U.S. FOOD & DRUG ADMINISTRATION

PUBLIC MEETING ON PATIENT-FOCUSED DRUG DEVELOPMENT FOR PATIENTS WHO HAVE RECEIVED AN ORGAN TRANSPLANT

September 27, 2016

9:02 A.M. - 4:59 P.M.

Food and Drug Administration

White Oak Campus

10903 New Hampshire Avenue

Silver Spring, Maryland

Reported by: Erick McNair,

Capital Reporting Company

C O N T E N T S

P R O C E E D I N G S

MS. CHALASANI: Good morning, everyone. Good morning. My name is Meghana Chalasani, and I'm from the office of strategic programs within the Center for Drug Evaluation and Research here at FDA. My colleague Sara asked me to start off with a little joke about the Beltway and traffic, but I don't drive. And most of you guys apparently didn't have a horrible commute. So, you should give us FDAers some tips, because it's hard to get here in the morning every day. I will be co-facilitating the discussion today with my colleague Sara Eggers.

Today's meeting, conducted as part of the agency's patient-focused drug development initiative, is focused on hearing from patients who have received an organ transplant. Later this afternoon, we will be having a more scientific discussion with patients, patient advocacy organizations, health care providers, academic experts, and industry on various aspects of clinical drug development intended for patients who have received organ transplants, including medication adherence and experience with intervention.

Dr. Edward Cox will be providing some opening remarks in a few minutes. But first, let me start by asking my colleagues sitting here in the front to state their names and their role within the agency.

DR. COX: Good morning. I'm Ed Cox, director of the office of antimicrobial products within the office of new drugs in CDER, FDA.

DR. ALBRECHT: Hello. My name is Renata Albrecht. I'm the director of the division of transplant and ophthalmology products within the office of antimicrobial products and OND, FDA.

DR. BELEN: Hello. Good morning. My name is Ozlem Belen. I am a deputy director for safety in the same review division as Dr. Albrecht.

MR. VELDIDALA: Good morning. Ergun Veldidala (ph), medical officer in the same division.

DR. CAVAILLE-COLL: Good morning. I am Marc Cavaille-Coll, medical officer in the division of transplant and ophthalmology products at CDER. Thank you.

DR. MULLIN: Hello. I'm Theresa Mullin. I

direct the office of strategic programs, and I'll say a little more later. Thanks.

DR. CAMPBELL: Good morning. I am Michelle Campbell. I'm a reviewer in the clinical outcome assessment staff in the office of new drugs, CDER.

MR. VAIDYA: Good morning. I'm Pujita Vaidya, from the office of strategic programs.

MS. EGGERS: And I'm Sara Eggers, from the office of strategic programs.

MS. CHALASANI: And we also have Graham Thompson, from our office, as well as Shannon Woodward, who are helping us today.

Now, to give you all a brief overview of the agenda -- it's a busy one. We will first spend a bit of time providing background on our patient focused drug development initiative, and on organ transplantation and available post-transplant treatment options. And then we'll hear how the information we learn at our PFDD meetings, like today's, is and can be used.

Then we will move into our discussion with patients and patient representatives. Our two main

topics are life after receiving an organ transplant, and post-transplant treatment regimen. Sara will be providing some more details about the format at the start of those discussions. We have time set aside later today for open public comment. While the primary discussion this morning is focused dialogue with patients and patient representatives, the open public comment will give anyone in the audience the opportunity to make a comment. To participate in that, you will need to sign up at the registration table. Participation is first come, first serve. We'll close that sign-up sheet later, at the end of our first break, which is around 10:45. The time allowed for each speaker will depend on the number of participants who express interest -- likely one to two minutes each.

For a few logistical and housekeeping points, there is a kiosk right outside where you can get food and beverages. There is an option to preorder lunch. Restrooms are located behind the kiosk. At any point, if you need to get up for any reason please feel free to do so. As I mentioned, we

will be taking a 15 minute break around 10:45. Lunch is from 12:30 to 1:15, and then we have another 15 minute break this afternoon, around 2:50.

I do want to ask at this time that you all silence your cell phones. This meeting is being transcribed, and a live webcast is being recorded -- both of which will be archived on our website. With that, I'd like to welcome Ed for opening remarks.

DR. COX: Great. Thanks. Well, good morning and welcome, everyone, to this meeting on patient-focused drug development for patients who have received organ transplants. I've introduced myself, but I'm Ed Cox. I'm the director of the office of antimicrobial products, and Renata and I work together. Our office reviews the drugs that prevent rejection in organ transplant recipients.

I want to thank you all for joining us here today. We're happy to see so many folks here -- patients, caregivers and advocates in the audience. I understand we also have a number of people, too, on the web who will be joining in and listening in to the meeting. So, I think that's great. So, there are a

lot of folks in the room, but there's also a lot of folks out there on the web that are watching us too. And we appreciate your willingness to be part of the meeting, and sharing your experiences with us. It really is what provides, in essence, the value to the meeting. So, we're very grateful for that.

We're excited for the opportunity to engage directly with you, and to learn about the symptoms that matter most to you, the impact that organ transplantation has on your daily lives, and what factors you take into account when selecting a post-transplant regimen, and, you know, just quite simply the things that you like and that you don't like about your transplant medications.

In our discussion today, we'll be focusing on various types of experiences that are present among organ transplant recipients, and we'll delve into changes into your post-transplantation therapy regimen, and what aspects of your care have changed over time. Marc Cavaille-Coll, from the division of special -- special transplant and immunologic products -- or, ophthalmologic products -- will provide more

background on organ transplantation and will also talk about available treatment options in just a few minutes.

We understand that organ transplantation is a life-altering experience, with physical, emotional and social impacts, and that there is an unmet need for patients. It's the FDA's responsibility to ensure that the benefits of a drug outweigh its risks. Therefore, having this kind of dialogue is extremely valuable for us, because hearing what patients care about can help us lead the way in figuring out how to best facilitate drug development post-organ transplantation, and understand how patients view the benefits and risks of various drug products in this complex area. For example, what we hear today from you can help us understand how to develop better endpoints, to measure the aspects of post-organ transplantation management that are important to patients.

I know we also have representation from industry, academia and other government partners in the room and on the web, and while FDA plays a

critical role in drug development we are just one part of the process, and I'm glad to see a high level of interest from folks from the various different parts that play a role in drug development.

FDA protects and promotes public health by evaluating the safety and effectiveness and quality of new drugs, but important to keep in mind that we aren't the ones that actually do the clinical trials. The drug companies, typically working with patients and research -- with the research community -- are the ones who actually conduct the clinical trials and submit the applications for new drugs to FDA. It's then FDA's responsibility to evaluate this information and to evaluate whether the benefits of a drug outweigh its risk. The benefit/risk decision-making is an integral part of our review process, and we look forward to incorporating what we learn here today from the patient's perspective into thinking and how we evaluate our evaluation of benefit and risk as we look at treatments for managing organ transplantation. So, once again, we're here today to hear the voice of the patient. So, thank you for your participation. Thank

you for joining us today. You are, in essence, what makes this meeting what it is, and I think that's great. We're grateful to each of you for being here, and your willingness to share your experiences with us. It really helps us to understand and appreciate your perspective on these issues.

And just so that folks know, this morning is really the patient focused session. We also have a scientific session in the afternoon, and we welcome and would help that many of you could stay so that we can also have the patient perspective as we move to talk about the scientific aspects in the afternoon. So, with that I'll turn the podium over to Theresa Mullin, who will provide some background on FDA's patient-focused drug development effort. So, Theresa, the podium is yours.

DR. MULLIN: Okay.

DR. COX: Thank you.

DR. MULLIN: Thank you, Ed. So, as Ed said, I'm going to take just a few minutes to tell you about this patient-focused drug development initiative. This is the context and the initiative that we -- has

been the vehicle for our scheduling and planning this meeting, and others that we have done so far, in the last few years, and will do a few more next year.

And it got started -- this idea of having a meeting focused on only hearing from patients and their caregivers, where their caregivers have input to give us as well, back in 2010, when we were having discussions about this. We recognized that we had this benefit/risk assessment framework that we were developing, but we realized that patients are really uniquely positioned to tell us about the benefits that would be most meaningful to them and the things that would bother them, and really their perspective on their disease. And this was sort of missing as an overarching source of input for us, because we had only at that time the patient representative program, where you have an individual patient who would be asked to join discussions and maybe weigh in on what we call in the government a particular matter -- which is to say, about a particular drug and decision-making around that, and that, of course, means we also have to put that person through conflict of interest

screening, and this tends to really narrow the possibilities and the timing and our flexibility in trying to get the input of the community. And so, we didn't really have a mechanism at that time.

We only were able to have one person help us think through the patient's perspective. Sometimes those people didn't have a disease that we were thinking about t that time either. And so, this is a more systematic way to gather that information and get the patient's perspective, to have these meetings where we try to bring everyone that we can into the process. We work with the advocacy groups, and with a care provider community to try to help us let patients know about it. And I want to also welcome the people on the webcast. Thank you for joining us on the webcast, as well. That's a key feature of these meetings, because it helps us to enable more people to participate in the process. And you'll see our facilitators bring them into the discussion as well. And so, this helps us to really get that larger community involved. And we made a commitment to do this as part of our reauthorization of the

Prescription Drug User Fee Act in 2012.

We can -- we said we would do at least 20 of these meetings. And guess what? This is the 20th meeting. But they're so popular among the review divisions that we actually have more coming next year. We're going to exceed that number. But this is what we've set up to systematically get this input. And at the time we made that commitment we thought 20 sounded like a big number. But, we were quickly told by a lot of patient groups that that was way too few meetings, and that they were concerned that we might not be able to get to their condition and their concerns.

And so, we went through a process where we asked the review divisions to help us identify what diseases they could think of and conditions where they would really like to -- they think it would really help them in particular to hear more from the patient community. And that produced about 40 diseases that were like the top 40 in their minds, and we published that in the federal register to get comment. We got about 4,500 comments about that list. We had to then go back and do the very hard thing of trying to winnow

it down to more like the 20 that we were going to be able to do. As a result, we're going to do 24, and we've come up with another mechanism called externally led meetings to try to help us to hear from other groups as well, because these meetings patients have really enjoyed having the opportunity to speak at these meetings. They've been useful. So, we have this other process as well.

And here's just a quick overview of the diseases and the conditions that we have focused on in the past few years. And you can see where we are today. And there's quite a range. I mean, we wanted to find conditions that were chronic in general, had an important symptomatic or a loss of functioning that might be -- an effect on functioning that was important to patients, and affected a wide range of ages. And that's not a whole lot of -- those criteria are met by many diseases. And you can see that range here. And here we are today, with our meeting focused on patients who have had an organ transplant and what your experience is, including with your -- the medications you take after the transplant.

Now, each of these meetings is tailored to the condition that we're exploring and listening to and hearing from you all about. A very diverse group of patients from different disease advocacy groups came to us to hear how we were going to run this process, because they were very interested. And they actually helped us come up with what they thought were good basic questions that they thought resonated with all of them. And so we have some of those in the mix of what we will -- or, Meghana and Sara will be asking and talking about today.

And we have also tailored and brought in other questions that the review divisions have particular interest in, and want to hear more about as well. And they will be asking you questions as they feel the need to, in the course of the discussion, if they hear something that maybe -- we heard sometimes that -- from the division that they hear things in these meetings that they've never heard before, that are not reported in the literature. It's a very unique opportunity for them to learn and, in some ways, almost start problem solving around things that

they're hearing. So, it's very exciting. And so, we'll also talk about what topics are currently of concern. And we've learned, as I said, a great deal from these -- the input of these meetings.

One of the most concrete and near term outputs of these meetings is what's called a voice of the patient report. We keep a docket open so that those on the webcast and those in the room, and others, can submit other information that you may have that you think is relevant to what you've heard today, or you want us to know. And so, we leave that open for a little while after the meeting, so people have time to submit information that they might want us to know about. And after that's closed, we analyze very carefully what comes in that docket. As you heard, we are doing a transcript of this meeting. We analyze the transcript to try to really capture what's been said. And we try to make these documents one that reflect very faithfully what we hear from you, in the words of the patients as they are conveyed to us. So, we think this has been a useful reference tool for us. We also have heard from patients who have been in

these meetings and felt the reports were very useful to them, as well. So, that's just the first step. And we're really building on what we've learned here in our next five year plans for trying to further sort of capture the information from patients more systematically, as well, in clinical trials and in other ways, to build even more -- build it even more into our decision-making. So, with that -- I think that's my last slide. Yes. I'll turn it over to Marc. Thank you.

DR. CAVAILLE-COLL: Good morning. I'd like to present to you an overview of organ transplantation and available post-transplant treatment options in the United States. Organ donation and transplantation to treat end-stage organ disease is lifesaving, transformative and restorative for patients with a serious condition. The number of donated organs -- or, donors recovered, represented in blue below, and the number of transplanted patients annually, represented in green, has not kept up with the increasing number of patients on the waiting list, represented in yellow.

Organ allocation in the United States. The National Organ Transplantation Act of 1984 established the organ procurement and transplantation network which maintains the organ registry and ensures equitable allocation of organs in the United States. Regional organ procurement organizations identify equitable -- identify suitable donors and collect donated organs. The united network of organ sharing operates the OPTN and allocates the organs from the OPOs. The scientific registry of transplant recipients, also created by NOTA, conducts ongoing evaluation of the clinical and scientific status of transplantation in the United States. Much of the data that will be presented here comes from their annual reports.

The types of organs transplanted annually in the United States include kidney, liver, pancreas and intestine, as well as heart, lung and heart/lung. The majority of the organs are recovered from deceased donors, but with a substantial contribution of living donors in kidney and, to a lesser extent, in liver transplantation.

Here are presented the number of patients active on the waiting list on the left, and total transplants on the right for the decade of 2004 to 2014. Approximately 17,000 kidney transplants are performed per year, with an increasing number of patients on the waiting list, in excess of 60,000. About 7,000 liver transplants are performed, and about 2,600 heart transplants are performed. Only in lung transplantation has the number of transplantations increased and number of patients on the waiting list decreased.

Polypharmacy is the rule in solid organ transplantation, with all the challenges of managing drug interaction and complex daily regimens. There are medications to prevent and treat rejection, including induction immunosuppression with intensive combination regimens, maintenance immunosuppression with less intensive combination regimens, and additional medications for treatment of acute rejection. Thus, the need for medications to prevent and treat viral, bacterial, fungal and other opportunistic infections, as well -- there’s also the

need for medications for treating the existing or preexisting underlying medical conditions, such as hypertension, diabetes, and hepatitis C that led to the organ failure. And there are also need for medications to treat the emerging complications of the immunosuppressive regimens, including hypertension and new onset of diabetes.

Let's look at some of the treatment options for immunosuppression use in transplantation. There are agents used for induction treatment, lymphocyte depleting agents, polyclonal IgG antibodies derived from horse or rabbit, Interleukin-2 receptor antagonists, monoclonal antibodies modified to be humanized or chimeric that bind to the alpha chain of the interleukin 2 receptors and inhibit cell proliferation. There is a high dose of other agents used in maintenance also, round out the induction immunosuppression.

Maintenance immunosuppression usually uses a combination of two to three agents, below. Glucocorticoids are used for both induction and maintenance immunosuppression as well as for treatment

of rejection. Calcineurin inhibitors, namely cyclosporine and tacrolimus, are the agents around which additional agents are added to complete the immunosuppressive regimen. Purine antagonists include azathioprine, mycophenolate mofetil, that inhibit cell proliferation. The inhibitors of mammalian target of rapamycin, modulate mTORi, and also impair cell proliferation. And there is at least one costimulation blockade that blocks CD-80 costimulation of T lymphocytes.

Here are represented the immunosuppression used in adult kidney transplant recipients per year, from the SRTR. The majority of kidney transplantations receive a regime of tacrolimus and mycophenolate, and about two-thirds are receiving steroids at transplantation and one year post-transplantation. The vast majority receive some form of induction agents, two-thirds receiving T cell depleting agents and about one-quarter receiving interleukin-2 receptor antagonists.

In liver transplantations, similar to kidney transplantation, the majority received tacrolimus and

mycophenolate. 80 percent received steroids at transplantation, and still 40 percent are receiving steroids at one year post-transplant. There is an increasing use of induction agents in liver transplantation as more patients come to liver transplantation with impaired renal function.

Similarly, in heart transplantation tacrolimus and mycophenolate is the regimen used in the majority of the patients, the majority receiving corticosteroids. About 50 percent are receiving induction immunosuppression. Let's take a look at some of the outcomes. Again, five year graft survival in kidney transplantation is about 74 percent of deceased donor recipients, and 86 percent for living donors.

In liver transplantation, five year overall graft survival is about 70 percent, and there are more than -- now more than 72,000 liver transplant recipients that are alive with a functioning graft, with many more pediatric recipients reaching adulthood every year.

In heart transplantation, five year graft

survival is about 76 percent, and there are more than 28,000 heart transplant recipients surviving with a functioning graft. Most of them had undergone transplantation after the age of 50.

There were about 2,000 lung transplants performed in 2014, and the five year survival is about 55 percent in that population. Graft survival in intestine transplantation has improved over the past decade, and the number of functioning -- patients with functioning intestinal grafts has steadily increased from 2003 to more than a thousand in 2014. 42 percent are pediatric intestinal liver transplant recipients. The number of pancreas transplants has declined since 2004.

Future challenges. New approaches are needed to increase organ donation procurement and decrease discard of procured organs, to prevent and treat delayed graft function, to prevent or treat antibody-mediated rejection, to individualize treatment using biomarkers, genomics and systems biology, to induce durable and stable immune tolerance, still the holy grail, to minimize adverse

reactions associated with the IS regimens and to integrate the use of novel concomitant agents and manage drug interactions. Above all, the risk/benefit of new/old approaches and interventions need to be assessed from a patient's perspective.

Thank you for your attention. And now, I'll turn the podium over to Michelle Campbell.

DR. CAMPBELL: Good morning. My name is Michelle Campbell, and I am with the clinical outcome assessments staff. The clinical outcome assessments staff advises the clinical review divisions in the office of new drugs, upon request, regarding clinical outcome assessments, which include physician or clinician reported outcomes and, most importantly, patient questionnaires that are commonly referred to as patient reported outcomes. We review these questionnaires to ensure that they are measuring the most important and bothersome symptoms and impacts to patients, and that they are measuring these concepts in an accurate and reliable measure. Today, we'll briefly present on how we utilize the information from the patient-focused drug development program and

meetings, and how we aim to incorporate patient input into clinical study endpoints.

You may be wondering how is this information we use in the PFDD meetings, and what do we do with what we hear from our patients -- we have these meetings, but where do we go from here. How do we take this valuable information and generate clinically relevant patient-focused endpoints to a place in clinical studies. So, I hope the next few slides I can answer some of these questions for you.

One of the main advantages to having these PFDD meetings is that it gives all stakeholders the opportunity to listen to the patient voice. We find it very useful to hear the patient experience, particularly to hear what is important from their perspective, and how you describe your symptoms and impacts in your own words. We hope it helps give drug sponsors ideas about what are important symptoms and impacts to measure in clinical studies, and later make the investment to develop or select questionnaires to measure these important concepts, as well as engage in future FDA discussion. The information from these

meetings also helps inform how we at the FDA review patient questionnaires and drug applications, to see if they adequately are assessing the patient's perspective of their medical condition.

While the PFDD meetings provide initial input, we also strongly recommend that drug sponsors or other researchers who are developing these questionnaires engage with additional patients who are -- or, to using qualitative research, either through focus group interviews or one on one interview interactions, as well as gather input from other experts, such as physicians or caregivers. The goal of this is to confirm that the questionnaires include important yet relevant information, to ensure that the questions and instructions in these questionnaires are clear and understandable to patients.

Another advantage of these meetings is that it helps us to think about clinical study endpoints. So, what is an endpoint? In the case of a patient questionnaire, the study endpoint would be how the questionnaire's score is going to be measured and analyzed in a clinical study. For example, if

patients reporting that the most important treatment benefit to them is symptom improvement, then we would encourage that the drug sponsor to develop or select a symptom questionnaire using good measurement principles and meeting regulatory standards. The study endpoint could possibly be changed in the questionnaire's score during the clinical study, which would measure the amount of symptom improvement. One key consideration is that there are many things that are important to patients that are discussed during PFDD meetings and/or in patient focus groups or interviews. However, not all of these things lent themselves to be measured in clinical studies for drug approval, as they may not be impacted by treatment, making it difficult to interpret its results.

Here at the FDA, we focus on efficacy and safety. So, for example, financial well-being may be an important concept for patients, but may be minimally or not at all impacted by treatment in a clinical study setting. So, encouraging drug sponsors to consider selecting important concepts that can measure treatment effect as key study endpoints.

Financial wellbeing and other important concepts that are unrelated to treatment can still be measured, but perhaps in exploratory purposes. For organ transplantation, study endpoints that include patient questionnaires will be helpful to provide additional supportive evidence of benefit.

At the FDA, we have to uphold laws and regulations. Within these regulations, there are regulatory standards for assessments like patient questionnaires that require methods of assessments of subjects' responses to be called well-defined and reliable. Thus, when we describe these findings of these assessments in labeling, those statements are not potentially false or misleading. So, not only do we recommend drug sponsors to engage with patients to develop questionnaires using qualitative research, we also recommend that they perform appropriate quantitative research or statistical testing that show that the questionnaire is well-defined and reliable. Both qualitative and quantitative research can tell us whether the patients can understand and respond as intended to these questionnaires. Additionally, these

tests can provide an estimate of what a meaningful change or improvement is on the questionnaire. Patient involvement also is extremely important in determining how to interpret what a meaningful change or improvement is.

We recommend that drug sponsors seek input from the FDA as early and often as possible in their drug development programs. In some cases, if a patient questionnaire does not exist then existing questionnaires may be modified, or a new one developed. It is important for drug sponsors to start the process of selecting or developing these questionnaires early, and use them early and often in clinical development to gain experience with them before using them in a phase 3 clinical trial to confirm clinical benefit.

So, we have two pathways to provide advice to those interested in using patient questionnaire or patient reported outcomes or other clinical outcome assessments in clinical trials. First is within the context of the individual drug development program. This is where we encourage drug sponsors to begin

discussions as early as possible, preferably in the pre-IND stage. So that if any work is needed that needs to be done, we can go ahead and have those discussions early.

The second pathway is outside of the individual drug development program. This is through our drug development tool or DDT qualification process. In this program, we can work with questionnaire developers, patient advocacy groups, sponsors, researchers to develop and qualify questionnaires for use across multiple drug development programs. We work with many stakeholders, including consortia, patient groups, individual academic investigators, and drug developers within this program. Once qualified, this tool becomes public available for use.

So, key takeaways is that our PFDD meetings are the starting point for developing patient focused outcome measures and endpoints. The outcomes of these meetings will support and guide the FDA's risk/benefit assessment and drug reviews, and patients' input ultimately helps determine what is measured to provide

the evidence for treatment benefit, how best to measure the concepts in a trial, and what is meaningful improvement.

At this time, I would like to turn it over to Sara so we can begin our discussions.

