously dying or has a serious,

life-threatening infection.

With that in mind, as I understand the discussion over the last couple of days, there seems to be a continuum from the non-physician homebrew to the doc's office that is making use of non-standardized material to the more standardized medical centers, as we heard from Dr. DuPont, to the industrial commercialization product, to, then later, an understanding of how we would use an artificial mixture of very well defined individual components that could be put together that for all time would then be active pharmaceutical product that would then be studied. And it seems that going from one end of the continuum to another, you're getting increasing characterization, increasing standardization, and increasing opportunity to better study and understand potency and efficacy and safety and also increasing opportunities to commercialize. And in that regard, that spectrum, if you will, the very different levels of involvement, do you at the FDA see a

difference in how you would regard the approval path or the usage path, to put again in context, we don't regulate medical practice?

I would enjoy hearing a way for you to get me less confused about that.

DR. SLATER: So, clearly, the different paths are going to be treated differently, clearly the commercialization route is intense, analytical, long-term commitment that, I guess what I've been trying to say, I said, even the closer to home brew end of the continuum is still a biological product that needs to be subject to IND investigations, but --

DR. EISENSTEIN: But how are you going to regulate the individual at home who calls one of the gastroenterologists and tries to get some advice? I don't understand how that works?

DR. SLATER: Yeah, understood. We share our confusion about how these things are going to be handled.

DR. STIBITZ: We're going here -- I

just want to make a point -- you can ask questions of other people besides Jay.

SPEAKER: But I'm going to persist. So, John (inaudible) from (inaudible). So, since you've decided to regulate this as a biologic, and obviously you've been thinking about parallels, such as the Office of Cellular and Gene Therapy, I was thinking -- I was a bit surprised that you didn't make reference in your talk to the live biological products guidance and I was wondering how you lens this in those terms, whether they're parallels or philosophies you'd apply to this, especially to something like Lee's product.

DR. SLATER: First of all -- Wellington, you wanted to --

DR. SUN: I can ask a question later.

DR. SLATER: Yeah, I didn't treat it because we haven't quite made the connection with that as to how to regulate them in parallel, so you're right.

MS. DUFF: Hi. My name is Catherine Duff. I'm not affiliated with anyone or

anything and I'm not from around here, you may be able to tell as I go on. I seem to be the only actual member of the public that's here at the public forum and I think, at the risk of annoying those who are trying to avoid a long commute, I'd like to make a brief statement. And I'm very nervous, so please bear with me.

DR. RUBIN: Don't be nervous. Just take a deep breath. We're all happy to listen.

MS. DUFF: To start, I'd like to clarify that I was not invited here by anyone and no one has paid my expenses. I'm one of those people who call and email you everyday. I've had eight episodes of recurrent C. dif and it's now antibiotic-resistant. I cannot find a doctor who will perform an FMT so my husband and I did it at home ourselves. Within 24 hours my symptoms were gone and I remained symptom and toxin-free until the next time I had to take antibiotics.

At that time, one of my team of physicians agreed to perform an FMT without

knowing what an IND was, that one was required, or that a CPT code had been assigned. He did perform it in his surgical outpatient clinic and again within 24 hours, I had no symptoms. I remain symptom-free and toxin-free of October of last year.

People are desperate for this treatment. As doctors, clinicians, researchers, administrators, you know the stories of your patients, but you have not lived our lives. You have not felt our dwindling hope and our growing sense of despair. I now wonder each and every day if I will be able to have another one if needed, what I will do if it ceases to work, and what will I do if I encounter a different superbug.

Currently physicians use many, many biologics. The risks are explained to and generally accepted by the patient. Speaking for the hundreds of thousands of people that cannot be here today, please go forward, be bold, be courageous, find a way to quickly, without several years of preclinical and clinical trials, allow qualified doctors to

perform FMT with tested donors and signed consents without fear of regulatory consequences.

If your spouse, child, parent, sibling, or best friend were dying from antibiotic resistant C. dif, I imagine that all of you would want them to be able to try FMT and I imagine that most of you would agree to be the donor and to even perform the procedure yourself if necessary. People are dying everyday, today, right now.