MS. EGGERS: Good morning, everyone. I hope that you gain appreciation of the complicated that FDA, our colleagues, have to think about every day when they come to work. And now it's time to turn it over and think about and hear from you about what you think about. And if I don't have to make a joke about the Beltway and the traffic, then we are having a good day. We're getting off to a good start. I'd also like to say before we get started that we've done 20 meetings now, and the energy in the room today -- we always have great energy in the room, but it's particularly strong, positive and constructive in today. So, I think that's also a good sign that we're going to have a great discussion. If you are a patient or patient representative, if you are someone with an organ transplant or care for and advocate for, and you are sitting in the back, we strongly encourage

you to -- if there's room at a round table, to join and we can see you better, if you want to join in our conversation.

I'm going to give a bit of overview about our discussion today. As Meghana mentioned, we have the two topics for discussion. And we're going to go through those in two different sessions. It's all in your agenda. But, to boil it down, what topic one is talking about what are the most significant changes in your health since you received your transplanted organ or organs; what are the symptoms and post-transplant health effects that have the most significant impact on your life; and what worries you most about your health post-transplant.

And then the second discussion, we will focus -- drill down more into treatment regimens, looking at what you're doing currently to manage your health post-transplant, both the medications that we talked about -- that Marc talked about today, and other things that you may be doing, and how well those treatments helping you manage your most significant symptoms and your health effects; what are the

downsides to those treatments; and, if you could craft an ideal treatment what would it look like -- what would be some of the features of that treatment.

So, for each of those two topics we're going to have a panel of people living with an organ transplant to go through some comments and tell their story, very succinctly, to set the context. And I'm going to ask the topic one panelists to come up now, if you can, and just take a seat up here. Make your way to the front. We have -- you'll see we've -- have a wide range of ages, and we've identified several organs to really, we hope, give a rounded idea of what life is like.

And then we're going to broaden the discussion. We're going to come out -- Meghana and I will come out in front, and we have microphones that will come to you, so that you can build on what we hear from the panelists. We're going to ask that you state your name -- first name only is fine. But state your name before answering, so that we can capture it in our notes. And state also what organs that -- what organ or organs you have had transplanted. That's

important to set the context. We will be moving around. We're not going to be focusing on kidney and then liver. It is an open discussion, and we're trying to find the common themes throughout. So, you know, if we've heard a lot from kidney and you have a liver organ, you know, raise your hand and we'll round out that way. Okay.

You'll also have a chance to answer polling questions, and that is for those in the room today and also on the web. And I want to give a shout-out to the web participants. You are very important, because not everyone can make it around the Beltway in Washington, D.C., to get here. And we often find that the perspectives of those on the web is somewhat different than the perspectives shared in the room. So, please participate through the comment boxes. We will have a chance, we hope, to go to the phone lines in the topic two discussion, to get a person or two on the phone. So, please participate as often and as much as you want to over the web.

For the polling questions, both on the web and in person, it's really a discussion aid. Please

don’t look at this as a scientific polling or survey result, and please don’t report on it in that way. It’s really to see who do we have in the room and what perspectives are you sharing -- what are you thinking about.

We’re going to hand out clickers. I think those can be handed out now. So, we’ll -- they’ll be distributed, and it should be self-explanatory. You’ll click whatever letter corresponds to the choice that you see up when the polling question comes. We’re going to ask that patients or parents of patients only participate. Okay.

And as Theresa mentioned, the conversation doesn’t end today. We very much value your continued dialogue, through the public docket, as she mentioned, which is our vehicle to engage in dialogue with our constituency. It will be open until November 27. You can share your experiences. If you didn’t get a chance to fully participate, as much as you wanted to today -- I think most people would say that, by the end of the day, that there’s more that they wanted to say -- please send it along. Reference if you’re in

the room or participating on the webcast -- that you participated, please, and that you're building on. But, if you know people who were not able to join today or have not -- maybe didn't know about the meeting in your dialogue with them, encourage them to submit responses to those questions that we asked you today and share their story. It's very important to us. Anyone can comment. So, if you're, if you're someone other than a patient, or a patient advocate or caregiver, you can send along comments as well.

We have other resources. Anyone in our office of strategic programs, that -- we introduced ourselves today -- come find us. But we also have an office of health and constituent affairs. They run the patient representative program. Is there anyone here from OHCA, as we call them? Okay. I think they're on the website -- on the web link today. But, you can reach out to them if you have follow-up questions or if this excites you, to participate in this way, and you want to participate more broadly in other ways.

We also have our professional affairs and

stakeholder engagement, or PASE, and -- is Chris in the room today? He might also be participating on the webcast. They also facilitate communication and collaboration between the center for drugs and patient health care stakeholders. So, you can reach out to anyone -- if we're sitting up here or if we're -- if their name is mentioned, please reach out.

A few ground rules, to make sure that our discussion is as effective and respectful as possible. We encourage patients -- people living with an organ transplant -- to contribute to the dialogue. And caregivers and advocates are welcome too. FDA is here to listen. My colleagues will help Meghana and I with some detailed questions, as you see fit. Please feel free. We may not be able to answer all the questions that you have today. Send those in the docket, if you have a question -- a burning question and it hasn't been addressed today. Also, similarly, the industry representatives and the academics and researchers in the audience -- they are primarily here in listening mode too, but if you have thoughts please share those through the docket comment as well. We also have the

open public comment period that Meghana described earlier this morning. If there's something that's outside of the topics of health effects and treatments that you want to discuss, then open public comment.

We really -- this will be a very organic discussion today. We do have some topics that we want to make sure that we get through. So Meghana and I -- we have to play the timekeepers, and we will move along as we have to. And so, we hope that the docket you can expand. Remember that the views expressed today are personal opinions. They're very personal, and often very sensitive. So, respect for one another is paramount. I don't -- I think I'm preaching to a choir here, so -- we just want to make sure that we're all on the same page. And really, let us know how the meeting went today and how it's going. Find us during breaks. But also, at the end, please fill out an evaluation form. It does help us. Even though we've done 20 meetings, we still learn something each and every time about how we can improve. Okay.

With that, we can start some polling questions. It's both a practice and gives us a good

sense of some of the characteristics of the folks in the room. So, if you'd get your clickers -- anyone need a clicker? Okay. We have a couple more clickers needed here.

FEMALE SPEAKER: Sara. Sara.

MS. EGGERS: Yes.

FEMALE SPEAKER: Our CDRH colleague has joined us.

MS. EGGERS: Okay.

FEMALE SPEAKER: Can you allow him to introduce himself?

MS. EGGERS: Yes. Arturo, would you like to introduce yourself?

MR. HERNANDEZ: Yes.

MS. EGGERS: Oh, and turn your --

MR. HERNANDEZ: Hi. My name is Arturo Hernandez. I'm a medical reviewer for devices in organ transplantation, for organ preservation -- solid organ transplant.

MS. EGGERS: Thank you, Arturo.

DR. MULLIN: Sara.

MS. EGGERS: Great. Okay.

DR. MULLIN: Sara.

DR. MULLIN: Yes, Theresa.

DR. MULLIN: I think it would help if people could keep their hand up, if they don't have a clicker, so Shannon can see them.

MS. EGGERS: Yeah. Anyone still need a clicker?

DR. MULLIN: If you need a clicker, just so she can -- knows you need one.

MS. EGGERS: Okay. In the back there. Okay. So, where do you live? You click A if you're within the Washington, D.C., metro area, or B if you're outside of the metro area. Okay. All right. Okay.

This is typical. We typically have about two-thirds of participants who are traveling, and we give a special shout-out to you. You had to probably fly or drive or take a train, and then get around the Beltway. So, thank you.

Have you received an organ transplant? Okay. So, it -- we have quite a few -- we have about -- let me do some math. Approximately 20 folks in the

room who have had an organ transplant. And we are going to ask now the remainder of the polling questions that it's answered by you, or, if you are here representing someone who is not able to answer or is not here today, then do the polling questions. Okay.

Let's move on to the next one. What is you or your loved one's age? If you're on behalf of someone else. Okay. Let's see. So, we will be discussing primarily the adult perspective today. We have a wide range of adult ages. I'm going to put a special shout-out for pediatric perspectives. If you're on the web -- can we have the web numbers, please?

MR. THOMPSON: We're got 5 percent from 18 to 34, 21 percent 35 to 49, and 47 percent 50 to 64 and 26 percent 65 or older.

MS. EGGERS: Okay. Great. So, again, a shout-out for the pediatric perspectives. They often differ. We will get as much as we can out today, but I think this is a place where the docket comment is going to be extremely helpful.

Do you identify as male, A -- B, female? Okay. So, we have -- oh, this looks funny. It's a good thing I read the numbers and not just look at the height of the bars. I'm going to take the numbers, that we have a pretty even mix of men and women here, in person, and on the web?

MR. THOMPSON: Thirty-nine percent male and 61 percent female.

MS. EGGERS: We squeeze the most that we can out of the technology we have here at FDA. Okay.

What type of organ transplant have you received? And if you have multiple -- I think this is a check one only. So, if you have multiple just click F. Okay. So, reflecting, I think, the statistics of who has organ transplants, we do have -- half of you in here are kidney -- have a kidney organ. And multiple -- I think some of the multiples have kidney as well. Followed by lung. Okay. So, a little bit less representation of heart and liver. We will squeeze all we can out of that today. But, again, if you are on the web -- can we have the web numbers?

MR. THOMPSON: Forty-five percent kidney

transplant. 20 percent liver. 20 percent lung. And 15 percent multiple.

MS. EGGERS: Okay. So, encourage all of you to participate on the web, particularly the heart and liver -- by the web or the docket -- as well. So, we can get as much as we can. And pancreas also. I'm sorry.

Okay. What is the length of time since you received an organ transplant? Okay. Okay. So, we have several who have lived a long time with their organ -- with their transplanted organ or organs. But, we also have a -- several in here, in person, who have -- are really new to this. Your perspectives may be a lot different. If you are one of those people who have -- are new to this, let us know in your comment, so that we make sure we can tease out. On the web?

MR. THOMPSON: Four percent less than one year ago. 19 percent for one to two, three to five and six to ten years ago. And 38 percent for greater than ten years ago.

MS. EGGERS: Great. Thank you. Okay. Have

you received more than one organ transplant, or received a retransplant? Okay. So, two-thirds of you here have done this multiple times.

Did you receive your organ transplant from a living or deceased donor? If you don't know, press C. Okay. Okay. So, most -- two-thirds of you here today have received an organ from a deceased donor.

Have you experienced organ rejection? A yes, B no. Okay. About half. Okay. We'll get into some of the issues with that today. Okay. On the web?

MR. THOMPSON: We had 39 percent saying they had experienced organ rejection, and 61 percent saying they had not.

MS. EGGERS: Okay. Great. Then, we're about ready to move on to our discussion. And we'll go down, starting with Jim. We didn't actually meet in person. Hi, Jim. But before we get started, I'm going to ask you when it's your turn to -- and I just want to say that we received many, many comments from people who expressed interest in providing comments as part of the panel, and they were so informative. We

encourage you to submit those to the docket as well, so that we can take all we can from what -- the comments that you've sent in. So, I want to thank you. Thank the panelists for preparing their remarks, but also thank you, who have -- who submitted your comments. It was very, very helpful to us in planning.

And with that, we'll start with Jim.

MR. GLEASON: First, on behalf of myself and some of the others that I represent from various transplant organizations I lead, thank you for all you do to make our lives better and safer.

(Applause).

MR. GLEASON: Yes. When people ask how has a heart transplant changed my life, I respond my most significant change is that I'm still alive and active. At the age of 50, given just two years life expectancy from a virus-induced cardiomyopathy, back in 1992, the heart transplant in '94 has allowed me to live a fulfilled and active life for 22 years now, living to see seven grandchildren born. The earliest two are now in college. With no prior health issues -- not

even taking aspirin -- my heart was attacked by an unknown virus -- idiopathic cardiomyopathy -- requiring hospitalization and a heart transplant, I now take 30 plus pills a day, both prescription and over-the-counter. Very expensive brand name and generic drugs that prevent rejection and keep me otherwise healthy.

I've dealt with the typical post-transplant issues, including various cancers -- prostate cancer in 2000, many skin cancer, kidney cancer in 2012 -- and living with Type 2 diabetes for the past ten years now, a common side effect of the specific drugs that I take today. I live a fully functional life in retirement today, having returned to full-time employment just three months post-transplant for 12 years, until reaching normal retirement these past ten years now.

Most of my life challenges can be attributed to the immunosuppressant drugs and advancing age, as I am now 73 years old. Specifically, the cancers -- especially the many skin cancers -- are well-known to be high risk for patients with organ transplant, both

with growing years after transplant and with normal aging. The meds taken in the early post-transplant years were toxic to the kidneys, and when the kidneys began showing damage due to those meds new drugs had come on the market that were a substitute for the cyclosporine, with tacrolimus as a less toxic med but still with its own side effects -- that diabetes I came down with in 2006.

The only worry I live with is the concern for those cancer risks, and personal finances as I age, given the heavy cost of the meds, even with Medicare and gap insurance support. Each day is a gifted extension to the life that was threatened those many years ago, now living with a strong heart gifted by a 38-year-old stranger in their dying.

What's changed over time? With a heart transplant, you begin with heavy doses of those meds and weekly heart cath biopsies. Both tapered down over time, with the invasive heart cath less frequent, finally stopping at the five year point, and the meds at a long-tem standard dose much lower than those first six months. My current regimen seemed to be

working perfectly, with semiannual clinic visits and testing, we catch issues early and treat them with minimal pain or damage. Overall, I have experienced ideal treatment with a great transplant team and the other doctors, for all those 22 years, which I will happily celebrate this October 19th, again. Thanks again for a unique opportunity to share this amazing heart-filled life adventure with you.

(Applause).

MS. EGGERS: Thank you, Jim. And now we'll have Jeff.

MR. GOLDSTEIN: So, I too would like to thank you for this unique opportunity to share my perspective on a double lung transplant, 13 years July of 2003. So, we did see some slides. Some of you may not be aware, but a lung transplant has some of the worst long-term outcomes of all solid organ transplants. And none of the medications I take were designed for lunch transplant. So, I often say that lung transplant, and that means all transplant as well, is just exchanging one set of problems for others.

I'm very fortunate to have effectively avoided major rejection issues. My lungs have been mostly stable. My pretransplant disease and my need to take immunosuppressants has put me at risk for skin cancers, which I deal with daily -- and as you can see, has affected my Hollywood good looks. All transplant recipients are at risk for kidney failure, as a result of long-term anti-rejection meds. And in addition, it has been suggested that my loss of hearing is a result of prescribed antibiotics.

Managing drug side effects -- fear, anxiety and feeling different every day is a real challenge, along with fatigue. It is the most frequent issue I manage, as I tire easily, while sleep is restless and mostly incomplete. Other than regular changes of anti-rejection meds and the addition of skin cancer reduction medications, my therapies have remained mostly constant. But these issues do impact my daily life. I often struggle with staying focused and managing my time, and energy levels can vary widely. There are bad days and good days, but still it beats the alternative. I am very fortunate, as on the best

days my symptoms are manageable and tolerable, and I try not to let them dictate my lifestyle. When they are at their worst, I listen to my body and respond accordingly. I have -- on occasions where I was unable to do something I planned or hoped to, I accommodate the inconvenience. My motto has been get busy living.

So, what has changed? I avoid the sun as much as possible, and no longer fish the waters of Florida Keys, trying to reduce my skin cancers. I worry daily about bronchial obliterans disease, cancer rejection and leaving my wife widowed, in that order. I would like to take this opportunity to encourage the FDA and pharmaceutical companies to consider developing treatments that make the lives of all post-lung transplant recipients better, safer and thus more rewarding. And I'd like to -- I'm known for leaving everybody with a quote, and I hope you'll find this one interesting. Our scars are a reminder that the past was real. Hannibal Lecter.

(Applause).

MS. EGGERS: Thanks, Jeff. He warned me

there would be a chuckle or two. Now, we'll go with Leilah.

MS. SAMPSON: Right. Now I have to follow that. I don't have any jokes. I'm a newbie. My name is Leilah, like the Eric Clapton song if anyone has heard of it. And I'm truly blessed for this amazing opportunity to be here and share my experience. I'm only nine months out from a kidney transplant, and this is a completely new life for me. The last time I was healthy I was 19. I am now 28, as of last week was my birthday. First birthday with my kidney.

I was diagnosed with SFGS, which is scarring of the kidneys, that progressed to renal failure. And I spent five years on dialysis, and the deceased donor list. However, I acknowledge I will always be a renal patient, which still means paying extra close attention to my health. And many believe that you get a transplant, it's a cakewalk, and you're healed forever. Surprise, it's not. Post-transplant wasn't a day at the beach for me. Sure, I'm very grateful, but you have to fight for your organ the same way that you fought to receive it. A couple of days after my

transplant surgery, I experienced a drop in my hemoglobin and platelet levels. Initially, we thought my disease, FSGS, was recurring and attacking my kidney. However, after plasmaforesis, which is exchanging of donor plasma, to wash out antibodies, two blood transfusions and multiple biopsies, we found that it wasn't reoccurrence but just not the right combination of immunosuppressants for me. So, once I was switched from prograf to cyclosporine, coupled with prednisone and cellcept, everything turned around immediately.

I simultaneously experienced a serious bout of pneumonia from lack of movement and deep breathing due to pain. So, use those spirometers. They actually work. From there, the next few months would be trial and error with water intake, even being readmitted due to severe dehydration. But, I tested the limits and I learned from it. Luckily, I only needed a couple of days of IV fluids and I was back on the right track. I worry about losing my kidney due to dehydration, because on dialysis we were so fluid restricted and now it's hard to immediately adjust

back to drinking more water.

I also started back exercising, and that's still in a trial and error phase. I think that's going to be a lifelong trial and error phase for me. But I was trying to reignite my old 19-year-old healthy athletic self. But I found myself spiking my creatinine levels. Now, I listen to my body and I start with walking, biking and yoga for short periods of time. I'm also finding that if you had anxiety and depression prior to transplant -- guess what? You still have it. But I've been with a therapist for over four years, and continue to do the work on myself while adjusting to life post-transplant. And it definitely takes some adjusting, too. But, I'm honoring the process.

Now, for example, seeing this stubborn acne on my face caused by steroids and hormones brings me some anxiety about just how immunocompromised I was told that I would be. However, I haven't been sick or had any infections. But, we'll see after the plane ride home. So, when I put it into perspective, I think I could live with the acne. Maybe I'm not as

immunocompromised as I thought. When everyone got sick at work, I washed my hands frequently, carried Lysol -- and they thought I was rude because I said stay away from me -- but it's necessary. You have to take care of yourself.

Also, I found by living a more stress-free and meditative life helps reduce both anxiety and depression. I send my kidney and myself unconditional love, gratitude and self-compassion, to try out different things until we find a balance. My kidney, Phil, obviously is a trooper to put up with me. But he knows I love him and we will continue to thrive. I encourage you all to give yourself a little bit of love, self-compassion and honor your process, whatever it may be. Thank you.

(Applause).

MS. EGGERS: Thank you, Leilah. And now Michael.

MR. GARRETT: Good morning. My name is Michael Garrett, and I'm in my 62nd year. I was diagnosed with Type 1 diabetes when I was five, and my first transplant occurred in 1990, when I was 35, and

that was a very early -- at least in the transplant game -- kidney pancreas, done here locally. I also had a living related kidney transplant, also in 1990, because you can't keep a good immune system down. And I had a second pancreas only transplant in 1990.

My biggest or my best answer to question number one is that I'm still here. I had a -- I checked once with insurance tables, in 1960, and male diagnosed at age of five with Type 1 diabetes in 1960 had a life expectancy of approximately 31 years. I've now doubled that, so I guess something is working.

The second question about post-transplant effect and symptoms, I can say my wallet is a little lighter. But at least I have a wallet. Physically, there are affects from transplant, and most assuredly the drug therapies. I have muscle aches, outbreaks of cancer, skin and otherwise, and less resistance to viruses and infections. I sometimes wonder, though, if some of these are due to my advanced age.

Question three about what I don't do now, because of transplant therapies -- the answer is not much. But I am not as active as I once was

physically. But again, how much is transplant related and how much is age related. I'm losing my vision, and you can probably tell from this. But this seems to be the fault of long-term Type 1, and not the fault of the therapies. On good days, I plow through and on bad days I take a break.

My experience with transplant organs has changed over time. I have received four organs in transplants, and have rejected or lost three of them. The first two were due to acute rejection, and the third -- well, I was told ten years on a pancreas was about all I could expect. So, I'm definitely looking for therapies to protect transplant organs for a lifetime. And of course, on a -- as a side note, I realize that the scientific community has pretty much decided that Type 1 diabetes is an autoimmune disease. And so, I never thought that getting a pancreas transplant was a cure for Type 1 diabetes. It's merely another form of therapy. And logically speaking, at least in my small brain, if it's going to attack a natural pancreas it's going to attack the transplanted ones also. So, probably what's going to

be happening from my own point of view is that pancreas transplants are doomed to failure until we figure out how to cure Type 1 diabetes.

As far as most worrisome, probably organ failure first, followed by cancer and major infections or illnesses. But I've stayed relatively healthy over the past 26 plus years, despite being so sick. Thank you.

(Applause).

MS. EGGERS: Thank you, Michael. And now we'll have the Lindsey.

MS. LINDSEY DUQUETTE: Hello. My name is Lindsey, and I'm 14 years old. I received my kidney transplant from my dad in 2012, when I was ten. I'm so grateful to him and everyone directly involved in my care, including the doctors, nurses, and child life. But very importantly, I am also thankful for the people who helped me who didn't even know me. Specifically, I mean the researchers and other transplant patients whose efforts in the years before my journey helped me to get where I am today.

To understand my gratitude, I will tell you

a little bit about my eight year battle with idiopathic SFGS. Over the course of eight years, starting when I was two and a half, I endured 172 hospitalizations, 22 surgeries, hemodialysis, peritoneal dialysis, countless medications, including steroids that compressed my backbones and left me in a wheelchair, and one black box drug administered 13 times over a year and a half. I missed my entire first and third grade years. I was sick, sad and lost my childhood.

How has life been since my transplant? Awesome. It's been a huge difference. I grew five inches in the first year after my transplant. I'm only taking seven pills twice a day, instead of 21 pills twice a day. I have no -- I have had no recurrence of SFGS. I have more energy. I don't have any pain. I can eat normally -- no more gross renal diet. I can go to school. I can have sleepovers and spend time with my friends, and I have a life.

It's not perfect, though. I have some unique challenges for me as opposed to other students at my school. I have some orthostatic blood pressure

issues, not due to renal insufficiency, and daily morning fatigue. I tend to feel nauseous every morning, and need to stand up slowly. I can't exercise as much as I would like to. I don't have much stamina in gym class. I lost all of my childhood vaccine tethers during the course of my disease. This is going to be tough, because I am not supposed to get sick. But, of course, I will always be immune suppressed. I have to drink 85 ounces of fluids daily, and this can be hard when you're running from class to class all day. I used to overload my body with fluids when I got home from school, just to get my required amount in before the end of the day. It was not good for my body, and worse with my morning nausea problem. It's becoming a little easier to drink now, now that I am in high school.

Personally, I do not have any adherence issues but I do understand where other teenage transplant patients might. It is hard to remember to take your meds every 12 -- 12 hours exactly. It's hard to drink as much as we have to. And it's hard to keep away from infectious people. I know I'm going to

need at least one more transplant in my lifetime. I know that I'm going to be on these potentially toxic anti-rejection meds for the rest of my life, and I understand that I will always have to be so careful not to get sick.