I have a wonderful husband, three amazing daughters, and two small grandchildren, and I want to live. All of us just want a chance to live. Please, do something not only for me, but for all those around the country and everywhere who have no insurance, no financial resources, no computer with which to Google information, and no hope. Please do something quickly.

Thank you.

(Applause)

DR. STIBITZ: We'll go up here.

DR. RAMESH: After the van Nood

study in New England Journal, which was taught by the Data Safety Monitoring Board, and I am pretty sure if I'm part of the Data Safety Monitoring Board of Dr. Brandt and Dr. Kelly's study, after about ten patients are enrolled, you will clearly see that it will be very unethical to continue the study forward. Of course, they have an arm where you can cross over and get the fecal therapy, which is good.

So, how does FDA or anybody who's going to do any randomized study going to wrap around the ethical aspect of taking this further when the differences between the arms, both anecdotally and in the randomized study, so far, is overwhelmingly superior?

DR. SLATER: So, I'll say it again, the purpose of this workshop was to initiate a dialogue with the scientific community and with the public regarding how to go forward with this. I think your point is well taken. I think there will be some people who will conclude that that study is the end of the story. I think there will be many people who will conclude that that study is the end of

the story. I think there will be many people who will say that there are many unanswered questions and that further types of studies, perhaps informed by the results of that study, should proceed.

DR. RAMESH: Because the efficacy -- looks like, to me, everybody in this room agrees, the efficacy is well established and none of the proposed studies, so far -- I'm only talking about C. dif at this point -- are looking for any safety related issue. There is no disease transmission that has been recorded and as for its future safety, which is a very important issue in terms of obesity or hyperlipidemia or whatever, heart disease and that kind of stuff, not a single study is addressing that issue, which means the FDA has to go on for a very long period of time before it states conclusively, or the FDA takes a stand saying, okay, we will go ahead and approve everything and we'll address this issue as a post marketing -- just like a drug.

DR. SLATER: Point taken.

DR. SAUK: Jenny Sauk, Mass General.

I'm wondering if the FDA can approve FMT for recurrent C. dif with the evidence that we have. Of course, with all the other indications that people are trying to do FMT for, I believe that should be regulated, but we have so much evidence to date that FMT seems to be safe. Is there any possibility that as a physician it is very difficult, when I have sick patients, and you know, we are lucky enough to have an IND, but in other areas where there are no resources available for a physician to provide this service, it's extremely harrowing to the patient and to the physician to not be able to help them. And I'm wondering, just for this indication, if this is something that might be entertained to just -- to be allowed, to be considered?

DR. SLATER: I think you're raising a good point. I think it could be considered. Wellington has been raising his hand.

DR. SUN: This is Wellington Sun from FDA. I just also want to kind of reemphasize that the purpose -- that this workshop is for this exchange of information

with the medical and scientific community on this very challenging topic, which I think crosses different paradigms.

If this was only a drug, like an antibiotic, I think we wouldn't be here and so the pathways that we have right now are designed with -- not certainly with stool in mind, so in a sense, we had to adapt our regulatory paradigms to fit this particular instance.

But I think also it serves for us to, as a community, to take a step backwards from looking at what has been done so far. I mean, the history of medicine is littered with very well documented, surely effective therapy that does not bear under the scrutiny of randomized control trials, and so far, we have only a single one looking at the efficacy of just therapy, and we do not have an extended amount of safety information with prolonged and careful follow up.

So, given that, and I think the purpose of the IND, which is for -- to build safety into our investigations, I would like

to throw the question to all the practitioners and the researchers, we heard, for example, support for a registry. So, in your mind, how could we structure such a registry to answer the questions about safety and effectiveness for this therapy that, I think, everyone would like to see?

DR. KELLY: Okay. I might not know what I'm talking about with this, but -- so, only one person can sponsor an IND, but they can allow a number of co- investigators to operate under their IND. I don't know if there's a limit to that number, but let's say there was one or a handful of investigators who held the IND and other investigators operated under their protocol, collecting efficacy data and collecting safety data for a period of time.

In our expanded access IND it's six months, but you could conceivably say, oh, they would get a one-year telephone call, but all of that information would then have to be entered into a national registry and it would be the duties of the investigators at each of

those sub-sites to enter that data in. Is that something that could work, that could enable people to get treated over the next couple of years?