Here are some items on my post-transplant wish list. How about a transplanted kidney that will last the rest of my life? Fear of toxic medications and it would be great if meds could be taken just once a day. Rituximab and all my other meds carry the huge risk of cancers over my lifetime. That's pretty scary. Monthly blood work to check my tacrolimus levels is annoying, and it's worse if I get sick. Then I end up getting labs every two days until I get better. Will constant sticks in my vein cause me access issues later in life? Will it be hard for me to find another kidney someday, due to increased antigen sensitivity. What if I want to become a mom someday? Can we make it so that pregnancies will not increase my PRA? I wish I wasn't so susceptible to sicknesses due to my immune suppression. I would love to have to drink less. It would free up some time. I

know I'm not the only one wishing that. Will I be able to get health insurance on my own someday? What will happen to me when I start showing signs of ESRD again, and need a new kidney? Will I lose my job? Those are my thoughts and concerns. Thank you for listening.

(Applause).

MS. EGGERS: Thank you all -- very much to all of the panelists, who provided a -- what we hope is a reflective set of comments sharing your perspectives and experiences. We always start by asking did you hear yourself, your thoughts, your experiences in at least one of those panelists up there? Okay. That's what we hope, and that's what you guys have provided. So, thank you very much.

Is there anyone with a liver -- we didn't have liver on the panel, I don't believe. Anyone with a liver -- who wants to briefly share, your experience, if it -- especially if it's a little different.

FEMALE SPEAKER JEAN: I don't know how different it is. I have primary biliary cirrhosis,

and required a liver transplant. It came on rather suddenly. I thought I had the flu. And then I started bleeding internally. So, that's the onset. Prior to that, general childhood and adolescence and young adulthood, I had no diseases. My basic concerns are -- have been reflected. I'm -- I had a heart attack, and it was otherwise unprecedented. And I now have diabetes, and this I believe is from the drugs.

One of the things that you had asked about was an ideal or a preferable treatment. And I don't know where the research is on this, but what I would hope for is a mechanism or a method for pretransplant suppression, such that when this transplant occurs it is not a foreign body to the human and that subsequent to that they -- it may be for a short time, but would not need lifetime drug therapy.

MS. EGGERS: Thank you very much, Jean.

FEMALE SPEAKER JEAN: Yes.

MS. EGGERS: Is there anything on the web? Is anyone putting comments in yet?

MR. THOMPSON: There are a few questions related to treatment, but not much on symptoms yet.

MS. EGGERS: Okay. So, I'll take this as a reminder to those of you on the web -- I don't know if you can see us or the people in the audience. But please contribute your thoughts during the course of this meeting, and we will summarize them periodically.

So, what we noticed in our team as we were going through the panel comments that came in, as we were talking to the panelists, is the overall gratitude, that has been heartwarming. The gratitude for you to be here today, and be able to be here today. It is very helpful to have this big picture, and I think you've said it strongly. So, as we continue and as we go through the day we encourage you to voice the significant impacts or downsides. Don't be afraid to tell us what the downsides are. We know of your gratitude for having the transplanted organ. In the spirit of continual improvement, we're going to be focusing primarily on challenges that you face, and what you would like to see in making drugs better. So, I think we've never heard such gratitude in our meetings before, and so it really is heartwarming.

So, now, I will get off my emotional state.

It really -- it does -- it's emotional. You have made it such. Well, let's do a polling question, then. That will bring us back. So -- oh, this is a hard one. What comorbid conditions -- and you can check all that apply -- have you experienced post-transplant, if any? I'm not going to read through the list. I'll let you read through it. If you have not had any comorbid conditions that you're aware of, then you would click I?

MALE SPEAKER: All of them?

MS. EGGERS: Yeah. You can do all of them, if they all --

FEMALE SPEAKER JEAN: If cancer, is that --

MS. EGGERS: It would include all cancers.

MALE SPEAKER: (Inaudible).

MS. EGGERS: Things that you acquired, things that you acquired post-transplant.

MALE SPEAKER: Okay. Only post-transplant.

MS. EGGERS: Uh-huh. Okay. So, the infections of A and F are -- we've heard -- we heard about those. You're concerned about infections, and you've experienced infections. We might dig into that

a little bit. Followed by D, the depression or anxiety, as we heard Leilah say before. I will let the panel -- if there's any that you would like to follow up on, in particular -- if something surprises you. And while you're thinking about that, let's talk about infections, just for a few minutes. We're going to be bouncing to many, many different topics. We'll only spend a few minutes on this. We heard about the risk of infection, and worrying about it. Let's talk about your experience with infection -- anything that surprised you about an experience with infection, post-transplant. We'll go here to Dan, and then back there. And again, state your name and your organ, please.

MR. BONNER: Hi. Good morning. My name is Dan Bonner. I'm a liver transplant patient. And I think what has surprised me with infections -- particularly EBV -- is how over time my EBV levels would start out very low, you know, around 200, and then work their way up to over 2,000. But then with no sort of medical intervention at all, my numbers seem to come back down to below 200. And I find that

to be odd, because during that time my immunosuppressant levels weren't changed at all, in any way. But, at one point, at the same time having kidney enzymes that -- or, a creatinine level of 2.8, around there, is the same time EBV was going up. And then magically, my numbers came back down. So that, to me, was a little bit surprising, considering the lack of medical intervention.

MS. EGGERS: Okay. And then back there.

MR. LENNON: Good morning. My name is Jack Lennon. I had a three time kidney transplant recipient. So, most probably surprising -- and I'm sure most of the others in the room have experienced this -- it's not just that we are more susceptible to the viral infections that the doctors will check on a regular basis, but it's also the -- you know, the seasonal flus and the infections that you would catch at school or at work. And the worst part about those is that, A, you're more likely to catch them because of your, you know, decreased immune system. But also the fact that you can't kick it. Right. It's -- I want a super antibiotic, because, you know, I -- my

brother will get better in two days. I'm out for a week, right. Or sometimes even worse, it really lays you on your back and you have to be admitted for something, you know, somebody else is just going to be able to, you know, normally function throughout the day with. And so, you know, it's that concern about really the impact of the infection and what it can have on your daily life.

MS. EGGERS: Uh-huh. Right. We saw a lot of heads nodding -- a point that resonates. Okay. Let's -- anything else on infection? Okay. One more.

MR. FOWLER: Yes. My name is Kevin Fowler, 12 year kidney transplant recipient. I think the whole aspect about infections is -- the question is is that what's really happening in terms of my concern is the cancer risk. And then I think it underscores the need to have tailored therapy, the need for diagnostic, yada, yada, yada. But that's the larger issue, right.

Am I on too much medication, or am I right enough? Besides the inconvenience that it results in too.

And then the other thing, too, is just to

point out is that there's a lot of people that are losing their organs due to those hospitalizations, because of the fact of the cumulative effect of all the antibiotic use, and the fact that sometimes patients don't take it serious.

MS. EGGERS: Okay. All right. Thank you, Kevin. Okay. We heard about diabetes from a couple of you on the panel. Is there any perspective on the onset of diabetes that has surprised you? Anyone else want to -- okay, we'll come here to Jean.

FEMALE SPEAKER JEAN: Just one quick thing. My endocrinologist is of the belief that there is a difference between normal weight diabetes and metabolic syndrome. I'm not obese currently, nor have I ever been. Nor have -- do I have a profile of really high sugar intake. I mean, I like sweets too, but -- so, he's -- his belief and his -- he says the status of the research now is they're looking at normal weight diabetes as being something different. And I don't know what the status of that is, or how well accepted that is, but it would be interesting to find out.

MS. EGGERS: Thank you, Jean. Our colleagues have indicated that they would like to hear a little bit more about depression or anxiety. We heard Leilah -- oh. Okay. Go ahead, Jeff.

MR. GOLDSTEIN: I just wanted to say something about the diabetes issue. So, I don't know if this is the case for all solid organ transplants, but in the lung transplant world it's not unusual to get diabetes post-transplant. And for some of us, it goes away once our medications are stabilized.

MS. EGGERS: Okay. Okay. Thank you for making the point. Okay. So, now, thinking about depression and anxiety, as Leilah pointed out if you had it before it doesn't go away. Any other thoughts on your experience with depression or anxiety that you'd like to share? Okay. Go ahead, Kevin. And on the web, please, too, write in your comments.

MR. FOWLER: I think this kind of goes back to that this is a huge issue, right. And I think that -- kudos to the agenda this afternoon. They're going to deal about that with adherence or nonadherence, which is a byproduct. But, I go back to my first year

and a half transplant. I had it easy, in comparison to many people. But that whole psychological adjustment -- most physicians don't understand it. In that first year and a half, I struggled tremendously. So, I think it's a large issue because of a lot of different reasons. But, if you're looking to improve it for patients is now how do you improve the patient journey by really understanding the emotional side for the patient.

MS. EGGERS: Uh-huh. Okay.

MR. FOWLER: That is a huge issue.

MS. EGGERS: Okay. So, that's raised another thought here. And then we'll go --

MS. JEFFERSON: Hi. My name is Nicole Jefferson. Kidney transplant, 2008. One thing I wanted to discuss with the depression issue is although I had my transplant in 2008 right now it's in the process of failing, so I'm going through trying to get listed again. And that's one of the things that's come up, is the depression -- the anxiety, the feelings of disappointing my donor. Although deceased, the process of her dying again now that I'm

losing this one. And although I see a therapist, that's something that I didn't think about in the beginning. I didn't think I would -- I was told it would last four to six years. However, I never understood that the time would come and how I would feel, and that it would put me in an anxiety mode or depression mode.

MS. EGGERS: Okay. I'm sorry. We have someone on the -- something on the web, and then we'll come here.

MR. THOMPSON: We've heard a few symptoms on the webcast, including tremors, GI issues including diarrhea, broken or restless sleep. One person specifically was talking about how her chronic sinus issues have been surprisingly limiting to her, because she is restricted from taking medications that might help with them. So, they linger much longer than normal. And a few other experiences like that.

MS. EGGERS: Thank you. And we'll come here.

FEMALE SPEAKER HEATHER: So, my name is Heather. I have a lung transplant, and I had one 10

years ago -- now 11 -- and it lasted one year. And then my native lung came back somehow, even though I had IPF. And now I have a new one last October, and it's fantastic. But one thing that my husband and I discuss a lot, especially in this first year, is the feeling that we truly have PTSD.

MS. EGGERS: Uh-huh.

FEMALE SPEAKER HEATHER: And I think -- I don't, you know, I don't say that lightly. But, it's -- you have a sneeze, and you freak out. And, I mean, and what that causes is your body reacts. And we have a lot going on. We have to, we have to heal. You know, we have to calm down. You know, your body has to have time. And I -- our doctors don't -- you know, there's always a social worker involved. But really, they're not giving you the things you need.

And I -- you know, most of us don't want to take another medication. I fortunately meditated. I learned to do that. I calm myself down that way. It's helped with pain, all kinds of things. But, it just -- even with all of that -- and for a little bit, I was on celexa. But, you know, it was decided, you

know, it was going to cause some more issues with my medication and if I could be away from it, try and be away from it. So, you know, it -- but I think this is just such a common thing that even our caregivers go through and -- you know, it's quality of life, you know. And that's what we're trying to do our best with. So, if that could be somehow part of the protocol, whether it's medicated -- but with, you know, figuring out that -- those medications that won't hurt us as much as they will help us. I think that's something that --

MS. EGGERS: Uh-huh. Uh-huh. Thank you to you, Heather. And what was your name, in blue? Nicole. Nicole. Make really great points, I think, that we will probably hear again, about the trauma of when the challenges sets in and when the worry sets in. So, thank you for that.

There is one more polling question that we will have here, about the comorbidity. For our understanding, if you could get your clickers out. Which statement best categorizes the source of your comorbidity? As best you can. We know this is

sometimes hard to know or to differentiate. But one of these that best categorizes it. You didn't know there would be a quiz, when you came today. Yes. Oh, okay.

Can you -- what other -- the other health effects that you've had that you have experienced post-transplant that you could reasonably think could be because of your transplant. How did you, how did you -- to the best of your knowledge, how did you acquire that? Was it -- do you know if it was transmitted from the donor of the organ? Did you get it when you got the organ? Was it prior to your organ transplantation? That would be B. C, was it acquired, you know, in the community because of immunosuppression or infection. Or, was it acquired, as you could best guess, as an adverse event effect of a treatment that you were on. Yes.

FEMALE SPEAKER: (Inaudible) is not listed up there is Barre syndrome, from (inaudible).

MS. EGGERS: Okay. So, Barre syndrome from?

FEMALE SPEAKER: I don't know if this applies to anyone else, but I've developed Barre

syndrome, from -- possibly from the repeated endoscopies that have been required. And I don't know if that's unique, or if that's -- but it's not a category. It's a post-transplant surgical intervention that wasn't listed.

MS. EGGERS: Thank you. Okay. Let's see what the responses are. But, I think what we'll take away from this, maybe even more than the responses, is the difficulty in answering this type of question and understanding how your -- how all the pieces fit together and where you might have acquired it. It's easy for us to come up with the question, and we don't always appreciate how it might be to answer the question. But with that said, we have someone in the back.

MS. COHEN: Hi. I'm Ellen Cohen -- well, Ellen Griffith for purposes of my transplant. My kidney's name is Ben.

MS. EGGERS: Hi, Ben.

MS. COHEN: But, anyway -- for my brother, who was my donor. The issue of comorbidities -- I don't know how much research there is being -- has

been done on differences in hospital post-transplant protocols. When I had my transplant -- I have a long history, genetic history, going back generations of depression. And I was terrified of -- I knew that some medications -- post-transplant medications made depression worse.

My transplant center, you virtually -- well, they generally, as a practice, do not give you prednisone after you leave the hospital. Other transplant centers that I know of from being on web groups routinely put people on long-term prednisone. So, that -- it seems to me that this issue of comorbidities, somewhere there is a side issue of what are the hospital protocols and how do they compare -- how do they affect the comorbidities.

I also -- I had my transplant in January -- kidney in January, in the middle of that incredible flu season where several types of flus were going around. I never caught anything. And most recently, I did catch a cold that has disabled people for weeks, and I'm over it. I caught it last week. It's gone. Why are immune systems different? Why am I somehow

almost as healthy and almost as immune as I was before my transplant?

MS. EGGERS: I can see the envy in Jack's eyes as he -- as you hear about how healthy -- thank you for raising those questions. And now, we're going to move on to -- oh, yes, go ahead. Leilah.

MS. SAMPSON: Okay. I have something to add.

MS. EGGERS: Uh-huh.

MS. SAMPSON: My situation is quite unique, because when you think of something being transmitted from a donor we typically think of infections or viruses. And my donor actually committed suicide while in jail. And so, he was a high risk donor. And throughout multiple testing, I didn't get any infections from him, no HIV, no viruses. However, since I did already struggle with depression, post-transplant I felt the depths of his depression. And it's interesting, because I've talked to other transplant recipients and they will say, like, if they got an organ from a woman who is in menopause, they will feel the sweating.

MS. EGGERS: Uh-huh.

MS. SAMPSON: You know, they'll take on some of those symptoms. I mean, why wouldn't you, if that organ has been with this person all of their life through all of their experiences. And I knew my depression was under control, and it was days I would just lay in the hospital in the dark. I would have horrible thoughts. I would just -- I would sink to such a -- like, a low that I've never experienced before. I knew it wasn't mine.

And, of course, with the help of an amazing therapist she helped me to just decipher, you know, you have to just send him love and let him know that this is going to be different this time, you know. I always let my kidney know that he'll never experience those depths of depression that he did, to take his own life. And I think that's something we don't typically look at, because it's not tangible. It's not something you can measure. But, it was very real for me.

MS. EGGERS: That's a profound point, about the reality that you have another being that you have

acquired, that you're sharing with. So, thank you very much.

So, we'll move on to another polling question. Yes.

MS. CHALASANI: So, I think the topic one panelists really set up how life after transplant changes, after -- as Leilah said, it's not just perfect. You have to find that balance. And so, there's a lot of lifestyle changes. So, if we can start with this polling question. Which aspects of your personal care have changed most significantly? Skin care, hair care, dental care -- D is eye care, E is dietary needs, and F is other areas not mentioned.

MALE SPEAKER: (Inaudible).

MS. CHALASANI: Yes. You may check all that apply. Okay. So, 72 percent skin care, which goes back to the skin cancer risk that everyone has kind of been mentioning this morning. We have 68 percent with dietary needs, and then a variety for all the other. Let's talk about -- so, we've talked about the risk of cancer but we haven't really talked about some ways that you guys have changed your lifestyle to manage

some of those risks. Does anyone want to kind of tell us how they avoid the sun and so forth?

MALE SPEAKER: Avoid the sun.

MALE SPEAKER: I'm sorry. I thought someone was speaking for me there a second. I think just the thing about the skin is that -- I mean, basically, it's trying to cover my body as much as possible. But, I think the issue is a lot of times it was kind of unreported as an issue at the time of transplant. As well as overall -- a lot of these other issues that are being listed here, many of these issues were really not counseled upon 12 years ago. So --

MS. CHALASANI: Okay. Anyone else? I think Nicole --

MS. JEFFERSON: Hi. I think one of my biggest issues is C, dental care.

MS. CHALASANI: Okay.

MS. JEFFERSON: I didn't realize with the transplant and the medications that I would be on that my dental care would have to be so intensive. The bone loss in my -- and the gum pain, also in addition -- and I guess this goes into it with the dental, the

bone loss in my teeth. Also with my legs. I had severe bone problems, and I actually broke a hip pretty early on onto it. And that would be my biggest thing.

MS. CHALASANI: Okay. What about dietary needs? I don't think we've really heard much about that.

MS. EGGERS: The dietary --

MS. CHALASANI: Changes due to constipation, diarrhea, weight gain or weight loss.

FEMALE SPEAKER: All right. Well, mine just simply relates to the diabetes. It's, you know, it's a struggle to keep that A1C in line and when I don't it's very depressing, because my appetite really hasn't changed. So, that's been significant for me.

MS. PIERCE: I'm Mary Pierce (ph). I am a double lung transplant, 23 years out, which makes me a bit of an outlier. The dietary needs -- with all the drugs that we're taking, particularly the antibiotics, I think we all deal with diarrhea, irritable bowel, those kinds of issues. And it takes a good balancing act to make sure that we do everything we can to

maintain that. Weight gain is a huge issue for most of us. We've got to watch everything we do, everything we take in. And the additional challenge for all of us, I think, is watching the -- what we eat -- the cleanliness of what we're eating. Make sure we wash things, stay off a salad bar, don't eat anything that's prepared for us that we're not sure of its origins.

And then, in my situation, I've had eye problems and a problem with veins and cataracts. And I would imagine that many of us have -- well, you can see the cataract tissue is very visible. And then hearing loss -- I'd be curious to ask that specific question, how many of us have had hearing loss due to the side effects of the drugs.

MS. CHALASANI: Raise -- at any point, you can feel comfortable to raise your hand. So, thank you for the question. Hearing loss?

FEMALE SPEAKER: Here I am. I'm a ten year heart transplant patient. And, yes, the dietary needs -- I mean, I can check off everything. But the dietary needs are particularly challenging at the

moment. In fact, it nearly got in the way of my joining you, because I cannot heal from diverticulitis since April. And it's painful and dreadful. The constipation or the diarrhea, you never know what you're going to have one day to the next. But, it is chronic and it gets in the way of a normal schedule, and nearly interfered with my being able to come. My doctors only gave me permission on Friday.

MS. EGGERS: I think Michael had one comment.

MR. GARRETT: Well, when this -- I got into this game as a Type 1 diabetic, so I was used to watching my diet. But, most everybody that I was friends with back in the early days -- the prednisone therapy was quite prevalent, and everybody would blame their overweight on taking all that prednisone. Of course, I did have one doctor that told me that my problem was an overactive fork.

MS. COHEN: On the lighter side -- I'm still Ellen Griffith Cohen, and I'm still a kidney transplant recipient. My biggest fear for infections is that I am a lifelong -- not only nail biter but

biting the cuticles and the skin around my nails, all of which is, I thought, a very good source for infection. And so, one of my post-transplant changes has been going for a manicure every two weeks. I recommend it.

MS. EGGERS: I think we have one more.

FEMALE SPEAKER MARY JANE: Jane. I am a kidney transplant, 21 years. And my biggest challenge is the dietary needs, but not of those conditions up there. It's the sodium intake. I struggle every day to figure out what to eat when I'm not at my house. The sodium intake at a restaurant -- I can't tell -- if I want to order a grilled chicken and then go look it up online, it has so much sodium in it and I am very, very sensitive to that, especially with the medications that I'm on. So, for me the dietary needs. And I would love to see the restaurants instead of putting the fat, the calories, put the sodium intake in there. Put the other stuff in there that people who have transplants can choose healthier options, so that we know how to eat better.

MS. EGGERS: Thank you, Mary Jane. Graham,

anything from the web?

MR. THOMPSON: So, we've been getting a lot of stuff on the web. Thank you very much for participating. A few symptoms that people have been mentioning -- several people mentioned blurred vision. Again, we heard about tremors and restless sleep. Joint and bone pain. Damage to the lower GI and GI issues. Various skin cancer issues. Losing hair. A few people mentioned hearing loss. Hypoparathyroidism, and in terms of depression or anxiety three people mentioned that they had disease reoccurrence, which may prevent them from getting another transplant, which is a scary thought for them. And also, people worried about having to live the rest of their lives on dialysis.

MS. CHALASANI: There's a lot, as far as lifestyle changes and management. So, please feel free to expand upon all of what you've heard here, and anything that we may not have gotten to in our public docket. We read through all of the comments, and they're all part of the public record.

MS. EGGERS: And, Meghana, so, I'm looking

at the clock. And we -- we're going to dip into the break, for a -- five minutes. So, we'll shift it all back. So --

MS. CHALASANI: Okay. Great. More time to talk.

MS. EGGERS: I'm the one who got to make those calls, and I will make that call.

MS. CHALASANI: So, I kind of want to ask everyone in the room right now what has surprised you the most about your health, post-transplant? As far as, like, impacts on daily life. The most surprising.

MS. PROUT: It was being alive afterwards. So, that's all I have to say.

MS. CHALASANI: Yeah.

MS. PROUT: I'm Jean Prout. I'm 12 years out from a single lung transplant.

MS. CHALASANI: We have Jack --

MR. LENNON: I think -- so, Jack Lennon again, three time kidney transplant recipient. I think the thing that surprised me the most is that even though you're stable, how much the consideration of having a transplant comes into daily decision-

making. For example, you get hired on at a company and they offer you additional supplemental life or supplement disability. Right. I'm 28 years old. Normal 28-year-old male, I don't need that, you know. But, me thinking, you know what, I've been in dialysis. I know what that's like. I should probably get that. You know, same thing with just, you know, any type of going to, you know -- I haven't been feeling very well recently, should I go in and get my labs checked. It's just this sort of simmering worry, and then every once in a while you're like, oh, I got -- I do have to make the consideration for this, either for today or planning long-term.

MS. CHALASANI: Let me narrow the question a little bit. So, what negative health effect post-transplant has surprised you the most? Anyone? I think we have.

MR. LEE: Hello. My name is Austin Lee, and I've had two kidney transplants. I had one that lasted 14 years, and one now that's doing great. It's been six years since I had it. And they're both from living donors. And negative is that -- it's kind of

funny, because I'm a two-year-old teacher. I work with toddlers. So, getting sick. Like, you know, colds and flus and -- but actually, in my first year of working in childcare I really got sick a lot. I worked around infants. But as time went on, I guess like my immune system got better. Because I really haven't had much, you know, issues with flus or colds. But that's pretty much -- and it probably speaks for a lot of people who have had organ transplants. It's just, you know, just getting sick and your immune system. But, that's pretty much it for me.

MS. CHALASANI: We're going to let -- Marty has your --

MR. MARIN: Hello. My name is Marty Marin. I'm a liver transplant, six and a half years ago. I think the thing that surprised me the most is I do have a lot of trouble with my eyesight nowadays, and hearing. The good news is, however, I started off with about 20 hairs on the top of my head and look at this gorgeous head of hair now.

MS. CHALASANI: Thank you very much, Marty. I do kind of want to see -- I know we have a couple of

folks in the room who may have received their transplant as a pediatric patient. I know we have Lindsey, who is currently a pediatric patient. But, was anything strikingly different as far as health impacts post-transplant? Do we have anyone?

MS. EGGERS: And if you're on the web, please contribute.

MS. CHALASANI: Yes. On the web as well.

MS. EGGERS: If you're a caretaker or a teenager.

MS. SCHWARTZ: Hi. My name is Lindsay Schwartz. I have a five-year-old son who received a kidney transplant when he was two and a half. So, he's about three years post-transplant. And it's been an incredible change in his life and our life. He was born in renal failure, so he spent two and a half years on peritoneal dialysis at home every night, for 12 hours. So, his kidney transplant has dramatically changed his life -- it's given him life. And it's given us parents -- it's given us our lives back. It's -- there's only a very few negative things. He's in kindergarten. He's there today, spending the whole

day at school drinking his water. He still has a feeding tube to give him his medications. We're trying to wean him. But it's difficult as a pediatric patient, because -- I'd like to get him on pills, but to get him on pills he needs to be at specific doses. And we can't make the changes -- the little miniscule .1 amount changes to his doses on pills.

So, we're kind of stuck in this no man's land of wanting to push him off his feeding tube, to give him even more of a normal childhood -- not at the nurse's office multiple times every single day, changing dressings and those kinds of things. But we just aren't able to get to that place. And he's not able to drink the two liters of water, you know, as a five-year-old. He's doing great, but he's not there yet.

So, it would be great if we could make some changes to compounded medications or, you know, pills in different dosages.

MS. EGGERS: Okay. Great.

MS. CHALASANI: We have one more comment, over here.

MR. MIDDLEMAN: Hi. My name is Michael Middleman. Three time transplant recipient, two from cadaver, one from living. My first transplant was when I was six. So, the things that I see as very different is, one, when I was a pediatric patient -- that was from a cadaver -- the care in the hospital and post was very different. I'm treated, I don't think, as well as an adult patient as I was when I was a child. I -- that's very true.

But I also think that afterwards sort of the way my body has rebounded has been very different. And then also, I think a third thing has been sort of the care protocols. After my first two transplants, there was a lot of restriction around -- you know, wearing the mask and doing all these things afterwards. And the third one was in 2001, and there was like no restriction. So, no premeds before going to the dentist, no wearing a mask and going to matinee movies and -- you know, none of that stuff. So, the restrictions have gone way down. Maybe that's also a lax in care, as well.

MS. CHALASANI: Okay. Thank you, Michael.

Let's tease apart some of these daily impacts a little bit more. I think we have another polling question. What are the most bothersome impacts of your organ transplantation on your daily life? Please choose up to three impacts. A, ability to participate in or perform activities; B, ability to fall asleep at night; C, ability to sleep through the night; D, ability to concentrate or stay focused; E, ability to care for self, family and others; F, impacts on sexual intimacy; G, emotional impacts; and H, other impacts not mentioned.

Okay. So, half of you -- D, ability to concentrate or stay focused. Cognitive. Okay. Nearly 50 percent, ability to sleep through the night. And then a little of everything else as well. Other impacts not mentioned, first off. Would someone mind sharing with us what those impacts might be? Anyone? 22 percent. No? Okay.

Ability to concentrate or stay focused. Can someone expand on that? Is that at work? A time of the day? Is there something that triggers that possibly?

MS. JEFFERSON: First, I want to go back to other impacts.

MS. CHALASANI: Okay.

MS. JEFFERSON: I think one of the impacts that's not listed up there is the social aspect of things. The kidney failure, the transplant -- invisible disease. So, people see me and they don't see a person who doesn't feel well, a person who has issues and can't walk that far. So, people will say well, come on -- especially at work. When I changed departments, they may not know my situation so they don't understand why I can't walk to the other end of the building. Because my legs give out or I'm tired or I don't feel good. So, I think social impacts would be a big one.

Also, if I park in the handicapped people look at me funny, because I get out and they don't understand why I am walking what looks to be okay, but I'm really not okay. But the ability to perform activities such as work -- work is an issue. Sometimes I'll wake up and there will be issues from the night before, where I couldn't fall asleep, or

just the medicine may make me feel sick, depending on when I take my prednisone or different things like that. So, that's an issue that I have with both of those.

MS. CHALASANI: Great. Thank you, Nicole. I think Lindsey was going to add something.

MS. DUQETTE: Staying, like, concentrated isn't a problem for me, because when I take tests and unit tests I tend to rush. But then I try to slow myself down by looking at stuff in the room, but then I can't regain that focus. I just -- I don't know. I kind of go off into another world. And my tremors, they kind of affect my handwriting. And that affects it as well.

MS. CHALASANI: Thank you, Lindsey.

MS. EGGERS: We'll have time for a few more. We knew we wouldn't be able to get into all of these. But this gives us a sense. And we'll probably be revisiting some of these themes --

MS. CHALASANI: Throughout.

MS. EGGERS: -- in the topic too, and in the afternoon.

MR. GLEASON: Can I just add to the question on H? Something that didn't get mentioned, I'm sort of surprised, that -- is the bothersome regimen of taking pills on a timely basis every single day. And the coordination of those pills, some of which have an impact on each other.

MS. EGGERS: Yes, we will get into that in the topic two discussion, in some depth.

MS. CHALASANI: Yes.

MS. EGGERS: I just -- I'm keeping an -- I think we're going to need to go to a break.

MS. CHALASANI: Sara is playing bad cop today.

MS. EGGERS: So, we'll take a couple more. Yes.

MR. MIDDLEMAN: Hi. This is Michael again. I was just talking, sorry. One thing that's been particular bothersome for me, which may seem like a small thing, is being on the job market. I have a lot of things in my background and for a resume related to kidney world and transplant world, and I get questioned about it a lot. And I'm pretty sure I've

been discriminated against because of that, and employers that look at you and say is this person going to be out again for -- you know, be out for six months. So, I'm -- it's always a struggle to kind of -- how do you answer that and how do you talk about that. I have no good answer for it, except that it's happened and it's hard to deal with.

MS. CHALASANI: Thank you, Michael. I was going to say please expand on the docket comments. Like I said, we read all of them. The link is on the agenda, as well as on the slides, and we will email it to you guys as well. We'd love to hear a little bit more detail and more insight on all of these issues. We originally had a 15 minute break. Should we make it --

MS. EGGERS: I think we can -- I think topic two is just going to be building on this. So, we will take a 15 minute break.

MS. CHALASANI: Okay.

MS. EGGERS: And please come back at 11:10, and we'll get started promptly. Topic two panelists, if you could just make your way up to the front when

you come back in.

MS. CHALASANI: Thank you, everyone.

MS. EGGERS: Thanks.

(Off the record at 10:55 a.m.)

(On the record at 11:11 a.m.)

MS. CHALASANI: I'm going to start calling out people's names, if you guys don't start getting seated. I memorized them during topic one. So, just a couple of quick logistic reminders. I think we may have some folks that may have joined us for this topic. And so, if you are a patient or a caregiver and you don't have a clicker, would you mind raising your hand so that we can help you get a clicker? I think we have one right there. Okay.

I would also like to remind everyone that after this topic we do have lunch. But then after that we have an afternoon session. And while we're calling it a scientific workshop, it's -- and it's a little bit more technical, there is definitely a lot of interaction with the patients and the patient community. So, we really encourage you guys to stay for the afternoon session, if you're able to.

So, topic two is where we want to hear your experiences with current approaches to managing your condition, a little bit more specific and a little bit more on the complexity than topic one. And including, like, what ways are they most effective and in what ways are they not effective, and any other downsides. And similar to topic one, we're going to have five panelists share their comments to kind of set the context. So, Piper?

MS. BEATTY WELSH: Hi. My name is Piper Beatty Welsh, and I am a two time double lung transplant recipient, due to a genetic disease called cystic fibrosis, or CF. Just a little bit of background. CF is a recessive inherited disease that really affects the entire body, but is most commonly thought of in terms of the lungs and digestive systems, where it causes a very thick mucus to build up, leading to progressive organ damage. I was diagnosed with CF in infancy, and have therefore spent my entire life dealing with the realities of complicated chronic illness.

I received my first double lung transplant

in 2010, at the age of 28. And my second in 2013, after a brief but intense struggle with chronic allograft rejection. I am currently 34, coming up on three years post-transplant with my second set of lungs. I am also a staff member at the cystic fibrosis foundation, but I'm here today to talk about my personal experience as a lung transplant recipient.

One of the things I would like to focus on today is the interplay between my routine to protect my lungs post-transplant and the rest of my body, which still suffers from complications relating to CF. I remember hearing a surgeon say, and we actually -- I think Jeff touched on this -- but, I remember hearing a surgeon say that lung transplant should not be considered a cure, that it's actually trading one set of problems for another. In my case, I traded one part of my original disease -- the lung disease, which is often fatal -- for post-transplant life. But I still maintain all the other aspects of my original disease.

Cystic fibrosis creates difficulties in absorbing certain nutrients and vitamins, and can also

create difficulties in digestion that make it really tough to maintain steady drug levels. This has been a challenge for me personally, especially in relating to immunosuppression drugs and particularly tacrolimus. My doctors and I have tried several solutions, ranging from adjusting my digestive enzyme therapy to sublingual dosing of the tacrolimus, to actually adding on additional drugs to try to increase and stabilize the amount of the drug in my bloodstream. Especially after having gone through chronic allograft rejection once, I am acutely aware of the need for stable immunosuppression levels. This continued CF-related complication also means that my CF care center team remains an integral part of my care post-transplant.

Another struggle for me is the ongoing steroid therapy required for maintaining my lung transplant. Because CF impacts the pancreas, it makes us naturally more susceptible to a form of diabetes known as CF-related diabetes. The steroids have definitely heightened the risk for me of diabetes-related complications, particularly because, as

someone with CF, I also have to maintain a very high calorie diet. This is particularly frustrating when combined with ongoing steroid use, and the potential for these drugs to cause things like calcium loss in the bones, which is also a big concern for me as a woman living with CF.

In an ideal treatment world, I would love to see mechanisms of drug delivery that really target the lungs specifically, through nebulizer or other direct delivery, in order to help alleviate some of the problems with systemic steroid use or poor absorption issues. Additionally, working to make the post-transplant routine steroid free and a concentrated effort on reducing the side effects and systemic damage to other systems caused by immunosuppression drugs is important, not just to make post-transplant life easier to manage but also to improve the overall health and longevity of people post-transplant.

And one other issue I'd like to just touch on quickly is emotional care post-transplant. We've been talking a lot about that today. And the importance of mental health. Managing a transplanted

organ means dealing with a wide variety of effects from drugs and other changes in the body, and we as people, not just as patients, need support and attention paid to that part of the process. I was fortunate enough to have a team that recognized this challenge, even in patients like me who are very much used to complicated medical routines and appointments. I started on an antidepressant to help me manage my anxiety around caring for my new organ and adjusting to the new normal after surgery. In the now almost three years since my second transplant, I have been able to find a number of effective ways to manage this additional stress, and have decreased the dose of my antidepressant accordingly. However, I am extremely grateful to my doctors for proactively helping me to manage the emotional impact of the complicated medical experience of lung transplant.

MS. CHALASANI: Thank you, Piper.

(Applause).

MS. CHALASANI: Dan?

MR. BONNER: Hi. Good morning. Again, my name is Dan Bonner. I'm currently 43 years old. I'm

a liver transplant recipient, class of 2005. I had a liver transplant due to a disease called primary sclerosing cholangitis, which is basically a disease where the bile ducts in the liver will continue to close until the patient experiences liver failure, and would eventually die without the use of transplant for that condition.

I'm going to go a little bit off topic from my scripted comments, because my scripted comments echo a lot of what has been already said. So, I'm going to try to incorporate other things in here from a more scientific perspective, to the best of my ability, in the hopes that it would add greater value. But just like many others, I'm coming at this from a perspective of immeasurable gratitude and humility for the second chance. So, I'm sure that that's already taken into consideration.

Immediately following my transplant, my post-transplant immunosuppression include prednisone, tacrolimus and cellcept. However, I had found out that my liver donor was CMV positive while I was CMV negative. This presented an interesting scenario,

because it required me to have a different medication, called cyclosporine, for a hundred days after I was transplanted. To the best of my knowledge, I didn't think that there was any sort of negative impact to cyclosporine, other than it just allowed me to continue to have a CMV positive liver when I myself was CMV negative. However, also in the hospital I experienced a severe bout of rejection, at which time I was treated with a thousand milligrams of Solu-Medrol, as the initial protocol, which proved not to work.

And then I was upgraded to a medication called OKT3. OKT3 has since been removed as a prescribed medication for rejection, due to its level of toxicity that it presents to the patient. And just to sort of give a sort of quick synopsis of how toxic is it, I had met a woman in my transplant travels who had rejected multiple times and they wanted to give her a third round of OKT3 and she refused and passed away several days later. So, the level of toxicity of OKT3 was just -- is just too great, and not used anymore. But what makes it sort of important for me

about OKT3 is when you look at ten years plus down the road now for someone like me, there are studies that are being done around OKT3 and the use of cyclosporine that will predict things like PFC recurrence, graft survival and patient survival, which is something I think that at the time the medical community was unaware of, of how these drugs affected not just the immediacy of the situation but also the five and ten year out time frames that someone like me has had the benefit to live long enough to figure out.

So, when we're talking about drug development it's interesting to me to think, you know, I would like for some consideration to be given into not just treating that disease or that particular situation but what are the impacts five, ten years down the road that we -- that may not come up in those initial discussions, for that medication, but may come up down the road later on. In terms of my own medication treatments, though, I've been given tacrolimus, cellcept, and prednisone, as I said. My tac levels have been adjusted accordingly, depending on my situation. I would say the biggest concern now

I have is cancer, like many of you. I had mentioned before my EBV levels have fluctuated greatly recently, resulting in an enlarged lump node in my lung, and I've been being looked at for PTLD, which is post-transplant lymphoproliferative disorder, which was -- EBV is an indicator of that. So, these are the types of things that I've personally experienced that I wanted to add that hopefully would have some value to this.

And then lastly, just to talk about what I think my ideal treatment would be -- my ideal treatment would be one where, like many of others, I don't have to take as many pills, I don't have to take them every 12 hours, that I would get back some energy levels that I don't currently have, I would be able to spend some time in the sun and, as silly as it may sound, I'd love to be able to drink socially again, because as a liver transplant guy alcohol is a big no-no. So, I'm looking forward to someone who can create a medication that would allow me to drink socially again, or make non-alcoholic gin. I would prefer either one. So, thank you.

(Applause).

MS. CHALASANI: Thank you, Dan. Deborah?

MS. HEFFERNAN: My name is Deborah Daw Heffernan, and almost to the day I'm celebrating ten years with my new heart, from Massachusetts General Hospital in Boston. Prior to my heart transplant, I suffered nine years of heart failure following two massive heart attacks, each caused by a shocking spontaneous coronary artery dissection and requiring open heart surgery. After almost 20 years with heart disease, despite no family history, being thin, fit and having perfect health habits, like all of you I'm very glad to be here, in all its meanings.

Two disclosures. My husband is a retired founding officer of a biotechnical company. Also, I am the author of a book featured on the 2002 Oprah show about young women having heart attacks. The next book on my transplantation experience will be out in about a year.

The FDA has asked me to focus specifically on what am I doing to maintain my life with a transplanted heart, and all I can think of is that

Emily Dickinson could have been writing about all of us, and in my case definitely it's been my experience that life is so astonishing it takes -- you have little time for -- to do anything else. My transplant cardiologist, Mark Simergrand (ph), prepared Jack and me by saying you will not be restored to the health you enjoyed before you got sick. You are exchanging one set of problems for another.

While others may breeze out the door in the morning, I am already preoccupied with preventing rejection, infection and cancer, the heart transplant graduate's main causes of illness and death -- not heart disease, interestingly enough. This is the paradox of cardiac transplantation. The very operations, procedures and daily medications that give us life also make us sick. The main culprit -- immunosuppressants. From life, my daily preoccupation begins with the prevention of infection. Face masks and hand sanitizer are with me everywhere. Every cough in a crowd is a gunshot. Even a little cold can become deadly. It's taken years to establish systems and protocols for cooking, cleaning, socializing, and

basic affection. Days begin with double-checking, ingesting, digesting, monitoring, managing side effects of my meds. Plus, ordering, confirming and sorting them. I have spent hours scheduling, preparing for, enduring, and recovering from daily, weekly, monthly, quarterly and annual checkups, tests and horrible procedures -- all of which you know all about. My life depends on these drugs and procedures -- a heart transplant graduate's primary therapies.

But, my life also depends on counterbalancing therapies that I've cobbled together through time-consuming trial and error, always with the permission of Mass General. My discipline begins with eating well and exercising every day, even if all I can do is twirl my ankles in the air from my sickbed. I use supplements, psychotherapy, and body therapies to help clear toxins and blockages in both body and mind, and to ease contortions and pain from multiple operations, as well as the meds.

But I've had no rejection episodes during the first five years of highest rejection risk, and I like to think I participated in that result. And no

rejection episodes during the second five years, of vascular damage risk. And now I'm more than ten years out, because I'm just a month later.

I've had to let go of many aspects of normal life, including people who do not respect a fragile immune system. I hope specifically for better approaches to immunosuppression that target organ specific response. Because I think we may be further along, maybe, in that than regenerative cell biology. Excuse me, generative cell biology. But, living consciously is the best way I know to honor my donor, clinicians, husband and family. And if you're interested, I can go into more of these details during a discussion period.

(Applause).

MR. LENNON: Good morning, everybody. Thanks for the opportunity to participate, first of all. You guys heard me in the topic one. My name is Jack Lennon. And I was born with posterior urethral valves, which is a blockage of the urinary tract in the womb. Which causes the amniotic fluid at the time the fetus's urine to back up into the bladder, up

through the urethras and then just sit in the kidneys, until you're born. So, literally had kidney disease all my life. So, not exactly sure what normal is, necessarily.

So -- but, I received my first kidney transplant at the age of seven, from my father. But, after 14 years of the chronic changes from a couple of rejection episodes, as well as the damage from the immunosuppression meds, that kidney failed and I had to go back -- I had to go on dialysis for the first time. Luckily, that was a short-lived period of time, and received a kidney from my mom in 2008. Unfortunately, that never really took. The kidney never functioned as well as what the doctors, as well as myself and family, had hoped. And despite adequate drug levels, via the laboratory monitoring, I came down with antibody-mediated rejection. So, a little bit of a cautious optimism with the medications. So, that kidney transplant from mom only lasted five years, as a result of that antibody-mediated rejection, and I had to go on dialysis for the second time, this time for a much longer period of time,

before receiving a perfectly matched kidney from my older brother, which I am now two and a half years out from and doing extremely well, knock on wood. (Applause).

MR. LENNON: Thank you. And it better last a long time. I'm running out of family members. So, if I've really learned one thing from listening today, as well as my own experiences, there's no such thing as a simple transplant patient, and -- medically, socially, emotionally, et cetera. And so trying to craft a medical or treatment regimen to those individual patients is extremely difficult. Especially when I like to think of it in the framework of what I like to call the holy trinity, which is longevity -- how long the organ will last, want it to maximize the life -- the health of myself, as the patient, and then the quality of life associated with the longevity and health, and the treatment regimens that you have to undergo. So, currently, I'm on seven pills, in addition to a monthly infusion called belatacept, which is the main immunosuppressant, which is fantastic, as it has significantly decreased the

worry of missing that medication dose once or twice during the week or during the month, and I -- it's very easy for me to make the one hour appointment every month, instead of getting caught up with friends and -- oh, man, I forgot my meds, I got to go back home, et cetera.

So, you know, one of the other things I'll mention that we got into in the first topic is managing it as a pediatric patient, there was a lot of caregivers that had to participate in my care as I grew older. And my mom still nags me and calls me just about every week -- have you missed any medication doses this week. And I know -- thinking ahead, you know, I've had three. I -- hopefully this one lasts for quite a while. But I know that it may not. It might not last until my time is up, per se. And so the need for more kidneys -- you know, another kidney transplant down the road is inevitable, and having caregivers at the end of -- you know, when -- are you able to maintain that treatment regimen yourself, and I'm sure we've all had experiences in the hospital when you can't self-advocate, and you're

really at the mercy of the drugs and the treatments and the providers who are giving you those drugs and treatments.

And lo and behold, I have worked, now, at Cincinnati Children's Hospital in the kidney transplant program, and the doctors and nurses don't always know what they're doing. Medicine is an art and a science. And so, it is a little bit of trial and error, as I'm sure we've all experienced, and so the last piece -- and I think this is -- really sums up kidney transplant, and all transplant really, is the rosebush analysis -- or, analogy, which is, you know, from the sidewalk of the casual observer, you know, a rosebush is really pretty. You know, it's really nice, and that's the gift of transplant. Oh, you got your kidney. You look so much healthier. You can do all the things -- you know, you can -- you're back to normal. But, there's a whole lot of work behind the scenes and a lot of thorns and a lot of scrapes and scratches, that it really takes to make that rosebush bloom and be successful. So, thank you.

MS. CHALASANI: Thanks, Jack.

(Applause).

MS. WAGER: Hi. Thanks, Jack. My name is Bobbi. I'm a two time kidney transplant recipient. My first transplant -- my primary -- the primary disease was pyelonephritis. I had my first transplant in January of 1983. Due to their protocol back then, I had my spleen taken out, helping with the immunosuppression. My drugs at that time just consisted of imuran and prednisone.

However, with these medications I was in and out of the hospital each year at least twice a year, for acute rejection episodes. My husband -- his favorite thing was to pick me up at the hospital, because he wanted to see how much hair growth I had on my face, did I have the acne come back, did I have the buffalo hump. But, he also was not sure what person he would pick up at that time, because of the mood changes. So, my nickname is Sybil.

Okay. The second transplant -- my first transplant lasted 15 ½ years. My second transplant has now lasted over 18 years. My drugs -- my drug treatment regimen has changed. I am still on

prednisone. I've added prograf and cellcept. Due to the side effects of these medications, my treatment regime also now include blood pressure meds -- diovan and metoprolol. I take nexium for the gastro reflux -- gastro esophageal reflux disease, lovaza and crestor for cholesterol and triglyceride management.

I also take several medications on an as-needed basis. Valacylovir, because I have suffered several bouts of CMV, and with my spleen missing my nephrologists trusts me to be able to take that medication when I feel I need it. Otherwise, I end up in the hospital. I also take neurontin, due to a degenerative bone disease caused -- of course, we blame everything on the steroids -- of my spine. My new treatment regimen includes now getting an injection of avastin, which is off label, in my right eye due to the retinal disease.