DR. BRANDT: As part of that question, though, who is responsible for -- who's responsible for the data? My understanding is that it's the sponsor of the IND. Therefore, such a sponsor would have to have a significant staff devoted just to that purpose, and if the participating physicians were not complete in terms of the data they gave you, then that would place you in a vulnerable position because you would not have met all of the rigor of what having an IND implies.

So, it places you, the investigator, the sponsor, at risk.

DR. HOHMANN: Since nobody's talking, I'll talk. Hi. Libby Hohmann from Mass General Hospital. I have an IND. You know, we've talked a lot about the registry and it seems to me we should get together the professional societies, you know, perhaps AGA,

IDSA, Scott mentioned perhaps we should consider communicating with the complementary and alternative medicines section at NIH, and, you know, seek, perhaps collaboratively, funds to put together a registry that's independent of any one investigator and then everyone who's doing this around the country could -- we could come up with a data set that everybody agreed was appropriate, and we could all enter data independently into something like a red cap database, which many of the CTSA institutions subscribe to.

So, I think that would be a worthy goal that we could put together.

While I have the microphone, I'd just like to make one other point. I also run the IRBs at our institutions and "compassionate use" is actually an outmoded term. We hope that all of our care is compassionate, right, it's "single-patient uses", and those can either be emergency uses where you actually don't need to go to the IRB in advance of doing that treatment, or non-emergency uses, and that's the way you can

look at that. And I wonder if the FDA could answer who we should contact if we have an emergency use, because for every other kind of investigational product, you can communicate with a drug company and an FDA rep and get such an immediate emergency use if that's appropriate.

DR. GRUBER: This is Marion Gruber. I would like to answer that. While we were having a discussion, listening to presentation, I received a request for an emergency use of an FMT and so I immediately contacted the people in the divisions who handle that and they got in touch with the treating physician.

So, you would contact, in this case, the Office of Vaccines because we, for various reasons that have history, have been deemed the office that, you know, should regulate and respond to these questions.

So, you can, you know, I don't have the number in my head. I think Dr. Sun is the director of the Division of Vaccines applications, it's his people who really take

care of the request for emergency use, and you can always -- or a treating physician can always contact our Office of Communication and they will then put us in contact with the treating physician.

DR. HOHMANN: It would be great if they could disseminate the number or the contact, if there is one. Some of the other parts of the FDA have specific individuals that we, as IRBs, can direct investigators to, so that would really be helpful to the community, I think.

DR. KHORUTS: Can I also continue on that theme for a second? How quickly does this contact happen? We've talked mostly about recurrent C. dif infection and that's the bulk of it, but this procedure can be lifesaving for severe fulminant disease and the window of opportunity for that FMT to work before the patient either dies or goes to surgery may be measured in hours.

So, are you on 24 hours a day, 7 days a week? Because this always happens on Friday at 5:00 p.m.

DR. HOHMANN: Well, you know, again, just to perseverate on the IRB issues, if it's truly an emergency, you have a five-day window to do whatever you need to do, if the person's on the table, typically, these usually come from cardiology on Friday afternoon, but you have five days to do what you need to do and then contact or notify the IRB and the FDA, which is why I'd just like to get the contact for the person at the FDA to notify, because I think we may be taking that route going forward based on this.

DR. SUN: Yes, I just want to clarify further that the treatment IND is really reserved for those extremely dire situations where time is of the essence and there's none of the usual timeframe for the appropriate filing of the IND. It doesn't mean that those information will not be required. You would have to make that up after the fact.

But it's designed for those urgent situations, and then I would discourage the overuse of those treatment INDs, unless in the

setting of patients in extremeness because there may be -- I mean, the inclusion/exclusion criteria for such treatments, I mean, they would still apply. And we would hope that when this treatment is given, that still, for example, there is a consideration of donor screening and the usual safeguards we have, but again -- so, that takes some pre-planning of communicating that information to us. In other words, one shouldn't really have to wait until the very last minute to access this particular pathway, but it is available.

DR. ORENSTEIN: Bob Orenstein, Mayo Clinic. So, this is a really interesting discussion and I really like a lot of the things we've talked about and it sounds like there might be a couple solutions coming, but you heard from Cliff, 600,000 people get C. dif, 15,000 relapses a year. That's a big problem. We don't have three years to wait and there are a lot of patients like the one who just spoke up that really need our service in the interim.