The medications on my current regimen totally -- today, totally help manage the most significant symptoms I've experienced for transplant. For instance, if I don't take my nexium I can't eat or I can't swallow. If I don't get the shot of avastin

every four to six weeks, my eyesight in the right eye becomes distorted and I'm able to drive -- I'm unable to drive and carry out every day activities. My post-transplant regime has changed from the first transplant to the second, all dictated, as we all know, by the medications. Due to the 33 years of steroids, I see a retinal specialist, as you know, on a regular basis, a gastroenterologist, due to treating irritable bowel syndrome and GIRD, a urologist to treat the increased episodes of UTI, and a dermatologist.

Keeping a structured treatment regime has so improved my ability to do specific activities in my daily life. Because of this, I can continue to practice as a nephrology nurse, and practice, of course, a wife -- which I'm not perfect -- and a mother. My current treatment regime is such a small commitment to the benefits that I reap. I honestly do not think there are any downsides to the current treatment regimen. Sure, it does get difficult, annoying and frustrating keeping up with all the multiple physical appointments and the multiple

medications. But, reality is if I don't do it I lose a kidney and I'm back on dialysis, as we all know, and my quality of life would suffer. And adhering to a strict treatment, to me, is easy and it's a win-win situation. Because of transplant, I've been able to live a life that has enabled me to dream, that I thought at 23 years old I wouldn't live to middle age.

In my opinion, the ideal treatment for a patient -- a transplant patient -- would be to take a medication only once a day. And I know you all have heard that. But being a nurse -- a nephrology nurse in the field and working with patients in the CKD realm, I see recurring patients that are losing their transplants because of not taking the medication. I wish there was more data -- more studies for the patients that have had their transplants for over ten years, because I believe that's when the noncompliance or the nonadherence starts.

I want to thank again, as we all do, the FDA for putting this together. If there was a change, I would like very much that you get a drug that has, of course, less side effects, but get us to where we're

not taking as much steroids. I don't mind taking the other drugs. But the steroids over time, as we all know, cause so many problems. So, thank you very much.

(Applause).

MS. CHALASANI: Bobbi. I want to thank all of our topic two panelists. I think you guys really provided us with rich detail on the complexities of your treatment regimens, and it's going to be a great foundation to kick off the rest of the discussion. I saw a lot of head nods. So, I think what we heard here -- at least one of their stories definitely resonated with all the patients and the caregivers in the audience. Is that about right? Yeah. Okay.

I think we have a polling question. Thank you. So, let's see, have you ever used any of the following drug therapies to manage your organ transplantation. I'm not quite as skilled as Bobbi here with pronunciation. So, I'm just going to give you the brief. A, calcineurin inhibitors; B, glucocorticoids; C, purine antagonist; D, mammalian target of rapamycin inhibitors; E, antidepressant

drugs; F, opioid pain medicines; G, other drug therapies not mentioned; and H, I'm not taking any drug therapies. You guys can check all that apply.

MS. EGGERS: And does anyone need a clicker?

MS. CHALASANI: Oh, we need one more. Okay. Nearly all of you guys have taken a calcineurin inhibitor. Nearly all of you guys have taken glucocorticoids. 73 percent with the purine antagonist. Nearly 50 percent other drug therapies not mentioned. What are some of these other drug therapies not mentioned? I do want to point to that we do have a follow-up polling question that we'll talk a little bit about the nondrug therapies, as well. So, just the drug therapies. Would someone mind letting us know some of the others, particularly?

MALE SPEAKER JAMES: Yeah, I've added valacylovir to my regimen. I've had a couple of occurrences of the shingles, and I can't take the vaccine, since it's a live virus, as an organ recipient.

MS. CHALASANI: Thank you, James. Anyone else? Oh, yes, Lindsey.

MS. LINDSEY DUQUETTE: Rituximab, pre and post-transplant.

MS. CHALASANI: Okay. Thank you, Lindsey.

FEMALE SPEAKER: I have taken the valcyte -- the noxafil, which I guess is -- like -- I never remember the big long names. So --

MS. CHALASANI: You're in good company.

FEMALE SPEAKER: And I'm trying to -- there were other viral -- or, antifungals, I think, that aren't mentioned.

MS. CHALASANI: Okay. Okay. Okay. So, what are some of the biggest downsides that you guys have seen with these treatments? Maybe the side effects -- the most significant side effects. Nicole?

MS. JEFFERSON: I saw immediately after transplant was the weight gain with prednisone. I probably gained 40 pounds in a month. So, that was the biggest one for me.

MS. CHALASANI: I see a lot of head nods with that.

MS. SCHWARTZ: Hi. My son -- my five-year-old -- had the kidney transplant. The biggest issue

we've had is the mycophenolate, the cellcept. He became so neutropenic post-transplant, about three months. It just kept going down, down, down, until he basically had nothing left, and at that point then picked up a blood infection, which then, you know, sends him to a whole other set of issues. But, the cellcept has given him issues since the very beginning. And his team -- thankfully, they took him off the cellcept, and he did pretty well without the cellcept. But, it's not a long-term therapy for him. So, we're back on the cellcept and it's a constant issue and concern that it's not going to work.

MS. CHALASANI: Thank you.

MR. MIDDLEMAN: Cellcept, I am on it now but I would urge the FDA and the folks on this panel to study it more in pediatric patients. And the person that just spoke, I lost my second kidney because of mycophenolate. And at St. Christopher's Hospital for Children, the transplant program pretty much fell apart in the late nineties. I want to say almost 80 percent of the kids lost their livers, kidneys, hearts because of mycophenolate. And particularly on the

hemoglobin side, and our hematocrits dropped down to, like -- mine dropped to 4 and 5. So, I'm very hesitant. I take it now, but for the mother who just spoke I would be very hesitant -- I'll tell the FDA people -- to keep your kid on mycophenolate. I don't think you guys have properly tested it on pediatric patients.

MS. CHALASANI: Thank you. Any other comments?

MR. GLEASON: Jim Gleason. The prednisone, what a great roller coaster ride that was in the beginning, huh? But in our program -- I got off that in three months. And as I hear some of the long-term effects of that, I truly am blessed 22 years later not to have any of those issues anymore. Cyclosporine was the saving grace back in the early nineties, especially. And so when that got toxic to the kidneys, it was great to find that there were now some new medications on the program they could move over to -- tacrolimus. Of course, the negative of that is while I thought everybody that complained about diabetes -- how could that be, not everybody gets

diabetes -- well, guess what. Now I have diabetes for the past ten years, and I understand that even better. So, the negative of that is the diabetes.

MS. CHALASANI: Thank you. So, how many folks in the room are -- have concerns about effectiveness with these treatments? Is effectiveness a concern? Maybe a show of hands. I've got 10 to 15, for those on the web, if you can't see. Can you talk to us a little about some of those concerns?

MS. SAMPSON: Again, my name is Leilah. And maybe because I'm a newbie, I have a much different perspective. I'm doing well on my immunosuppressants, and prednisone. I was even on a 200 milligram taper initially, after transplant, because of the thickening of the wall of my urethra. And I didn't gain much weight. I'm still on prednisone, and I'm nine months out. And I've been on prednisone all my life, due to asthma. And I tolerate it well. And besides the prograf issue initially I had after transplant, that dropped my hemoglobin and platelets, other than that I feel like the cyclosporine and the cellcept I'm on have been doing very well, and I have very minimal

side effects. So, while, you know, it's important to hear about the negatives, I think it's also encouraging for the researchers to continue to do the research and hear from the patients that are doing very well on these drugs.

MS. CHALASANI: We have -- that whole table is very active.

MR. LEE: Thank you. Again, my name is Austin Lee. I've had two kidney transplants. And I just want to say for the cellcept, as far as like the negative I had -- because I had only took it for maybe about a month when I had my second transplant. Because it gave me like leg cramps, and then, like, they -- my nephrologist from Children's Hospital, she automatically switched me to a medication called myfortic. You guys probably heard about it. And I've been doing fine on that. And actually, I mean, it was kind of interesting. Because I used to take cyclosporine but I take -- well, I took cyclosporine with my first transplant and now I take tacrolimus, or I didn't really understand that. But that was just about it.

MS. CHALASANI: Thank you. We can take one more, maybe. I think we have Kevin.

MR. FOWLER: Yes. This is Kevin Fowler. I guess my question is not so much directed toward the side effects of these medications, or effectiveness, but just the general comment that there are really not a lot of options available for patients and physicians. So, that's my two cents. And then, related to that, then, too, is that, you know, I'm on a regimen of prograf for 12 years. But is that really the best regimen. Would belatacept be a better regimen for me at this point? The doctors really don't know.

MS. CHALASANI: Thank you, Kevin. So, one of the main topics of discussion for our scientific discussion this afternoon is going to be medical adherence. But, we would like to touch upon that a little bit right now, with all of you. What are some of the biggest challenges you guys have in maintaining, you know, your adherence to some of these treatments and your treatment regimen overall? Any significant challenges? Oh, yes. Bobbi.

MS. WAGER: I think the big thing -- I don't know how you guys feel about -- is taking these medications at the same time every day. Especially that -- the prograf. And I don't know if any of you guys do it, but I stay on brand. I don't -- my doctor -- I do not want generic. So, I stay on brand -- prograf and cellcept.

MS. CHALASANI: Okay. Anyone else? We have Nicole and Kevin.

MS. JEFFERSON: One of the things that Bobbi brought up about prograf and cellcept staying on brand -- and this also goes into what he was discussing about the mycophenolate -- I was at Baylor transplant center last week in Dallas, and they brought up a good point that I had never considered. And this is a question, I guess, maybe for the FDA also. There was one gentleman who lost his transplant after 19 years because the pharmacy that he was made to go to changed the vendor of the generic brand every four months. Whoever had the lowest bid. So, because the generic was changed -- and I almost believe that that was mycophenolate, because I've noticed that once I

changed from cellcept to mycophenolate now my kidney is 90 percent scarred. Are there -- again, I believe maybe the research was not done properly with mycophenolate. And what are you doing about making sure that there are protocols to say you cannot continue to change generic vendors to these pharmacies and things like that.

MS. EGGERS: Well, we will -- I think you are raising an excellent broader question, that is very much noted, even if we can't discuss it today. But bringing out your concern about the -- I'm going to say the interchangeability of these medications, as well as their just study, in general, and the protocols for that. So, we will definitely note that as a concern that you have and we had a lot of head nods here. So, thank you for raising it.

MS. CHALASANI: Thank you, Nicole. I think we have one.

FEMALE SPEAKER: In regards to the last question, I think something -- the broader issue is how much alike are generics. Because my understanding was that a generic was supposed to be the exact same

formulation, with the same standards as the name brand. But in regards to timing, I find getting it coordinated with food, especially for the diabetic medication, is the challenge.

MS. CHALASANI: Okay. Thank you. I'd like to follow up with a pediatric perspective. Any striking differences as far as medical adherence?

MR. LENNON: Yes. Yeah, actually. So, like mentioned I work at Cincinnati Children's Hospital as the program manager. And so, what we're finding in particular is that children want to be normal. They don't want to be seen as different. And so, part of it is the psychological I'm different, I have to take medications. The other big piece is there's no immediate sensation of the medicine working, right. You take a Tylenol or an ibuprofen for a headache. Your, typically, headache will go away. Right. Or, you take a medication and it's supposed to, you know, make you feel good. There's none of that. And so by the time you start feeling cruddy, to -- you know, it's already too late. So, at least that's what some of the stuff we found. And again, in pediatrics,

you’re depending a lot on the caregiver to be able to help manage that with the patient, while also building capability within the patient to be able to manage it long-term throughout transition into adulthood, and long-term.

MS. EGGERS: Can I ask a follow-up question, Jack?

MS. CHALASANI: Of course.

MS. EGGERS: Because it was raised here earlier. Briefly, if you can go back to your child self and say here’s the one thing that I wish you knew then about this, that you now know and you wish you knew then. Oh, putting you on the spot for a top of mind --

MR. LENNON: I do think -- the balance of -- which I now do because I’ve had to learn to do it, is the balance of now versus future. Right. So, the benefit -- again, going back to that whole -- what I refer to as the holy trinity, the longevity of the organ, the health that I’m able to maintain and the quality of life that I have as through managing my kidney transplant. There’s the consideration of all

of that now, and then there's also the consideration I have to look at in the future, five, ten -- way down the road, and do I really want to -- you know, when they put me on belatacept, there's no long-term outcomes yet. But, in terms of my ability to adhere to a once a month infusion, compared to twice month meds -- or, twice daily meds -- I don't know. I mean, we'll see. And that's sort of where the cautious optimism and faith -- cautious faith in some of these treatments and the providers providing them really come into place.

MS. EGGERS: All right. Thanks, Jack. So, I put Jack on the spot. But, the -- for those of you here, and on the web and in the room, those of you that have had transplants in childhood or in young adulthood and have worked your way and now you're in your mid-life, or -- I'll even -- you're closer to my age -- and thinking back on your transition, please put that in the docket. Because it's really -- it was asked by a researcher who wants to really understand what goes on in your head, and what you wish you would have known then. So --

MS. CHALASANI: Definitely. Graham, do we have any web comments?

MR. THOMPSON: So, we've been getting a lot of input on the web again. So, thank you for providing some inputs. On side effects, a few things mentioned. Developing hernias after physical therapy, developing stress fractures after taking steroids, or needing hip replacement. Cataract surgery as well. Problems with attention, and staying focused. Several people also mentioned weight gain, side effect from prednisone specifically. Also, acid reflux. Other people mentioned nausea more generally. Hair loss with prograf, and also diarrhea and other drug interactions. Mood swings, vascular necrosis, diabetes, swelling, damage over time, things like that.

For adherence, we heard things about difficulty with regular use at the proper time, with coverage issues again, uncertainty over generics, and a few other specific drugs were mentioned, and some non-drug therapies.

MS. CHALASANI: Thank you, Graham. I think

we have time for one more comment.

MS. PIERCE: Thank you. I'd like to go back to adherence for just a moment, and I think it relates to the elephant in the room. We haven't talked about cost, as yet. I've lost friends and known people that have skipped doses because they can't afford to buy all of them. We actually -- the Alpha-1 foundation did a survey of our patients. We had a note from one of our patients who indicated that Medicare had taken cellcept off his list of drugs that he could have, because it was not approved for lung transplant. And his Blue Cross plan then went along with that. So, lots of issues. And I'm sure we're going to talk about it at some point today, in terms of being able to pay for the drugs and the cost of insurance and finding insurance and all that. But --

MS. CHALASANI: Thank you, Mary. I think -- okay, maybe one more.

MS. COHEN: Hi. This is Ellen Griffith Cohen again. And one of the -- as I'm listening to this, when I got my transplant in January -- now, first of all, I should say I got it from my brother.

He was HLA identical to me, and I had not yet gone on dialysis. It was preemptive. So, I was in great shape except for my kidneys failing. You know, whenever I would see something saying how is your health -- great, except my EGFR is way down.

But, I've -- you know, one of the things we talked about is the anxiety post-transplant. Now, my first anxiety was that they hadn't sewed it in properly, and it was going to acute reject like across the room -- there it would go, you know. And it took me a long time to trust that it was really sewn in there. But, I -- one of the things, as we mentioned several times, is this -- you know, 12 hours exactly on time all the time. When I got home, I sort of looked at it and I said, okay, I have all these things that can freak me out and I'm going to assume -- and then I cleared it with my clinic -- that this 12 hours exactly on time really means actually relatively exactly on time, and I really kind of target about an hour of leeway. And again, I've cleared this with my clinic. My labs are absolutely stable. And I'm not putting the pressure on myself to do it perfectly

every single day.

I do carry -- I always carry in my purse my evening meds, so that -- because my first foul-up after my transplant was I went out to dinner at someone's house, and then realized I hadn't -- didn't have my meds with me. And I had to eat and run. But, I always have my evening meds with me. I always separate my prograf out on the day that I'm going to do lab work, so that I don't take it with my morning meds.

But, the terror that is put into patients about compliance -- and especially once you find -- if you go to the hospital, compliance goes out the window because -- and that's true, by the way. And I don't know whether that's in the FDA or the Medicare area. But, when patients are managing a chronic disease at home, whether it's dialysis, or whether it's -- there are a lot of -- not -- there are ten percent of patients dialyze at home. Or, whether it's post-transplant -- once you go into the hospital, you lose all control over your own disease. And one of the things that some of us are pushing for now is that the

treatment needs to follow the patient into residential settings. If I am doing home dialysis, I should be able to do it when I go into the hospital. If I'm doing my medications at home and managing my medications at home, I should be able to manage them when I'm in the hospital, and not have to have my care affected by other people's noncompliance.

MS. CHALASANI: Thank you. Thank you. So, both our topic two panelists and all of our topic one panelists really talked about the whole management of post-transplant life. And while the treatment regimens played one part, we also had a lot of drug -- non-drug therapies mentioned as well. So, let's talk about those a little. I think we have one polling question, to set up the discussion. Besides the therapies mentioned previously, what are you doing to manage any symptoms you have experienced because of your organ transplantation. A, dietary and herbal supplements; B, diet modifications and behavioral changes; C, complementary or alternative therapies; D, physical or occupational therapy; E, exercise and other physical activities; F, over-the-counter

products; G, other therapies not mentioned; H, I am not doing or taking any therapies to treat symptoms. Okay. So, we have nearly 80 percent diet modifications and behavioral changes. I think we touched upon that a little bit during our topic one discussion. E, we have exercise and other physical activities. 56 percent dietary and herbal supplements, and then nearly 50 percent for over-the-counter products. So --

MS. EGGERS: On the -- can we just -- on the web, can we get?

MS. CHALASANI: Oh, sure.

MR. THOMPSON: 66 percent for dietary and herbal supplements. 80 percent for diet modifications. 24 percent for complementary or alternative therapies, or physical therapy. 68 percent for exercise. 45 percent for over-the-counter products, and 18 percent for others not mentioned.

MS. CHALASANI: Very similar.

MS. EGGERS: Okay. So, tracking very closely.

MS. CHALASANI: Yeah. Very similar. So, by

a show of hands, how many would say that collectively the non-drug therapies or lifestyle changes give you as much or more overall benefit as your medications? Okay. Let's count. My goodness. I'm going to say that was around 15 hands. Maybe 20.

How many would say that your non-drug therapies are important, but they can't match the benefit of your medications? More hands than the first one. Okay. Maybe we'll say 25 -- maybe 30. Okay. How many -- one more, show of hands. Thinking about all of your therapies together, how many feel that you are managing your condition well right now? A lot of hands. Okay. So, for you guys that have raised your hands, how do you define being managed well. In your definition, what does managed well mean.

MS. EGGERS: So, just -- for the web, he's out -- you're saying you're out 26 and a half years. You're still living. Uh-huh. Okay.

FEMALE SPEAKER: I'm out 17 years, but my basic parameter is the results of blood testing. When I actually go into the doctor, you know, I'm the same

as I'm sitting here. It's only when we get those blood results back that there's any kind of real discussion. So --

MS. CHALASANI: Okay. Other folks?

MALE SPEAKER: Defined it as, one, not being on dialysis. I don't view that as an alternative. And then second, I'm working. That's how I measure success.

MS. CHALASANI: Okay. Great.

MS. SAMPSON: Hi. I'm Leilah. I would say a lot of trial and error. And initially, after I got my transplant I was up on a treadmill like a few weeks after transplant. I was in the gym. I'm like, oh, I'm healthy again, I have all this energy. But then I'd get my blood work back, and my creatinine would spike. So, I think, you know, just even with the meds and eating right and living a stress-free life, I think it all plays a major role in how you view your outcomes of your medications. I know that when I'm eating better and I'm exercising and I'm feeling better, I feel more compelled to take my medicine, because I see an outcome and I see a hopeful life and

future for myself.

MS. CHALASANI: All right.

FEMALE SPEAKER: I think for lung transplants it's, you know, your spirometries are continuing to be good, or your biopsy -- there's no rejection. That's -- you know, there's always bumps and -- and few hospitalizations, I guess, is the other.

MS. CHALASANI: Okay.

MS. EGGERS: You said acute -- okay, go ahead. Acute hospitalization? Fewer. Fewer. Fewer. Sure.

MS. CHALASANI: I think we have -- Dan, you want to go first.

MR. BONNER: I think when we talk about success, though, in terms of nontherapies, whether it be exercising or meditation, the -- by and large, I think that comes down to the individual. There hasn't been a doctor who has come to me that has said have you ever tried meditation, having you tried exercising. There's just an innate desire that says I want to live longer. And, you know, traditional

studies will say, well, if you eat right and exercise then that will happen. So, I think that that's -- so, when we talk about success, I think you do have therapeutic success.

And then I think you have non-therapeutic success, but I think the non-therapeutic success is much more difficult to quantify or qualify, because it really comes down to each individual and how much time and effort they put in to do that. And I say the differentiation, because I've never been -- no doctor or institution has come to me and say let me put you in touch with an exercise therapist, let me put you in touch with a dietician, let me put you in touch with, you know, a physical therapist that we think would contribute to the overall longevity of your organ, your health, your life, whatever it may be.

So, I do think that when we're talking about these success factors, you -- it now becomes very individualized. And I think that you have to be sort of very specific to each individual, of how much time and effort they put in and how much success they're getting out of it.

MS. CHALASANI: Okay. I think we're --

FEMALE SPEAKER: Yes. I just wanted to say that you really have to look at management under two different conditions. One, I've known people who go through chronic and acute rejection all the time, and never ever do well. And that, to me, would be you're not managing -- you know, the drugs are not managing your transplant.

But dealing with side effects from the drugs that you take, that you knew were going to happen anyway, I think that's a matter of acceptance. You know these things are going to happen. It's part of it. And that's it. But, there's a huge difference between acute and chronic rejection type things versus side effects from medications.

MS. CHALASANI: Okay. I think, Bobbi, you wanted to --

MS. WAGER: I have to agree with Kevin in regards to -- I think we all have to define what success is to us. And I -- after my first transplant, I set goals. The kidney was working. I took my medication. I was doing fine. But I set goals. It

was like, you know, I want to become a nurse. I want to advocate for myself. I went to school. I think stuff like that, to me, is a success. That I'm able to complete the goals. But yet my health still stays good. And I can work, which I couldn't before.

MS. CHALASANI: Okay. Let's take -- yeah.

MS. FELIX: Hi. My name is Latifyah Felix. I'm 15 months transplanted. I think that when we talk about managing -- kidney, by the way. When we talk about managing, it started long before our transplants. It started during the onset of our need for any kind of transplant. So, I think it's continuous. I think that this is where the anxiety, the stressors come in. It's continuous. For those of us that are kidney patients, even if a high-risk donor was involved, there was still some maintenance -- some management that you did in order to qualify.

It is quantitative in its effects on you, whether you're setting personal goals to manage that. Indeed, scientifically your labs will show whether or not your body is in compliance. Again, keeping in mind also the mindset. Although you're not being

referred to a dietician, maybe you should be. Because we know that all together things that work good for our new bodies, to maintain our old vessel. So, I thank you for the opportunity to comment.

MS. CHALASANI: Thank you. So, I know most of you guys raised your hand saying that you believe that your condition is being managed well. Was there anyone that believed that they're not being managed well right now? Maybe what aspects of your condition these therapies are not managing well, specifically. Kevin?

MR. FOWLER: The whole point is what do we really have to compare? Right. So, I mean, that question is -- there has to be another category in there, what's the comparison. I mean, there's essentially one gold standard right now in the marketplace. And unless you have other options for patients and physicians, it's very difficult to answer that question.