So, what I'd like to hear from the panel is, what do we do in the interim? You know, how many INDs are there in the United States? Probably not a lot. There's a clinical trial with 50 patients, that's not a lot of places to enroll clinical trial patients.

So, what do we do with the 15,000 patients who are really desperate for something that works? And I'll go back to what was brought up on day one. If your mother shows up with severe or recurrent C. difficile, are you going to not offer something that you know how to do safely, effectively, and say, I can't do it because the regulatory agencies in the United States have decided that this requires a special licensure in order for you to do it?

DR. SLATER: Again, this is part of the conversation. We heard the same numbers that you did and we understand that it's a big problem. You've heard from several investigators here who it sounds like are gearing up for relatively large-scale studies,

some of them seem way too small in the context of a need of 15,000, but maybe part of this conversation is that some larger INDs are really needed in order to serve that population.

The problem is large. It didn't arise over night, it arose over a period of several years, and it may take some time to solve it. I think what we've been trying to convey is that there are regulatory routes towards dealing with this short of licensed product development, investigational routes that should be accessible to large institutions, some of which we've heard from, either from speakers, and some of which we've heard from our attending audience.

I think there are some very large institutions that have the opportunity to do some large-scale studies that will both serve this population that clearly needs help, but also serve this same population in terms of developing the very best approach possible towards taking care of them. And I think that's what this conversation is exactly

about.

If the status quo were in a good place, we would have so much less to talk about, wouldn't we?

DR. ORENSTEIN: Well, I just -- you know, my point is, there's a transition period here. You know, these are solutions that we're all very interested in working in. I don't think any of us really want to be doing this. If we had a safe and effective product, we'd love to be giving the safe and effective product, but the situation is a little more dire and we need a transitional period in order to get to that state.

DR. SLATER: But I think that's the message, I think we recognize that we're in a transitional period and we're willing to work with you towards -- I mean, all transitions are hard, right, we know that.

DR. BAKKEN: Whether we have 15,000 relapsers or we have a higher percentage, perhaps 50,000 relapsers, I think their problem began in February when we were notified that the INDs need now to be

performed or to be filed, and they don't have two years to wait. So, the question is, how are we going to help these patients while studies are going on?

MS. HAYS: Excuse me, could I ask a question, Jay? Over here.

Is it possible -- and this is totally out of ignorance -- Ann Hays from the University of Virginia -- is it possible for one of two solutions to take place? Either, A, the FDA establishes its own IND, we would not be using Colleens, so that individual people could sign on, you would tell us what the protocol was, and what information you wanted to come back, and it would be a nice, simple form that we read, agreed on, took to IRB, and signed up. So, that's one option where the FDA has its own IRB for this particular illness, recurrent C. difficile. The other one would be if that was not even a potential option, which seems to me that would be the best, would be for you to establish a prototype IRB, also for physicians in the community to apply for, a nice, simple, rapid

application, they agree, they sign on, they send you all their data, and then we just wait.

But it seems like one of those two solutions is -- I don't know, it seems -- out of ignorance, it seems to clear and easy to be right.

DR. SLATER: Well, I think what you're describing is very attractive except for the idea of the FDA writing its own IND application for something that it has to review. That's something of a shortcut of the regulatory process and it also is a shortcut of the idea that we should be scrutinizing these IND studies carefully and that they should be the product more of -- of more minds than just our -- on the FDA side.

MS. HAYS: Perhaps the working group could design one or you could --

DR. SLATER: Now you're talking, and I think that certainly the idea of a professional organization, a scientific organization, perhaps a group of individuals that participated in this workshop the last

couple of days, would get together and put together a prototype submission that might be -- that might have a large number of participants, is certainly a thought.

DR. KELLY: Would one person still have to be the sponsor of something like that or could it be collective? And if one person was the sponsor, as Dr. Brandt suggested, you know, the full legal responsibility of that is a little overwhelming.

I guess, could they take your medical license if something went wrong? Could they take your house or your children away from you? Like, I'm just -- you know, agreeing to be a sponsor and letting people come onto your IND, I mean, obviously you want people who weren't loose cannons, who could follow the rules and do the appropriate follow up and protocols, but I guess it's just the risk of being an individual sponsor when you have a whole lot of people operating underneath you. That's the question.

DR. HOHMANN: How about the CDC do one like they do for some of the parasitic

drugs where they hold and IND that any investigator can sign onto? Benzenediols, some of the anti-malarials, these things leap to mind. I guess we lost the dude from the CDC.

DR. SLATER: So, then we can all agree that the CDC is going to do this, right?

(Laughter)

(Applause)

DR. STIBITZ: All right, let's go to the top, you have been waiting.

DR. VERSALOVIC: Jim Versalovic from Baylor and Texas Children's in Houston. I had a question, I guess maybe Alex and Bert could take a first shot at this to spread the pain up at the front.

As a pathologist and someone familiar with transfusion medicine, I've been thinking a lot in the past several months about the blood bank -- we've talked about it today -- blood banking, tissue banking, there certainly are other examples in medical centers that I think we could use to our advantage.

So, I think, clearly, the IND is one big issue here and a hurdle, but additionally I'd like to address the issue of donor specimens and all that fecal material, how we're banking it, how we're thinking about the donor pool, expanding the donor pool. We've come a long way in understanding the composition of the gut microbiome in the last five years as we have several here in this room that have been involved in HMP, and we know so much more.

And I think we're at the point where we understand that age, race, ethnicity, sex, all have a bearing on the composition and presumably the function of the microbiome, and I think we, as physicians and scientists, need to build that infrastructure of banking stool, but also expanding that donor pool so hopefully we can optimize donor-recipient matching.

I'll just make one more comment that is that I think these efforts could be in parallel. I am not -- and I'd be interested in Alex's and Bert's comments -- I am not

confident that we are going to reach the Holy Grail of a single mixture of microbes that are going to be largely applicable for any single disease because of the diversity in the population, and I would certainly propose that we're facing a long road, similar to blood banks, where there's been effort after effort to come up with blood substitutes.

These are complex biologicals and I think that we need to, in parallel, at a minimum, develop that donor fecal banking infrastructure and develop -- hopefully once we have it, have the opportunity to take care of so many patients. Once we have these banks set up, and hopefully optimized in terms of donor screening, safety, evaluation, the assessment of microbiome composition, we can take it forward, not only for C. difficile, but I'm thinking, obviously, of a number of other chronic GI diseases, IBD, et cetera.

So, maybe Alex, you could lead, and Bert follow, on how you consider this issue of the donor pool and expanding it?

DR. KHORUTS: I agree with

everything you just said, and that's part of our thinking, and perhaps we didn't start that way, we were just thinking of our own patients, but now that this machine is growing and rolling and consuming us in setting all this up, our donor pipeline is building up and as we're thinking about other diseases, in particular, C. dif may be a fairly low threshold of what you need to seal or what you need to achieve, but for things like inflammatory bowel disease, it very well may be that there are subtypes of donors that we don't yet have biomarkers for, but we could start collecting them, and we might find that a particular subset is the one that's therapeutics for ulcerative colitis or something like that.

And this is an opportunity, as we're collecting this material, also collect the metabolomic data as well as metagenomic data and try to make those correlations. They're all healthy donors, but some of them may be just genetically gifted healthy donors with not particularly beneficial microbiota, and we

can't tell them apart with all these screening tests that we've proposed.

So, I hope that, as our collection grows or as our banking grows, that there will be collaborators who will want to use this material and we actually would like to work with the FDA. We still haven't started that, but how do we work through these processes in recruiting different studies and support this infrastructure, which I think is the resource, for research as well as for clinical use, et cetera.

DR. DuPONT: The question that was asked is exactly why we're working with blood banks. I think it's an ideal place to work. They have a donor pool already established, people who donate blood or platelets or protein on a regular basis. They're people who like to give things and it's an ideal thing, but studying them, figuring out what we're doing and how they match up with recipients, I think everybody's focused so much more on the recipients assuming that all donors work, one-size-fits-all, but I think a

lot more needs to be done with the donor.

But I would suggest people developing new programs start with blood banks in their hospital.