MS. CHALASANI: Okay. I think we have one more.

MS. EGGERS: On the web, if you, if you can

comment. Often in these meetings it's the folks who are pretty well managed who are able to come and attend and join us in person. And at -- when we're talking about things that are not well managed, we draw -- we need to draw heavily from the web, from those of you on the web. Or, contributions to the docket. If you can share the stories of someone you know who has not been well managed, or encourage them to put their comments in.

MR. THOMPSON: I'll just add real quick that we've had a -- several people on the web wondering that exact question, on whether or not the webcast has a difference in terms of conditions being well managed or not. And several people have said that their adherence issues or symptoms seem to be somewhat more severe on a relative scale.

MS. EGGERS: Okay. Thank you. And keep those comments coming.

MS. HEFFERNAN: May I pop in for a minute? About the maintenance regime. My experience is that most doctors have no clue how to take care of themselves, in terms of basic health, and the medical

schools and that training has encouraged that. This is changing, thank heavens. But when it comes to you've been transplanted, this is great, we're focusing on all your biochemistry reactions, the mix of drugs -- time to go home. And so we go home, and we're faced with pills of drugs, how do you get them organized. And I think simple assistance with systems would help patients tremendously. I'll never forget when my husband said let's just make this card table for all the drugs, and that began my system of having a separate place to deal with my transplanted life. And therefore, to psychologically separate my real life from the life of someone who is chronically ill.

But, in terms of the additional weight on our time of taking care of ourselves despite the medications and the procedures, that's all on the patient. Nothing is documented. We're out there on our own. We're figuring it out. I see the most terrifying things on chat rooms, and I think that this is an area that needs to be developed. You're home, now how do you manage it, how do you explore things that will help you without hurting you, that come from

a complementary world.

MS. CHALASANI: Okay. Thank you. I think we have one more here.

MS. COHEN: Hi. I'm Ellen Griffith Cohen, again. I probably didn't get reflected in the 19 percent with other therapies not mentioned, because I hit the button just about the time you were tabulating it. But, both in the pretransplant area and in the transplant area, I think -- and this doesn't go to your drug development, but it goes to understanding the lives of transplant patients. That chronic disease is isolating.

Chronic disease, where you need a transplant -- and especially if there's a possibility of living donor transplant -- is incredibly isolating, because particularly people get angry because their friends say they will step up and then they don't, or their families won't step up and they get mad at their families. You become -- you know, every other one of these things is an individual thing.

The fact is that maintaining a support system pretransplant and post-transplant is a critical

therapy. It reminds me every time I am with my support system that I am important. And when I get low, or I think, you know, I don't want to do this anymore, or whatever -- and I can do that even with my transplant, because of my depression -- the reminder that I am a valued member of this society and that people care about me is a critical -- it's critical to adherence. That you take your drugs not just because of you, but because of the people who love you. My support groups include online groups, but it's also my church. I go to a transplant support group, and in fact tomorrow night we're going to be talking about spirituality and transplants. But, that whole area is so critical.

MS. CHALASANI: Oh, thank you. I think I have one more follow-up question. By a show of hands, how many of you had to change or stop medication -- a medication? Okay. I have around 20, 25. A few more went up. Okay. Why did you have to change or stop your medication?

MALE SPEAKER: As I said, the cyclosporine initially is toxic to the kidneys. And when the

kidneys started showing that, we were fortunate enough to have new medications. This is back in the -- around 2000 time frame. And so tacrolimus became the switch. Yes, it's toxic to kidneys but in a different way, or less so.

MS. CHALASANI: Okay. Thank you. One more, all the way back there.

MR. LONGINO: Kevin Longino. I'm 12 years out from a kidney transplant. I had the same issue. After about six years, cyclosporine (inaudible).

MS. CHALASANI: Okay. Thank you. And one more, and then I have a follow-up questions.

MR. GARRETT: Mike Garrett. I have -- you know, back in the stone age it was prednisone and cyclosporine and imuran, and then they got the brilliant idea to switch me over to prograf and cellcept. And I actually did better on the cellcept -- or, the cyclosporine and imuran, but it was mostly because the doctors didn't know how to prescribe the prograf, and I got very toxic for about six months because of too much prograf, until I finally found a physician who knew what she was doing and brought the

levels down. And, you know, things worked out very well since then.

MS. CHALASANI: Thank you, Michael.

MS. EGGERS: So, can I ask a follow-up question?

MS. CHALASANI: Sure.

MS. EGGERS: Those of you who have talked about your switching, or even the -- if you haven't raised your hand, what goes through your mind when it says -- when you hear that your drug is not working the way it should be doing? What are you thinking about at that moment? You hear your drug is not working. If this is a hard -- if I've asked a hard question, change the question around to however makes sense for you.

MS. CHALASANI: I think we have some --

MR. MIDDLEMAN: Hi. This is Michael Middleman again. Now that I'm an adult, and once I probably turned 15, I started reading pretty much every scientific publication I could on the medications. Because I will never, ever trust one that a physician gives me again, until I see and

believe the efficacy for myself, given what happened with the imuran change to cellcept, as a child. So, my feeling is always why change if I'm doing well. Like, don't change my medications at all, and that's my current doctor's thoughts, is everything is doing so well, there's no need to put you on another -- a different one. So, I won't do anything until I see, like, proven results of it on the market.

MS. CHALASANI: Okay. Thank you.

MR. GAMALITA: I was on -- Tom Gamalita (ph). Heart transplant, 2008. I was on cellcept and I lost all that weight I always wanted to lose on that drug, and they decided to stop it and it's there, well, God, I hope there's another drug that's going to work. I mean, that was the first thought with it. But, one of the things I've heard here, and I feel great empathy for everybody -- I'm a veterinarian, and I think you need a medical degree before you go through this stuff.

I mean, the people here that are not -- don't have that background, I feel for them because it's such an overwhelming amount of information,

understanding the drugs, how they work, what they work, alternative therapies. It's just a huge challenge for people that don't have a sophisticated level of training. And, you know, it's a lot of hard work to understand that.

And even if you have the training, it's so specific to the disease. I mean, I'm a generalist as a veterinarian. But, I certainly learned a lot because I had a 40 year warning that I was going to have a problem. So, you know, it was, God, is there another drug that will work.

MS. CHALASANI: All right. Thank you. I think we'll take one more, maybe Lindsey. Leilah, I'm so sorry.

MS. SAMPSON: No, no. Oh, you're fine. And see, I was going to talk about something else, but now to piggyback off of what he said. Actually, I was in school to be a nurse anesthetist before I was diagnosed with FSGS out of nowhere. And just that background in microbiology and anatomy, that definitely helped me as I could communicate with a lot of my physicians. And I had some knowledge. And I

really worry about, you know, what would my life have been like if I hadn't even had the small foundation that I did have to understand.

And I find that sometimes health care providers, they kind of undermine your intelligence and what they think you may be able to absorb about these medicines. And I would like to be more educated on why specifically cellcept works the way that it works, differently than prograf, just on a level that a patient can understand. Because I think that will also help us to be more compliant. Because instead of just blindly taking medicine because someone says, hey, this will work, you know, I'd like to know why, specifically, and where does it work.

MS. CHALASANI: How about the -- I was going to ask a pediatric perspective.

MS. EGGERS: Yes. Of course.

MS. CHALASANI: Okay.

MS. EGGERS: I was thinking the same thing.

MS. CHALASANI: One of our pediatric spokespeople, if anyone wants to volunteer an opinion. Or even the caregivers, maybe. What's running through

your mind, when they say that your child might have to change or stop a medication. Okay.

MR. LENNON: So, I am maybe -- probably not the only one in here who has been on cyclosporine, rapamune, prograf and now belatacept. That have been on the gamut. In addition to some of the other ones that were mentioned. And it's -- what I've come to realize, and this is how my parents trained me as part of the care team, which is the -- to look at the provider as an advisor of how to manage your care. And so, taking what they say as their advice -- this is what you should change to -- asking those intelligent questions, why should I change to this, what's the data, right, and then taking that back thinking -- you know, reflecting on and thinking about it, and then, you know, moving forward with a decision, you know, with your doctor in collaboration.

So, I think a lot of it, you know -- I know we preview the plan on all of our patients the week prior coming in. And we have our standard protocols of what we think people should be on, what these kids should be on. And a lot of times the doctors are

like, man, I don't know why that's working but it's working, don't rock the boat. Right. And then there's other times where they're like oh, my gosh, we've tried every single thing that we can possibly imagine, and we still can't get it to work.

And so, I -- part of it, I think, is just that open -- the communication between the patient and the providers. I mean, it's, it's hard to hear as a patient, but it's also somewhat reassuring when a physician says I sort of don't know what's going on, and can we try this, right, as an option. Instead of dictating what's going to happen. Can we work together to try to figure out a solution. So, thanks.

MS. CHALASANI: Thanks, Jack. Anything from the web, Graham?

MR. THOMPSON: We've been hearing a lot of very similar perspectives. Nothing else different.

MS. CHALASANI: Okay. Great.

MS. EGGERS: At this time, we're going to keep moving forward. We do want to make sure to allow for a few phone calls from people who aren't able to join in person, and who are on the web. And so if --

we're going to tee up the phone. We'll open the phone line for two or three callers in about five minutes. And what we really like to ask -- and you guys think about this too -- is what that maybe hasn't been mentioned yet if you could improve treatments what would that ideal treatment -- what's something about treatments that would improve. So -- but, before we do that we want to get a little bit of more wrap up the insight into your treatment decision-making that we've been talking about for the last few minutes. And we have a polling question to do that. We'll move to -- Graham, can you move to the next polling question? Again, another long one.

In addition to preventing organ rejection, of the factors that we have listed here which two would you rank as most important to your decisions about using a therapy to manage your organ transplantation. So, you can choose two of the following items. We understand that there are -- we would need five slides to put up all the factors that go into your thoughts. But, these were the ones that FDA wanted to know how you might think about in

comparison to one another. So, of the two, A, frequency of administration of the drug, such as twice a day versus once a day or infusion versus; B, the common side effects; C, the possibility of rare, but serious side effects, Such as nerve or liver damage; D, the possibility of interactions with medications for other conditions that you have; E, your access to this treatment -- for example, insurance coverage -- or, F, some other consideration that you think is really critical. Okay.

So, the most prevalent in the room is the common side effects of the treatment, followed by the possibility of rare but serious side effects. And of course -- and access. Which lower considerations in the room of the frequency, the interactions with other health conditions -- of course, that's dependent on what other health conditions you have, we know.

On the web, what are we hearing?

MR. THOMPSON: Sixty-one percent say common side effects. 48 percent say possibility of rare and serious side effects. 17 percent say possibility of interactions with medications. 69 percent say access

to treatment. 8 percent said other. Oh, and zero percent said frequency.

MS. EGGERS: We have covered a lot of these topics today -- I mean, already this morning. And I think we'll be talking about A, the administration issues -- how the drug is taken -- in the afternoon as well. Let me turn to my FDA colleagues. Anything on here that you would like to follow up on or ask. Okay. You guys, this has been such a rich discussion already. It's leaving us speechless. It takes time to absorb all of this.

So, then, let's turn to the -- in the room, here, think about, you know, as much time as we can take. We're going to take the hard stop at 12:30. So, you might not be able to talk about your ideal therapies. But we will try to get -- wrap -- work this into the afternoon, as well. But, let's take a few phone calls on this. And I have to say this. Operator, can we open the phone line? Can we take our first caller, please?

MALE SPEAKER: Hi there, Vanita, you can go ahead.

MALE SPEAKER DANNY: Hi, my name is Danny. I've got a question about the gentleman who talked earlier on the panel about the IV once a month. I was curious about the name of it, and the long-term effects.

MR. LENNON: Hi, Danny. This is Jack talking to you. So, the once a month infusion is called belatacept. And --

MS. EGGERS: Go ahead.

MR. LENNON: Good? Okay. It's also the -- which I believe is the sort of street name for it. It's also called nulojix. And so, the side effects, at least initially published -- and again, there's not a whole lot of long-term data on it -- but some of the effects, at least in the first year, is a higher rate of rejection within the first year of post-transplant, and then decreased rates of rejection post. And then you get your somewhat common side effects of an infusion medication, which are mostly tied around to the actual infusion itself. So, you get your headache. You get your swelling at the site of the infusion, et cetera. And if anybody has more

information, chime in.

MS. EGGERS: I -- well, we don't have to -- that doesn't have to be -- the meeting was never focused too much on the technical aspects of drugs. So, we will let that go. I'm going to assume that we -- the question was raised about infusion as a question of -- that -- of exploration, for those of you who have not done that as a possible alternative. Is there another caller?

MR. THOMPSON: Phyllis, your line is open.

MS. FRYE: Okay. Yes. I had a -- hi, this is Phyllis Frye. I'm a living donor of a recipient who has survived for 16 years post-transplant. Recently rejected. We did our transplant out of state, up near you, at Georgetown. And had to have follow-up here in North Carolina. And I'm going to make a comment as to what we can do to improve treatment, in terms of long-term treatment and what would an ideal treatment plan consist of. I would like to also add that I think we need to do more to facilitate long-term across state lines, because different transplant centers, for especially living

donor situations where we've had to go out of state and those donors may live in different states or -- the recipient could get treatment locally, and even long-term. As I said, one of the reasons my recipient rejected was simply being able to get local care at a local transplant center was way more difficult, simply because he didn't have the transplant at that institution. So, anything you could do to improve treatment for recipients locally, even if they haven't had the transplant locally, I think should be incorporated into an ideal treatment model.

MS. EGGERS: Great.

MS. FRYE: I think that should be included.

MS. EGGERS: Thank you, Phyllis. And you're reiterating a point that we've heard that has been sort of underlying all of this, is you could have the best drugs but in this case, for the organ transplant, it is the overall care and your ability to access the care and manage the complexity across the whole complicated system you're in. So, thank you, Phyllis, for that.

MS. FRYE: Yes. Thank you.

MS. EGGERS: Do we have one more caller?

MR. THOMPSON: We had somebody who submitted a question earlier who couldn't call in. Specifically about the flu shot, and wondering -- they're a senior, and they're wondering if they're on immunosuppressants whether or not they should get a regular flu shot, the higher strength flu shot, or neither.

MS. EGGERS: Well, I -- so, I will just reiterate that we - this is not a forum for giving out medical advice. So, I -- unless my panel -- we will have to leave that as a conversation between your health care provider or a health care provider.

But, it does raise -- in each question there's a point to be made, and this one raises a very important point about how do you manage even very simple things. I can just go and get my flu shot. And you have to think a lot more about that. So, we'll take that point out of the question. Any final questions? We're going to continue in the afternoon. Okay. So, let's come here to -- we'll hold this thought, and we'll go to Theresa's question.

DR. MULLIN: Well, I didn't think quick

enough last time, when Sara asked us. But in looking at the polling results, I would -- and how the common side effects of treatment were -- both on the webcast and here, the highest ranking in terms of most important to your decision -- I wonder if our patients could say more about what common side effects would you most like to avoid, that maybe you have experienced with your current therapy. But if that's the highest ranking one, is there even among those common side effects ones that are particularly high ranking. You'd like to avoid, in a treatment.

MS. EGGERS: We're going to go to the lightning round with this. So, no -- not much explanation, just name out the side effects.

FEMALE SPEAKER: Nausea.

MS. EGGERS: Nausea? Okay.

FEMALE SPEAKER: Fatigue.

MS. EGGERS: Fatigue. Here

FEMALE SPEAKER: Tremors.

MS. EGGERS: What is it?

FEMALE SPEAKER: Tremors.

MS. EGGERS: Tremors. Okay. Thank you,

Lindsey.

MALE SPEAKER: Diarrhea.

MS. EGGERS: Huh?

MALE SPEAKER: Diarrhea.

MS. EGGERS: Diarrhea. Okay.

MALE SPEAKER: Damage to the organ.

MS. EGGERS: Damage to the organ. Neurotoxicity, or damage to another organ. Okay. Hey, that lightning round worked. Okay. We have one more person who hasn't had much -- has a topic. So --

MR. RUSHACK: Yes. Thank you. My name is Mikolos Rushack. I had a bilateral lung transplant eight months ago, at HUP. And we have not really talked too much about rejections. I experienced two different types of rejections. Fortunately, very low level. Both of them are avon (ph) rejections. But the topic is very important, because the other option is either you die or you get another organ. I like to share my experience because I think it's -- it could be educational for others.

The first one I had a so-called HLA/DSA, which really means that it was an HLA type of antibody

rejection, which was level after the transplant, and the DSA just stands for, for those who don't know, donor specific antigen. And the -- if this is -- if the B cells which are producing this -- they produce sufficient number, then eventually these HLA antibodies could attack the lung, and this potentially could lead to graft failure.

So, I was very happy that where my transplant was done the -- my doctors immediately, even though my rejection level was low, immediately altered the problem. And I received a treatment which is off-label for FDA, but because it is a clinical hospital they were able to use a drug which is approved for several other uses. It is uximab (ph). And this uximab was administered four times during the month, weekly, and did a wonderful job. My level dropped from 38,000 to 2,100 over the course of like six months. And under 3,000 it means that essentially you don't really have any kind of antibody level rejection. But, it keeps going down.

So, I hope that this never comes back. Because logically, I sort of read about how it works,

and the way how it is supposed to work that essentially the immune system recognizes my donor lung right now as a friend, at least from the point of antibody creation. So, it would no longer generate those antibodies. The B cells which have been destroyed, like about 25 percent were destroyed, and the new B cells apparently are not recognizing the donor lung as an enemy.

So, what I like to do is to -- just to make sure that others have access to these kind of therapies. Because I have a feeling that there are so many hospitals which are doing transplants and they are not licensed to do this. If they are not licensed to do this and any other drug is available -- I'm not sure, but this targeted therapy -- I think this is really the future. This is the future in cancer therapy, but it is the future also dealing with these kind of rejection issues.

The other rejection I have is like at an avon, but it's a cellular level rejection and the only thing we can do is monitoring. It's just a little annoying that I have to go every couple of months. I

have to do bronchoscopy. I mean, that's a pain. If somebody could invent some other ways of monitoring, it would be great.

MS. EGGERS: Thank you.

MR. RUSHACK: Thank you.

MS. EGGERS: We've got a number of discussions that we weren't able to get (inaudible) about the challenges, and the opportunities (inaudible), and off-label products. We will make a note of that. We'll take one more quick one quick one, because you haven't had too much of a chance, and then we're going to stop for lunch. So --

MR. GHANDI: Thank you. My name is Mital Ghandi. I have -- I had a transplant six and a half years ago. A kidney -- sorry, I forgot where I am. We're talking about kidneys and hearts and lungs. It's so great to be here. So, thank you for having us. But, the one other thing I did want to mention -- in one of your questions, I know you had several, is other type of drug developments. It's not really a drug development but I have Googled it to no end but I'd love a portable creatinine monitor. And so, at

one point they are out there. And I know that the FDA has something called like a waived list of different tests that are, quote unquote, waived. I don't know what that means. But, you know, for the consumer or for me as a patient, I would love a portable creatinine monitor. At one point -- not only are they out there, but they wouldn't sell it to me because I wasn't, you know, a health care facility, either. Which I -- you know, which is ridiculous, you know what I mean. I would pay for it, or if not me maybe Blue Cross Blue Shield would pay for it. But, that's something that would definitely help kidney patients, at least.

MS. EGGERS: All right. So, we're ending on a great point. And we are going to end for lunch. Renata, please.

DR. ALBRECHT: Maybe you were going to say this, Sara, but even though the morning session is ending I think just to echo what Dr. Cox said during the introductory comments, we seriously hope that everybody can stay for the afternoon scientific session, and we've asked Sara and Meghana if even

during the afternoon we have an interactive dialogue. Because I think all of us here at the table, as well as the presenters for the afternoon sessions, really are very, very interested in hearing your comments. They've just been invaluable. You've brought up issues that probably in the back of our minds we knew were there, but you've brought them to the forefront. And for those of you who are willing to stay the rest of the afternoon, both here in the room and on the web, we really welcome you to do so. So, thank you.

MS. EGGERS: Great. And with that, we will break for lunch and we'll ask you to be back at around -- it's 1:15. 1:15.

(Off the record at 12:38 p.m.)

(On the record at 1:23 p.m.)

MS. EGGERS: Everyone, we're going to get started now. You can keep eating. In fact, I will be eating as well. It's a short lunch break. And please, another reminder, take bio breaks as you need them. This is a very informal discussion and format here. But, I'm going to turn it over to Ozlem to give a preface to our afternoon's discussion.

DR. BELEN: Hello, everyone. Welcome to the afternoon scientific session of the public meeting on patient-focused drug development, which will concentrate on medication adherence and experience with intervention.

We want to thank all of the patients, their representatives and afternoon session presenters for their time and effort. We have a very diverse group of presenters today from various backgrounds, and they are very excited about that. The afternoon scientific session will be made up of two sections, with four presenters in each one. And the first session will focus on causes of late allograft loss, and the impact of nonadherence, definitions, terms and background.

And the session -- second session will focus on interventions to mitigate on nonadherence. There will be a panel discussion after each session, with a break between the two sessions. And we welcome interactions with the audience during the panel discussion.

Our first speaker will be Dr. Peter Nickerson. And he’s going to present an overview of

late allograft outcomes and risk factors for premature graft loss.

DR. NICKERSON: Thank you very much. I want to thank the FDA for a chance to come and to share our -- some of our research that we've been doing. And I want to thank you. I've really enjoyed this morning, hearing the patients' perspective, hearing what are some of the keys issues that you're dealing with, and, in fact, many of the ones that you're dealing with are some of the ones that we're trying to solve. So, again, I want to thank you for your input. And we hope for this afternoon -- I think the panel is looking forward to ongoing input from you and help guiding us in some of our thinking.

So, I am going to focus on late allograft outcomes, and what we've been learning. In terms of disclosures, I do have some consulting relationship with Novartis and Astellas. I won't be discussing any off-label drugs.

You've seen this slide before, but essentially what it's showing us is over the last decade we've been using a combination of therapies in

our immunosuppression. Induction therapy, with T-cell depleting therapies, has become the dominant approach -- about 60 percent of our patients are receiving this in our centers. Calcineurin inhibitors -- tacrolimus has become the dominant CNI that we're using. In terms of anti-metabolite, mycophenolate, and about 90 percent of our patients receiving mycophenolate. mTOR inhibitors, rapamycin, for example, had a bit of a presence back in 2003 but it's diminished subsequently. And about two-thirds of programs are trying to go steroid-free, depending upon what type of patient they're dealing with.

So, this is where we've been for the last decade, and we really have nothing new to offer very much going forward at this point, in terms of what combinations we have to offer to patients. So, one of the questions is, well, how are patients doing overall. And this is my program in Canada, where we have almost a decade's worth of patients here -- 500 patients that we followed. We can see that half are from deceased donor transplants, and half are from living donor transplants. None of these patients had

donor specific antibodies pretransplant. We ruled that out with a cross match. And we were seeing acute rejection rates in the first year of about 11 percent. And I think this is pretty typical of most programs nowadays. And when we do death-censored graph survival, at one year 99 percent of our kidneys are surviving and at five years 96 percent of our kidneys are still functioning. So, again, I think this is fairly typical data that are coming from most centers over the last decade.