DR. KUNDE: I have a question specific for standardization of donor screening because we didn't talk that much so far. What stance FDA has or do you have any plan how are you going to standardize, or do you need input from the community or physician community or you already have set up a protocol in your mind? Because we have seen that different IND holders who are reviewed by different reviewers have different opinions.

DR. SLATER: Well, we certainly are open to input on what appropriate donor screening should be and we start with what the sponsors provide to us. I think we were influenced somewhat on the donor screening protocol from The AGA, but if -- but we've certainly heard at this workshop that perhaps some aspects of that need to be reconsidered.

So, again, this is, as far as we're concerned -- you know, the conversation began

when we first got our first IND submission, but as far as we're concerned, this is a good opportunity to expand that conversation about what donor screening protocol should be used.

DR. BAKKEN: The consensus document was in The American Journal of Gastroenterology, not The AGA.

DR. SLATER: I'm sorry. Thank you.

MS. JONES: And it wasn't sponsored by The AGA.

DR. BAKKEN: No.

DR. KUNDE: So, at this point you will consider individual application differently depending on what you see, but you will not recommend them, do this?

DR. SLATER: There may be inadequacies in the individual submission that our reviewers will point out and we'll negotiate with the submitter when it happens.

DR. MILLS: Phil Tarr wants to --

DR. STIBITZ: So, we have been talking for about an hour and according to the spirit of the law, we would be done, but according to the letter of the law, we would

go until 4:50. So, what do you folks want to do? Do you want to keep talking for another 15 minutes? I know some people may have to leave to catch planes. And Dr. Tarr, did you want to say something?

DR. TARR: Yeah, my light went on 59 seconds before the hour ended.

So, a quick question. You've talked a lot about adding on requirements as applications come in or you find new data. Is there a good mechanism for taking away requirements and notifying all the people who hold your IND so that you can reduce the cost and the effort at the various sites? If you decide that EBV screening is worthless, can you issue a notice?

DR. SLATER: I think that's a terrific question. I don't think there is a particularly good mechanism except that the IND process typically is one in which there is a lot of ongoing interaction, especially in the kinds of studies that we're talking about.

DR. TARR: There's not horizontal interaction between sites that you can count

on and perhaps you could --

DR. SLATER: Not that the FDA negotiates. We certainly would welcome the opportunity for there to be horizontal interaction among the sites, but the FDA operates bilaterally with each of the sponsors.

And there are good reasons for that.

DR. STIBITZ: I think we're -- why don't we take three more questions and then finish up? Is everybody okay with that? So, right here.

MS. McCLANAHAN: Sarah McClanahan. I come from a small health system. We don't have a research board, we don't have a clinical team to go out and do all these trials, but we have saved lives and we have given people a better quality of life. So, I'm going to have to go back to my doctor on Monday and say, you now need an IND to do this, to save people's lives. So, how long is it going to take for us to get something back from the FDA that says we can continue to save people's lives?

DR. SLATER: Well, I think the point of the conversation at this point has been that, yes, you do need an IND to continue to do this. It would be either tagging onto a larger study or if you want to work entirely within your health system, there is the expanded use option that's open, I think. It is a process. There is some paperwork. I can't tell you how long it would be. This would not be an emergency IND submission, so it would not be something where, as Dr. Gruber and Dr. Sun were talking about, could be achieved within a matter of hours to days, but it's something where we would work with you.

DR. SAUK: Jenny Sauk, Mass General. I'm just wondering, at this meeting today, if we could come up with another date where we're going to have some answers from the FDA about what we should be doing. I know today was a good discussion and yesterday as well and I think a lot of ideas have come together, but I don't think that there's many answers that came out of it yet, s far as what we should do.

And that was my first question, and the second one was, for the expanded access issue, I'm wondering if societies like the IDSA and AGA along with a phone number of who to call, if there's any paperwork that needs to be filled out that a community doctor doesn't understand how to fill out, if that could be provided so that somebody who's in this situation, when there's a therapy that we know is effective and you can't give it, it's very frustrating. I mean, I'm wondering if something like that is possible.

DR. SLATER: But correct me if I'm wrong. You have an IND already.

DR. SAUK: I understand how it felt before that, though, so I'm coming from both perspectives. It's nice to be -- but, you know, there's some people that don't meet our study criteria and so then we have to go into a different -- then it becomes very difficult for us.