But, what we are seeing is that patients are losing their kidneys or developing dysfunction in their kidneys beyond those first few years. And this is a long-term follow-up in this cohort, where we've looked out as far as 15 years post-transplant. And we actually see three-quarters of our patients -- 75 percent -- are actually having very stable function. They're doing well on their immunosuppression. But the other 24 percent have been developing some problems. And I'm going to deal with a few of these causes.

Eleven percent are other causes, and those other

causes are recurring kidney disease. So, one of the common things we see is recurrent IgA nephropathy in the kidney. We see some isolated T-cell mediated rejections late, in about 2 percent of our patients. IFTA is another way of saying scarring or fibrosis in the kidney. We see that in about 1.6 percent. Infection in the kidney caused by a virus called BK virus, leading to kidney damage -- .4 percent of our patients. And then there's a smattering of others.

But the largest thing we've been seeing is that about 13 percent of our patients are developing donor specific antibodies against the mismatched antigens in the donor kidney at some point post-transplant. 4 percent of the time this is showing up with an acute rejection. So, this is graft dysfunction, and we detect an antibody in the blood against the donor. And 9 percent of the time this is occurring subclinically. The kidney is functioning fine, but we find that there is an antibody in the blood when we screen the blood. And these patients subsequently go on to develop dysfunction at some point down the road.

We do see death with function. We have 10 percent of our cohort in this study that had died with a functioning graft, and most of those patients -- 9 percent of them -- had died with a stable functioning graft. Now, we expect and our goal is death with function. We want you to live the rest of your life with a functioning graft. What we don't want is premature death with a functioning graft, and that is some of the issues that we'll talk a little bit about later.

In terms of the incidence of donor specific antibodies post-transplant, in our program what we see is that about two percent of our patients have developed a donor specific antibody by a year post-transplant, and by 12 years post about a quarter of the patients have developed this antibody. Now, there's other groups that have shown higher rates -- 20 percent in the first year and 5 percent per year thereafter. But again, there is some discrepancies here, I think, in how people are defining these antibodies using the diagnostic tools that we have. And I'm not going to go into any deeper detail in

that, just to say that the true incidence is probably somewhere between these ranges.

In terms of what are the risk factors for developing an antibody after the transplant, it turns out how mismatched you are is one of the driving factors. When we first did transplants -- and this is one of the first transplants in the U.S., done in 1955 at the Brigham and Women's Hospital, where they had identical twin transplants, we didn't need any drugs. These were truly identical genetically, at all genes, and so you don't need immunosuppression when you're HLA identical.

What we've learned from the UNOS database, even into 2004, was that if you are mismatched at the class 2 region, HLA DR, you're at a higher risk of having graft failure late post-transplant. So, we know that the better you're matched with your donor the better you'll do. The other thing that we've been learning about these antibodies when they're forming is that they're largely against what are called HLA class 2 molecules, the DR or DQ molecule. And HLA class 1 mismatching doesn't seem to dry de novo DSA

formation quite so much.

The other thing we found out was that T-cell mediated rejection -- so, a cellular rejection early post-transplantation, if you have this kind of a rejection, it seems to put you at higher risk for subsequently developing an antibody somewhere down the line. And that may just be relating to the fact that you're allowing the immune system to turn on, and at some point it turns on enough that it allows an antibody to be generated.

And many groups around the world now have shown this association. So, we were showing this back in 2012 in Canada. Groups in Europe, Japan, and in the U.S. have also found this relationship -- that early cellular inflammation in the graft can lead to the subsequent development of these antibodies.

One of the things that we've also been trying to do, and I think it's related to a lot of what we've been hearing, is that we want to try and minimize our drug immunosuppression. We want to try and reduce it, so that we can reduce our side effects. So, this was a study that was funded by the NIH. It

was a multicenter study in the U.S. and Canada, where we had patients enrolled who had receiving living donor transplants. We made sure that absolutely at the time of transplant they had no evidence of any memory in their immune system towards the donor. So, this is truly going into what we call a naïve immune system. We gave them what is considered standard of care, in terms of immunosuppression. They had thymo as an induction therapy, and then received tacrolimus, cellcept and prednisone. And for the first six months, these patients had absolutely no acute rejection. We did a biopsy at six months to look in the graft to make sure that the kidney was actually doing fine, and the histology here was completely normal. And we tested these patients for antibodies, to make sure that their immune system hadn't started developing an antibody against the mismatched antigens.

And then we randomized the patients into coming off of their cellcept -- or, sorry, their tacrolimus over about a three month period. So, we did a slow taper, watching them very closely to see

whether they were going to develop rejection or not. And what we found was that as we started withdrawing the tacrolimus, we started having some acute cellular rejections and we started developing some donor specific antibodies.

And this was occurring frequently enough that the DSMB, the drug safety monitoring board of this clinical trial, halted the trial. We were supposed to enroll well over 300 patients into this trial, and they halted it after 21 patients, saying this is too frequent an event, you cannot continue this trial. It's not -- we don't feel it's safe to do so. And what that taught us was that just because you're doing well on the immunosuppression that you're on doesn't mean that reducing the immunosuppression is necessarily a safe thing to do. And that's a major message that the community had to learn. And I think -- because we see patients in our clinic and we say, you know, you're doing quite well, why don't we try lowering your immunosuppression a little bit. And I think that's a slippery slope that we can get into, thinking that you're doing well and all of a sudden we

get below that level and we see the immune system is capable of mounting a response and getting activated. And that's not what we want to have happen.

We look at nonadherence, and we found that this was a major risk factor for developing antibodies. And so, in patients who had reported to us that they had been missing drugs -- that their rate of developing antibodies actually was about 72 percent at 12 years, compared to only 19 percent in patients who were taking their medications as they were being prescribed. So, this is a major risk factor that we had identified.

And the other question is well, when does nonadherence occur. And this was an interesting study out of Minnesota, where they had 195 patients start using what are called medication event monitoring systems. So, in the pill cap bottle there was a little microchip, and a time and date stamps when you open the bottle and when you presumably, then, have taken your medication. And this was an informed consent study. They told patients we're doing this to see how well you're taking your medication. And what

turned out to be true is that 22 percent of the patients had -- were starting to miss 7 percent or more of their drug doses by two months post-transplant. So, nonadherence and missing drug medication is not something that happens years after the transplant. It actually starts actually early post-transplant. And I think this just tells us a couple of things.

One, that missing your drug is a very -- is enmeshed in a very complex world. You're living your life, you're trying to remember to take your medication -- we heard about that earlier -- and life, I think, gets in the way. And it's one of the harder things, and we're going to talk a lot about how we can help try and avoid this.

But, what this translated into for these patients was that they started having late rejections -- so, a year to two years later, after the transplant they were having more acute rejections in their transplant. And by three to five years post-transplant, they were starting to lose their grafts more frequently than those patients that were adhering

with their medication regime.

When we put this all together in a multivariate analysis, where we're trying to look at what are the independent predictors of risk for forming these antibodies against the graft post-transplant, what we found for antibodies that -- HLA DR was that it was nonadherence, how mismatched you were to your donor, and if you had these early cellular rejections preceding the development of antibody. For HLA DQ antibodies, again, it was nonadherence, how much you were mismatched to your donor for HLA, and the recipient age. And what the recipient age here was was that the younger the age, the more likely you were to form these antibodies. And this was independent of nonadherence, because a lot of times younger individuals are always being said well, they -- they're more likely to miss their drugs. That's got nothing to do with their adherence or nonadherence. It's got to do with their younger age. At a younger age, you probably have a more robust immune system and therefore you're more likely to respond to mismatched antigens.

When we looked at what was going on when these antibodies were formed -- and I'm not going to drag you through a lot of this in detail, because it's going to get into a lot of what are called histologic grading systems -- but suffice it to say that 76 percent or three-quarters of our patients that were forming these antibodies in their blood actually had histologic evidence of rejection in their grafts. So, there was a good correlation between the detection of the antibody and evidence of antibody-mediated rejection inside the graft. There was also evidence in these patients of having T-cell mediated rejection, concurrently. Only 18 percent had no evidence of rejection. So, just because you have an antibody doesn't always mean that you have rejection. But certainly, the majority did. And we started to see that there was some scarring also in these kidneys by the time that we were doing these biopsies. And we think that that was probably related to the immune inflammation going on inside these grafts.

Once they form these antibodies, if we look at time zero as the time we first detect these

antibodies, if you started out having what's called the subclinical rejection, where the antibody was there but your graft was functioning fine, it took about eight years for half the patients to lose their grafts. And if you had a clinical onset of rejection at the time that antibody first showed up, it took about three and a half years before you would lose your graft. So, this wasn't a sudden process of losing your graft. But, there was a slow progression to graft loss, once these antibodies were forming, in a fair number of these patients.

When we looked at what's the strongest predictor of fibrosis and scarring inside the filters of the kidney, we saw that it was the formation of these antibodies. And when we looked at what predicted whether or not you formed scarring in the interstitial compartment, in the tubules of the kidney, we found that that was related to early cellular rejection and, again, to nonadherence. So, again, thinking that nonadherence was leading to inflammation inside the graft.

So, this brings me to the summary slide,

which is when we do a transplant -- and I'm sorry I don't have a -- well, I guess I do have a pointer -- when we do a transplant there's a lot of factors that are going into how long that graft is going to last, or whether or not our patient is ultimately going to pass away with either -- hopefully at a natural lifetime, but we know that premature graft loss can lead to premature death.

Scarring inside the graft largely relates to a number of different things, but one of them is certainly rejection -- cellular rejection or antibody-mediated rejection. And the antibody-mediated rejection is preceded by the formation of these antibodies. And the degree of mismatching between the donor and the recipient is really what's driving the immune system to go forward. We try to counteract that by giving immunosuppression, but the immunosuppression itself has some toxicity, as we've been talking about, and it has side effects that put you at increased risk for metabolic problems, like diabetes, infection or tumor. And we can have recurrent disease or infection in the graft, and we

have also the comorbidities -- the illnesses that everybody has prior to developing their end organ failure that can be contributing to the outcomes. We know that nonadherence acts, as our inadvertent minimization of immunosuppression, can lead to acceleration of the immune response towards the graft. And so this is why we've been focusing a lot on nonadherence and minimization -- avoiding minimization inappropriately.

What are the keys to the future? Well, I think one of the keys is for us to think about how can we match better. When we have an organ available, how we can dial in tissue matching beyond what we're currently doing now, to try and -- if we were to do that, it would decrease the drive for this rejection response, which would mean that we could use less drug. That's one strategy going forward.

The other key is how do we actually understand better what is nonadherence, what leads to nonadherence, and how do we help the patient avoid nonadherence.

And then the third thing is we need new

drugs that have been immunosuppressive profiles with less drug toxicities and side effects, as we've been discussing already today. And with that I'm going to stop. Thank you very much.

(Applause).

DR. NICKERSON: Our next speaker is Dr. Rita Alloway, who is a research professor of medicine and director of transplant clinical research at the University of Cincinnati. Rita.

DR. ALLOWAY: Thank you. First, I would like to take the opportunity to truly thank members of the FDA and the patient community on behalf of the transplant professionals, for the spirit in which you have come today, in allowing us to better recognize the issues that are very, very important to you. And even though we know it, it helps to hear it yet again. I am going to lead in the next discussion in terms of talking about the aspects of nonadherence, focusing on definitions and identification, and also looking at the detection and risk factors.

In terms of financial disclosures, within the last 12 months my institution has received several

clinical research grants from a variety of sponsors of a variety of studies in transplantation. I'm on the advisory board for Genzyme-Sanofi and on the speaker bureau for Veloxis and Sanofi. This presentation does not include discussion of off-label or investigational use of any drugs.

So, the objectives I want to focus on today is to differentiate between medication nonadherence and compliance. I want to identify risk factors for nonadherence in solid organ transplant recipients, and I want to describe the measures to quantitate medication nonadherence. As we all know, medication nonadherence is an age-old problem. Hippocrates was actually credited with a statement in 500 B.C., "Keep watch also on the fault of patients which makes them lie about taking things prescribed." And as not to offend anybody's religious beliefs, I might want to offer -- this may -- noncompliance may have actually started with Adam and Eve, when she took the bite of the apple. But, we won't go there.

C. Everett Koop in 1985 went a little step forward, in basically trying to explain the

variability that we see in drug responses. Why does the drugs not work the same in all patients? And basically, he said “Drugs don’t work if people don’t take them.”

Now, I think that typically nonadherence, especially when we describe this to you as patients, sounds like a very negative connotation. But, I want us to let down those barriers and encourage you to believe that we understand why you are nonadherent sometimes. However, we are still here to try to help you and hopefully develop things in the future that will improve this. And I think what’s evident in transplantation is that we can no longer accept the status quo of any nonadherence that is occurring.

And to follow up with one of Dr. Nickerson’s quotes, as it -- as he has said many times before, is our first shot is our best shot for transplant success. I know many of you here today have talked about having the beautiful medical miracle of multiple transplants. But really, our first shot is our best shot. For biologic reasons, as he discussed, with the formation of antibodies, to the additional

comorbidities that come as we begin to add on the stronger immunosuppressants that you take with each transplant. Unfortunately, despite millions of investments -- of dollars in investments, we don't have a magic drug or procedure to render adherence irrelevant that is currently on the horizon. So, what are we going to do for the next generation of transplant recipients?

And hopefully, adherence does not continue to be neglected in the therapeutic process, and -- to such an extent that federal mandates may be necessary to properly resource adherence and symptoms. We want to provide the resources to facilitate good medication adherence.

Now, there are a variety of terms used to describe taking your medications appropriately. Two of the most common terms are medication adherence and medication compliance. Medication adherence is the extent to which a patient takes medications as prescribed by the health care provider, while compliance is described as more of a passive act of the patient following the provider's orders.

In a 2012 publication in the British Journal of Clinical Pharmacology, they have a really good summary article about the taxonomy and definitions of medication nonadherence. And while they fundamentally believe that these two terms are interchangeable, they feel like compliance focuses too much of a passive act of the patient, basically following specific directions that the provider may have given to them, while medication adherence connotates a more collaborative approach, with the patients and the health care providers. And hence, the words medication adherence have now become kind of our go-to terms, at least as present to discuss this concept.

And medication adherence is a behavioral process that is influenced by many, many factors, many of which we've heard today. It assumes that the patient has knowledge, motivation, skills and resources to follow the health care provider's prescription. Medication nonadherence can fall in two different categories. There can be intentional medication nonadherence, which is basically an active process by which the patient chooses to deviate from a

treatment regimen, or unintentional medical nonadherence, which is more of a passive process where patients may be careless or forget about adhering to their treatment regimen.

Now, the World Health Organization defined five dimensions of adherence, and these dimensions included health system or health care team factors, social or economic factors, condition or comorbid disease factors, therapeutic or medication factors, and also patient-related factors.

Our next speaker, Mary Amanda Dew, has basically published in 2007 a meta-analysis, which basically reviewed the literature that was available at that time, to look at the specific factors that had been reported in transplant recipients and categorize them in these dimensions. In terms of the social economic factors, younger patients, male gender, non-Caucasian, non-U.S. residents, poor social support, poor transportation and literacy were common factors that were limitations in terms of the social and economic factors.

In terms of the therapy or the

immunosuppressive factors, complex medication regimens, higher medication toxicity -- as we've clearly heard -- lack of medication education systems, and lack of pillbox or reminder systems were therapeutic-related factors that are common in transplant recipients.

Patient-related factors were that a history of nonadherence tended to predict the future nonadherence with the immunosuppressive regimens. Adolescence, psychological disorders -- as many have discussed today, related to depression -- cognitive impairment, substance abuse and negative beliefs of the medications were contributory factors to nonadherence.

Condition-related are basically high symptoms of distress. And I think, again, it's a common theme that we've heard today. The new disease that you have of immunosuppression is a stressful disease. And it's something that you must manage. Also, we heard loud and clear development of new onset diabetes, or basically diabetes that occurs in you after you're transplanted that you did not have before

transplant. And also, your increased time post-transplant.

Health care system factors, such as medication costs, poor access to medication, poor aftercare planning, poor physician patient relationship, and poor physician communication again related to the health care system and health care team factors that led to nonadherence.

So, when you -- any time you do a risk assessment analysis, you want to look at all these figures and -- factors, and attempt to differentiate which of these factors are modifiable and which ones are not. Any of these factors in which are modifiable, we want to try to develop a system approach to address these.

However, as we're focused today on patient drug development, you have to understand that for us to really have an impact on drug development from an adherence perspective, we've got to be able to measure at least pharmacoadherence -- your adherence to your medication -- in a proper way. When you attempt to measure pharmacoadherence, you have objective

measures, which may be direct and provide evidence that medication has actually been taken and consumed. Examples of that are actually direct observation, and we have one drug available in transplantation where we do that routinely.

We have indirect measures of adherence, such as providing evidence suggesting that medication is being consumed or taken, such as pill counts, tacrolimus drug levels, pharmacy refill records, medication possession ratio, and then lastly, subjective measures, which provide testimony that the medication has or has not been taken, often by self-reports or assessment of others. So, in terms of direct observations this is -- basically has the advantage of being objective, highly specific and non-invasive. However, there are disadvantages. Feasibility issues, they're very labor intensive, they're not practical, they may be expensive, and they're not actually an option for all transplant recipients.

Drug concentration monitoring, which we are very fortunate in transplantation, really since the

development of calcineurin inhibitors, to have drug concentration monitoring available to us. The advantages of this are its objective, it's part of our standard of care, and direct assessments of whether the patient has taken the medication, at least during that short period of time, is available for us to review.

Disadvantages are that this is really just a snapshot of the behavior of what's going on as we look at these levels. And unfortunately, it can be affected by a variety of factors other than pharmacoadherence, such as the way you metabolize or get rid of a drug, a drug-drug interaction, a drug-food interaction, and poor absorption. And I think that historically, before the broader understanding about all of the factors that impact drug level monitoring, we tended to maybe, quote unquote, assign nonadherence to a lot of the variability that we saw which may be attributable to other factors. And even though it's a very, very good marker and we can understand if the drug is in your system, there are a lot of other factors that we have to consider. It's

also costly, and it's an invasive test.

However, some more novel approaches have recently been introduced to look at the tacrolimus level variability, instead of just a single snapshot. And without going into the complexities of the study, basically patients that had a higher tacrolimus level variability over time, as measured here by standard deviations, basically were associated with negative risk factors or negative outcomes, such as late acute rejection, transplant glomerulopathy, which is a negative biopsy finding that's previously been described, or total graft loss. And even when we excluded death with function, variability that was associated in the tacrolimus levels that we monitored still predicted these negative long-term outcomes.

Another form of monitoring is actually electronic monitoring. It does have advantages of being objective. It can indicate the date and time a bottle or pill box has been opened, providing you a real-time tracker. With this specific information, it also can detect poor pharmacoadherence with the dosing schedule. So, for example, you may do very well with

your morning dose but very poorly with your evening dose. And it allows us to get an idea of what is working and what isn't working in regards to your medication regimen.

The disadvantages are cost, among other here, and basically it assumes that medications that are removed from the bottle are actually taken. Strategies to impact nonadherence have been incorporated into some recent publications, again focusing on the electronic medication monitor -- the MEMS system that Dr. Nickerson previously described. So, for sake of time I'm going to skip over this.

One of the other measures that we have of medication adherence are refill or pharmacy records. When we actually take the records from the pharmacy of the number that was dispensed, the date and time that was dispensed, and the dosage you may be taking to provide objective standardized data to identify patients who may not be adherent, the disadvantages of these systems are possible misinterpretation of the use when making dose changes, which are very common in transplantation, as you know, and that's one of the

real limits -- especially with tacrolimus -- of us effectively using these records. It assumes that prescriptions are filled or actually taken. It assumes that all sources of medication are captured. And that there is increased complexity when there is using multiple pharmacy records.

This data has actually been translated to a medication possession ratio or proportion of days covered, and basically used this formulas to estimate the adherence to chronic medication. Now, what is very frequently brought up in transplantation is while we tell you you must be a hundred percent compliant all the time, we really don't know what the optimal medication possession ratio is for any of our known immunosuppressants to date. And then there are self-reports, which I'm sure many of you have been asked to fill these out. And these can be, unfortunately, quick and inexpensive but unreliable. But if you think that the self-reports are unreliable, you should even see how worse reliable the clinician reports are that we provide. And we may think it's simple, quick and inexpensive, but it is highly inaccurate.

So, in summary, these -- an article -- chapter published recently in Clinical Transplants, by Dr. Tiffany Kaiser (ph), summarizes these methods to monitor immunosuppression and focuses on many other aspects of nonadherence. So, in terms of quantitative nonadherence, there are many measures of pharmacoadherence that are applicable to transplantation. However, there is no single perfect measure of pharmacoadherence. Multiple measures of pharmacoadherence are optimal to provide an accurate adherence assessment, and this is going to be necessary for us to introduce it in the future of drug development for transplantation. Okay. Thank you very much.

(Applause).

DR. ALLOWAY: Our next speaker will be presenting the prevalence of nonadherence after organ transplant, and it's Dr. Mary Amanda Dew. She is professor of psychiatry, psychology, epidemiology, biostats and clinical translational science. She is the director in the clinical epidemiology program at the Western Psychiatric Institute and Clinic at the

University of Pittsburgh School of Medicine. Dr. Dew.

DR. DEW: Thank you, Rita. Well, I'm really humbled after hearing all of the comments of everyone this morning. So, I hope that what I will tell you will be informative, and I think that actually some of the evidence really supports all of the things that you've said, and you might be pleased to know that some of it has appeared in the scientific literature, so that other health care professionals may have been forced to read it. So, on that note I'll begin. But only if I can make this move. Okay.

So, when we look at prevalence we're talking about counting things. And counting can be pretty boring. So, why do we have to count how many people are nonadherent. We need to know exactly how common nonadherence is in order to estimate -- in order to look at the scope of this problem, to estimate how many people are likely to have trouble with various elements of the regimen. And we need know how common the exact prevalence, in order to design and test interventions that are targeted to the right people and are cost-effective. So, adherence is really a

bread basket of different activities. It's not just taking medications after transplant. You all have spoken about the various other things that are required after transplant, and there are many things. And that's part of what makes this a complex problem.

There are two ways to study adherence. You can look at it from a quantitative perspective, where you ask patients to report on their adherence. You can use biologic measures -- all the approaches that Rita was just describing. Or you can use qualitative measurements, where you rely on patient descriptions of how they manage their problems and what kinds of problems they experience. And in fact, there are many studies within both of these categories, and there have been now several definitive systematic reviews that have tried to summarize all of this evidence so that we can have an overall picture of the nature of this problem. So, I'm going to talk about those reviews today, because there are too many individual studies to make sense of them on their own.

So, our group in Pittsburgh did three systematic reviews. We did three meta-analyses, and

we focused on post-transplant adherence to all areas of the regimen. We looked across all types of solid organ transplantation, and so we examined adult general transplant samples. We looked at a subpopulation composed of people who are transplanted after histories of substance abuse, which is quite common, for example, in liver transplantation. And we looked at pediatric studies as well.

So, this shows for the adult and pediatric studies there were 147 studies of adults, and that's on the left. And you can see that most of them involved kidney recipients, which makes sense because that's the most common type of transplant. And then heart and liver recipient populations were the next most common.

In the studies of kids, kidney recipients also were the most common, but liver was the second most common. And these studies came from all over the world, but primarily from North America and Europe. And then the studies that focused on relapse to substance use were mostly in the liver population. So, this slide shows, then, the distribution of areas

of nonadherence that were considered in these studies. And the length of the bar means more studies were done. So, the issue of taking medications has been most commonly looked at, and you can see that the bar is about half and half green and blue. The pediatric and adult studies were about equally as common. But, for the other areas of the regimen that you can see down on the left-hand side of the slide, there's been much more study of those problems among adults than among pediatric recipients -- even though many of those areas are equally important for the pediatric groups too.