So, I've come from both sides. So, I'm just speaking for a lot of -- of that feeling of not being able to provide this

care. We know how that -- a lot of us know how that feels.

DR. SLATER: Yeah, I understand. So, in terms of your IND, you could actually start to discuss with the FDA for expanded access as a (inaudible).

DR. SAUK: SO, that is no problem. I'm sort of speaking more in general, I think, but I guess the other -- the main thought, I had is coming up with a timeframe in which we'll have some understanding of what we should do to proceed for both the -- you know, for future studies in this as well as understanding what the FDA's stand will be on this.

DR. GRUBER: Can I make a comment -- a couple of comments? So, I think, as was said earlier, I think we had this public workshop to get scientific exchange, regulatory exchange, and hear your concerns and suggestions, and I think what we have to do, we have to do some internal work and really decide how we can, in this interim period, really provide some help, and so one

idea that we just had is we could, actually, on our CBER website, we could put some -- I don't want to call it guidance because guidance is a certain regulatory term, but, you know, the outcome of this workshop, I think we transcribe it, we could summarize it, we could come up -- we will be thinking about that, perhaps giving some, you know, helpful hints in terms of guiding through the IND process, what is really the minimum requirements, what is really an emergency use IND, when should it be used and what is the phone number, which, by the way, is 301-827-2000. That's our Office of Communication, and again, as Dr. Sun said, this is really for those situations where we're talking a life threatening situation, which is what we've heard today and that emergency use IND was already granted. So, that just took two, three hours to do that.

SPEAKER: Can you repeat the number?

DR. GRUBER: 301-827-2000. And there is an after hour number, 1-866-300-4374. And what we can do, we can really look at, you

know, putting something like this on the web and we will have further internal discussions, also how can we provide guidance, not only on the regulatory requirements, how is an IND submitted, what is an emergency use IND for, but also take into account some of the other suggestions that you had. Can we develop some -- you know, what is the information in terms of the manufacturing? What is the information about a clinical protocol? You know, things like that, and I just want to really go way out here and saying, nobody here at the FDA thinks that what you're currently doing needs to be stopped because it's bad. Okay? I don't want to say that.

What we wanted to communicate is we are also bound by certain regulatory requirements. These requirements are not only binding on, you know, physicians who want to use an unapproved drug for a certain therapy, they're also binding for us, and we may all have different perspectives and personal opinions on that, but as FDA regulators, we'll have to tell you just what Dr. Slater told you

today. That being said, there is no intention here that we feel that we -- you know, somebody has to put a stop on what sounds to be a very promising therapy. We just feel that, you know, if we get the data so that we can license this, you know, that would be even better than what is being done, you know, right now.

DR. RUBIN: I'm going to just fully endorse what you just suggested and say that if the FDA could develop a frequently asked questions site that at least answers some of the simple things about all this, it would be so helpful to the community, and then all of the folks here and everyone who hears other lectures about this, et cetera, will disseminate that and refer people back to a site like that. That would be a terrific advance from this two-day meeting as a next step.

So, I'm grateful you brought that up.

DR. STIBITZ: Okay, one last question.

DR. GISSER: Hi. Jonathan Gisser, Nationwide Children's Hospital. Columbus, Ohio. And just dovetailing on what we just spoke about, I would even want to take it one step further. I was wondering if it would be possible to have a workshop analogous to what we would have on the clinical side, a grant writing workshop where, because this is a novel regulatory paradigm, an FMT-specific, IND- specific workshop held by the FDA -- I'm taking it one step further than an FAQ, than a FAQ.

DR. STIBITZ: I'm going to go out on a limb and say I think that's a good idea.

Okay, I'm going to call an end to this and thank everybody, all the speakers, everybody involved in putting this together, for what, for me at least, has been a really fantastic workshop and go out, go forth, and do the right thing. Thank you.

(Applause)

(Whereupon, at 4:40 p.m., the PROCEEDINGS were adjourned.)

* * * * *

CERTIFICATE OF NOTARY PUBLIC

STATE OF MARYLAND

I, Christine E. Allen, 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.

(Signature and Seal on File)

Notary Public, in and for the State of Maryland

My Commission Expires: November 6, 2016