I'm going to walk through this slide because this shows the key results from these meta-analyses. So, you can see on the left the different areas of the regimen. And then these numbers are the estimates across all of the different studies combined. So, if you look, for example, at this first group, if you saw a hundred people during a one year period after transplant -- it might be the first year, it could be the tenth year, whatever -- you would expect to see 3.4 percent of them go back to using tobacco during

that one year period. With alcohol, it's 3.6 percent who would go back to using alcohol at levels higher than were prescribed. So, these problems -- substance uses of different types and attending clinic appointments -- are relatively low. They're on the left-hand side of the slide. So, not that many patients have trouble in those areas.

These ones down at the bottom are the lifestyle kinds of activities. Patients are told they should exercise, follow certain diets, have blood work and tests and so on. These are more common, so up to 25 percent of people seen within a 12 month period would have trouble with their diet, for example. And then unfortunately, taking immunosuppressant medications was up in -- among -- it's like the lifestyle things. It's a little bit more common than we would hope. So, about 23 out of every 100 people seen during a year would have trouble taking their medications that would rise to a level where they would be considered nonadherent.

Then, adding on the pediatric information -- what I just described you was for adults -- described

to you was for adults. The pediatric rates, then, are shown in green. And you can see that generally the rates are lower. It's important to note that this includes all age pediatric samples. So, you know, you know that parents have a big role for younger kids. Nonadherence to medications goes up a lot among the adolescent group. So, that's one important distinction here. But overall, the rates tend to be lower in pediatric groups.

So, then, what are the risk factors? We tried to look at them across all of the studies in our analyses, and actually we could not look at very many because very few studies have looked at risk factors. They often will report on rates of nonadherence, but then not go very far beyond that. But in our meta-analyses in adults, we found the ones that are shown on the left-hand side of the slide -- for example, for immunosuppressants, nonwhite ethnicity, having poorer social support and poorer perceived health were linked to having nonadherence problems. But the important thing is that those linkages were relatively weak. The size of these effects were small. It's not like

they were the major factors that anybody would point to and say, oh, I've solved the problem. Just focus on this factor. The only one that was really important was that people with pretransplant histories of substance abuse are more likely to have problems with that post-transplant. But you would expect that, because that's the nature of addiction. So, that just goes hand in hand with that kind of issue.

For kids, we couldn't look at nonadherence by specific areas because there were fewer studies. But we did find that in general factors like the stress of the parents, the behavioral functioning of the child, and the distress of the child were relatively important. But again, the sizes of these effects were relatively modest, which means that we can't point to a single factor and say that's the cause of the problem for everybody.

Now, I mentioned initially there's also been qualitative information. And in these qualitative studies, the investigators focus on trying to capture what the recipients tell us in their own words about the medical regimen, as well other areas of

transplantation. And if you look up these three papers, at the bottom of the slide the dates should be 2009, ’11 and ’16. So -- in case you’re interested in finding those papers. They focused primarily on kidney recipients, and they have looked at adult recipients as well as adolescent recipients.

So, in these qualitative systematic reviews, they found that looking across this whole body of qualitative literature, there are quite a few studies that have tried to look at this and get the patients’ own words. The first important theme was empowerment -- that patients want to gain a sense of control over the regimen, and many people here today have mentioned that. The importance of being able to manage, being able to organize, how a person can organize, who can help -- so, these are two illustrative quotes. “I discovered the possibility of maintaining control, even if you have to ask for help.” So, they didn’t have to do it all by themselves, but they could manage. “I’m good at planning ahead. I got this chart, this box I refill once every week.”

A second theme was fear of the consequences. And

you all have also discussed that quite a bit -- fear of graft loss, fear of adverse effects, and defining what is an acceptable risk that they can live with. So, one person said, “I do think we walk on a knife-edge all the time and you can just fall off of it [and lose the transplant].” And this person was talking about the difficulty of trying to have a life and manage all of these things, and the fear that it wasn’t going to work.

Then another person said, “To find out that I had cancer [due to the medications] would probably be more devastating to me than having kidney failure.” So, for that person defining an acceptable risk was that they had an overriding concern about cancer and that concern was greater than their concern about the loss of that graft.

A third thing was managing regimen demands -- forgetfulness, side effects, lifestyle disruptions. So, people like you have said things like, “The hardest thing is if you are someplace new or doing something new and remembering to take your medications.” Another person said, “I really had to

push for a [medicine] change because the doctors didn't think [that hair loss] was kind of a relevant thing to worry about." So, these lifestyle disruptions can be things where the patients do have to push their providers to convince them that this is important to them -- this is part of balancing what it means to have a transplant and go on with their lives.

A fourth theme had to do with overmedicalizing life -- fatigue at being a patient or self-management burnout. One person, who was very demoralized, said, "You can't call it living a life. I'm still living like a patient. I can't do the stuff I wanted to. I'm just dead!" So, that person really was burned out at that time.

Someone else said, "I was doing really well. I started thinking. I don't need all those pills. I just stopped taking them [little by little]. I was tired of them, they made me feel like a sick person. Then, of course, I went into rejection." So, the person realized that that wasn't the best choice, but they did it because of their other concerns and feelings of distress.

The fifth theme was social accountability and motivation. And I think many people have expressed that theme here today, as well. "This kidney was given to me by my wife. I have an obligation to take good care of this kidney." "You can't forget [your meds]. I'd be afraid to face my [doctor] if I did that. They don't say much but it's the way they look at you. You know they are disappointed in you." And all of us have been a patient, and I've said that to my husband -- my doctor is going to be disappointed.

So, the authors of those systematic reviews felt that those themes really were then reflected in five different kinds of behaviors that were observed and that patients talked about when they did these interviews. First, on the left, was not taking medications -- just refusing. Sometimes they refused. Sometimes it was inadvertent -- it was forgetfulness. Sometimes it was side effects. But that fell into the nonadherence level of behaviors.

On the other side is total adherence, where people are extremely vigilant. And I think many of

you who are here today are motivated by your extreme vigilance and by the fact that you've been able to master this and that you're hopeful that you can help other people to rise above some of these problems and maybe address some of the problems so they can master the regimen as well.

Then, in the middle is maybe where many patients lie. They want to be completely adherent, but they may be changing doses to minimize side effects. They may forget a dose. Or they may vary the timing of doses inadvertently due to other lifestyle factors. So, in general, then, what can we conclude from all of these reviews of the quantitative and qualitative literature? Nonadherence occurs relatively often. The rates are higher in adults. They are lower in kids, but if you want to look at the areas of greatest problem it's clinic appointment attendance.

Nonadherence is modestly associated with psychosocial risk factors -- the things that I showed you on that one slide. But, a limited range of such factors have been considered, and the effects are not

large. Patients most commonly voice the need to take control of their regimen but not let it control them, concerns about adverse effects and motivations for following the regimen, and that is what you have said here today. So, that -- it appears in the literature too, and I think that's very important that it's gotten into the literature.

And finally, if those of us who are professionals and work in this area would take time, I think, to attend this kind of meeting we could listen and then maybe generate some new ideas for better ways to address this problem. So, thank you.

(Applause).

DR. DEW: So, I'd like to introduce Robert Ettenger, who is a distinguished professor, emeritus, the department of pediatrics, division of nephrology, at the Mattel Children's Hospital at the David Geffen School of Medicine at UCLA.

DR. ETTENGER: Thank you very much, Mary Amanda, and thank you both to the FDA for inviting me -- I'm humbled to be here in the presence of so many, you know, real luminaries in the area. I'm just a

pediatric nephrologist. But, I most of all want to honor all of you who are going -- who have really shared with us today a lot of what it really means in transplantation, and something that we physicians really sometimes unfortunately lose a bit of sight of, as to the challenges that you're going through as well as the successes that you've had.

I'm going to -- I want you to focus today -- I'm going to try to go relatively quickly. So, I'm going to ask that you focus, when you do, on those things that are highlighted in red, because those are the important things that I want you to see about with regard to how adolescence and pediatrics differs from what you've heard so far.

Many of you do not know how to define adolescence, and allow me to do it as a pediatric nephrologist. Adolescence is the age at which dad becomes a two syllable word -- where they go, "Dad." So, just thought you'd -- you just might want to know that.

Adolescents have the best one year graft outcome. This is data from the NAPRATICs (ph)

database. But patients who are transplanted age 11 to 17 years of age have the worst five year graft survival. And most have attributed this in large part to the issues of medication nonadherence in adolescence.

After the first post-transplant year, adolescents have the highest graft failure of any age group. Now, this is a seminal study by Beth Foster in 2011. And what this is showing -- and let me address this specifically to this area right here, because this is the relative risk of losing a kidney allograft at a specific given age. Not when you were transplanted, but at a specific given age. And as you can see on the slide, things start to get bad at age 10, 11, 12 years of age, and then continue to go up to where they hit the maximal graft loss in the late teens and early twenties. This is true whether you count or don't count the first year of graft outcome. The point of this is that it's the age at which a patient is that really seems to register with graft failure. So, our patients who were transplanted as adolescents, they will tend to do badly. But,

patients who are transplanted as young children we expect will transit through adolescence, and those patients are equally at risk after a period of relative quiescence.

The graft failure that we see is most often due, as Peter said, to antibody-mediated rejection, likely secondary to medication nonadherence. And this is important. The donor specific antibodies that Peter discussed that are generated during adolescent graft failure due to noncompliance lead to ultimate prolonged waiting times for a second graft and subsequent poorer retransplant outcome. So, the first kidney is the best kidney, and we really need to pay a lot of attention to patients who are in their adolescents, because this is going to color their experience for the rest of their lives, if in fact they do develop donor specific antibody.

The prevalence of medication nonadherence in pediatric transplant recipients is shown here. And you can see that for liver and heart it's in the 30 to 32 percent range -- I'm sorry, liver and kidney, 30 to 32 percent range. Heart is a bit less. But when you

look at the percent of patients -- and this is data that I'm showing you here for renal outcome -- less than ten years of age it's 22 percent. Greater than ten years of age, 43.2 percent -- showing you how much more adolescents are at risk.

These are the selected factors associated with medication nonadherence in pediatric, but shown in red are the adolescent transplant recipients. And specifically, there are issues of low self-esteem, patients don't like to carry the medications with them and look different. Adolescents tend to have a busy lifestyle, and are sometimes disorganized in terms of being able -- and forgetful in being able to remember to take their medications. We've heard a lot about the psychological issues this morning, that may afflict patients, and this is certainly true in adolescents. We'll talk a bit more about those psychological issues of depression, PTSD, anger and denial a big later on. But, poor coping mechanisms can very well be seen in adolescents, who are not particularly good at coping anyway. And then finally, there are issues of social skills -- poor social

skills, deficient social support and reluctance to admit to friends or peers that in fact they have a transplant.

So, this is an MRI of -- busted. These are the unique psychosocial and developmental aspects of adolescence. You can see, this is the adolescent brain. The love lobe, the rebellion center -- all of you see this. I want to direct your attention to this area right down here -- right over here -- memory for chores, homework. And we have actually mapped nonadherence and meds. We have scientifically mapped this -- not. Thank you for that. Can I get a -- okay.

(Applause).

DR. ETTENGER: So, what are some unique psychosocial and developmental aspects of adolescence that impact nonadherence? Well, three prominent characteristics of adolescent behavior are risk-taking -- just think back to your own adolescence -- increased sensation-seeking, and the move away from parents to greater peer affiliation. As I've shown in red, that is an important point that we need to be

addressing. With regard to patient's cognitive and emotional neuronal networks, patients -- adolescents develop differently. Their emotional system circuitry develops earlier. The prefrontal lobe circuitry, which is the executive functions, the -- able to abstract -- that develops later. And the prefrontal lobe circuitry is necessary for executive functioning, which means abstraction, long-term planning, attention, response inhibition -- adolescents don't do these things well because they haven't developed the appropriate circuitry yet.

Finally, there's the issue with the adolescents -- the need for separation and individuation -- and adolescents will tend to experiment to see which values of patients they will adopt. Adolescents will question authority. And the question always is what happens if meds are missed. If there are no immediate consequences -- as we've heard this morning, well, I can get away with it now, maybe I can get away with it, you know, a bit later. And thus, the medical team -- the docs who say don't miss your medicines, we lose credibility when

adolescents are nonadherent without consequences.

Shown here is a scale called the barriers to adolescent medication adherence, which is actually quite a useful tool. I've listed four barrier types, but in red I think the important barriers for adolescents -- that I'm showing in this slide -- are, number one, that -- the adolescent reported barriers, almost 30 percent reported forgetfulness. Like not paying attention, I'm completely out.

Also, poor planning or poor scheduling. And notice that parents notice this even more than the adolescent -- 68 percent of parents reported that their adolescent transplant recipients had problems with planning, and 58 percent of adolescents reported that.

Now, with regard to the barriers of adherence, in the interest of time I'm going to direct you to the area in red. Barriers reflecting disorganization are not planning ahead and the desire to avoid others observing you taking your medications is a major issue. The kids don't want to be found out. This will lead -- is strongly associated with

medication nonadherence, and with emotional distress such as -- as I mentioned, anxiety, depression, et cetera. These in turn -- these emotional distressors are correlated with medication nonadherence. So, it's a cycle. And so, the more that these barriers are showing up and we can assess them, perhaps the better we can address them prospectively to keep kids from going on.

The barriers tend to remain stable over time, but poor adherence to medication is associated with a series of these barriers that can be measured during the time of transplant, and it's one of the ways now we're using in the clinic to assess how much we have to worry about the kids.

What about measuring adherence in adolescents? Directly observed therapy can become cumbersome and contentious between parents and adolescents. The kids don't like taking the medicines in front of their parents. So, directly observed therapy is an issue. Success with indirect measures, such as drug levels, is something I'm going to show you just a little bit, to how we can perhaps pick up

nonadherence early.

Electronic measurement systems seem like a good idea, but they can be limited if patients don't want to bring a separate electronic container or smart pillbox with them. And finally, self-report instruments are particularly limited in adolescents.

This is the results of a liver transplant study by Al Shemesh, et al, called the MALT study. And basically, the point here is that if patients have a -- if children have a large variability in their tacrolimus levels, they're more likely to have liver transplant rejection. So, these are a robust predictor of late allograft rejection, and following this in the clinic can inform our ability to hopefully head off rejection and address the nonadherence.

Finally, this is data that we have just published that's still not out in print, but is on the internet. And this slide shows patients with high levels of -- high coefficients of variation for combinations of both tacrolimus and sirolimus shown in the red circle. Those patients that are in this area are patients that have very high variability in

both their tacrolimus and their sirolimus levels. Previously, we have also published that high tacrolimus levels in and of themselves predict rejection. But importantly here, what this data shows is that in patients that are on this duel therapy you see that rejection is significantly higher when they have these high coefficients of variation for both tac and sirolimus, that self-reported nonadherence is very high, and most importantly, pursuant to what Peter said, the donor specific antibody is significantly higher in those patients. Those are going to make a problem for long-term outcome and for subsequent grafts.

With that, I have hit my time and I want to thank you all for your attention. And I'll turn the podium back to the moderator. Thank you very much. (Applause).

MS. EGGERS: Okay. Again, Sara Eggers. I got tasked with continuing on. They liked so much what we did in the morning that they want the same sort of facilitation in the afternoon. But, to everyone here, this is an experiment. But, I think we

can do this well.

Before getting in, I would like the folks -- the presenters -- the panelists up here who did not present, if you could introduce yourselves so that we know -- so -- yeah.

DR. CHISHOLM-BURNS: I'm Marie Chisholm-Burns. I'm the dean and professor at the University of Tennessee health science center, at the college of pharmacy in the department of surgery, at the medical school.

DR. FITZSIMMONS: I'm Bill Fitzsimmons. I'm with Astellas Pharma, global development.

MR. LONGINO: My name is Kevin Longino, and I'm the CEO of the National Kidney Foundation. I'm also a kidney transplant patient for 12 years.

MS. EGGERS: Great. We asked Kevin to be up here to serve as a voice representing and reflecting the broader patient community. And so, you can jump in at any point reflecting that. But we also have you here in the audience to provide the individual context of it. If there are any folks still on the web, feel free to pull in comments as well.

So, there are three discussion panels. And I understand we get to -- we can go to 3:00 with this. The one person signed up for open public comment. If you can come find me at the break, and we will discuss something. So, we get to go until -- for 30 minutes on this. And we have three questions to get through. And I think how it's going to be best to try to do this is a little bit of that lightning round format that we did at the end of the topic -- the morning discussion, where let's take the first question, how well do we understand the extent of nonadherence in patients post-transplantation.

We had four wonderful presentations that, I have to say -- I'm going to speak, I think, for my colleagues as well. They were so well-coordinated. Thank you for that. They really flowed together very nicely.

We heard a lot from you about the extent of nonadherence and the type, and I think by type I'm going to interpret this is the whys of nonadherence. Is that a fair interpretation? So -- how much is it happening and why is it happening. And I'm going to

ask just the panelists -- maybe we'll start with those of you who hadn't yet spoken.

Do -- let's change it -- all the things you've heard or what you're -- in your research, what concerns you the most? And just briefly describe that concern, either about the -- probably about the type of adherence, or how well we understand the extent of adherence. So, for example, it could be the aspect of wanting to live a normal life or other factors that have really resonated with you of concern. And then we can get some discussion going on those factors. Okay. My -- did the experiment sound -- make sense? So, let's start with -- I'm going to put Marie -- if you could, what surprised you -- what concerns you the most when you think of the types of -- why nonadherence is occurring.

DR. CHISHOLM-BURNS: I think what concerns me the most, especially at the beginning when I started researching this -- probably about almost 20 years ago, now -- is that how complicated it can be and how individualized it really is. And I think that that's what we heard this morning, from the recipients

here -- how complicated and how individualized. And with the complication, how much sometimes us in the health care profession -- it's hard for us to pinpoint or even slow down to recognize it, as well as having the time to do it. And how we need a multidisciplinary team to help with that, and how we actually really, really, really need you guys to tell us about that.

MS. EGGERS: Okay. All right. William, do you have any thoughts? What concerns you? What's resonated?

DR. FITZSIMMONS: Sure. Rita mentioned the difficulty in defining what's the critical level of adherence that's necessary. And I think that's an important component. Because we all say we would like perfect adherence. But, it -- none of us are perfect from that perspective. But, is taking 80 percent, 90 percent, 50 percent of your medications -- and this morning someone mentioned it's not always going to be every 12 hours, can I go plus or minus an hour around that -- two hours, three. We don't have answers to those questions and those are really important ones.

MS. EGGERS: So, both knowing it and then being able to communicate it back to the people living with the organ transplant, so that they're not making up their own sets of rules about, well, I think I can go -- 90 percent is okay. Maybe it is. Maybe it's not. Uh-huh. Kevin, anything?

MR. LONGINO: Well, I -- there were so many good things that were said this morning. It's really hard to add to that. But, I think -- I think the point that was just made is true. I think a lot of patients try to make their own guesses as to what's tolerable and what's not. And it would be important to know those things.

I think in terms of compliance, one of the things I haven't heard us talk about -- we talk about medications that have to be taken on the spot at 12 hours. But it's not just that. It's oftentimes you have to have an empty stomach for two hours and an empty stomach for one hour afterwards, and then if you make a mistake there then it throws off the rest of your day. And so, what happens if you did have a cookie accidentally and it's now inside of your three

hour window -- is that okay? Do you take your medicine at the regular time or do you -- or what? And nobody seems to have answers to that, and yet that's a big factor in the compliance. And adjusting just the logistics of the lifestyle.

MS. EGGERS: Okay. Thank you. A rich amount of considerations. So, let me turn it to the audience, and on the web feel free to comment. Take one thing that you've heard, and say let me tell you why that's such a challenge. Or let me tell you why that's not a challenge for me. So, we'll -- and we're not going to be able to take all the comments that we want to, but we'll hope to --

MS. JEFFERSON: A really quick thought -- thing I thought about earlier.

MS. EGGERS: And your name?

MS. JEFFERSON: Nicole Jefferson.

MS. EGGERS: Nicole.

MS. JEFFERSON: Most of us here are here because we're passionate about our organs and we want to keep them. I think a lot of the issues with nonadherence comes from people who don't really think

that much about their organs. And those are people who don't have a support system, don't have the family. So, I think the families being a part of the doctor's appointments is a very big part, because if you -- if a family member doesn't understand that it's important for me to take these medications, I may not remember and they may not understand why they're important. So, I think we have a good grasp on taking -- on our meds, and understanding it. But it's the population to there, especially in my community, that doesn't have the support or doesn't realize the importance of taking the medicine.

MS. EGGERS: Okay. You raise a very good point that I think we all know, which is that the -- you in the room, you are reflective of a patient population but you're not completely representative of the patient -- the entire population of people living with an organ transplant. We know that. So, even as you still -- you still have challenges. And so we still want to hear those as well. But, that is an excellent, excellent point.

MALE SPEAKER: I think Dr. Chisholm-Burns,

you hit it on the head. It's just -- it's a very complex issue. Right. So, it's not going to be like one little bullet is going to solve this. And to me, I think if you look at, like, for -- if you're kidney recipients, you have a very poor health literacy for CKD. It's one of the lowest health literacy rates out there. So, recognize that from a communications standpoint. Because so much of this comes down to communication. Right. So, how much of it -- and to be frank, is that the doctors are really struggling right now with the time they have. But, it goes back to a message that's appropriate to the audience. And the audiences are not all monolithic. But, to me, it goes back to that. It's about the communication, trust -- all the basics in relationship building.

MS. EGGERS: We'll take a couple more.

MALE SPEAKER: I would just add that part of the issue is actions are louder than words. And so in the medical profession, for example, you say take your medications on the 12 hours the best you can. And then you go in for a blood draw, and you're not allowed to take your medications and you're made to

wait until three hours beyond the 12 hours. Well, then, obviously it's not that critical.

Secondly, oh, we're going to do some testing and you can't take anything, including your medication, for 12 hours before. And then you get there, and the next thing you know it's delayed -- surgery is delayed, stuff like that, throughout 18 hours. And obviously, it's not that critical, then, if we can wait 18 hours.

And thirdly, when you're in the hospital forget any timing on your critical medications. I don't care if it's diabetes or it's immune suppressants, you're on their schedule. Not yours. And you can't convince them that this is really important, and by the way this is my 12 hours -- I'm sorry, this is when we give out meds. The actions speak so much louder than the words.

MS. EGGERS: Okay. We'll take one more from Piper.

MS. BEATTY WELSH: I think that engaging patients in their own care is also a really key part of it. I think that, you know, in my experience as

someone who has CF, one of the key components to getting people to take drugs is involving them in understanding how they're going to impact their bodies. Because if the only experience you really have -- the only thing you see the drug doing is causing you muscles, for example, then you're going to assume that that med is bad, you know. And I think it's very important to sort of explain -- especially when there are multiple immunosuppression therapies on the table. You know, why do I have to take prograf and mycophenolate and a steroid. You know, why is it not okay for me to miss any of these. And I think that additional level of empowerment also makes people sort of take control over the medication for themselves. So that, you know, we can stand up to a hospital, for example, that says well, we're in the ER so we can't order your meds and you'll be here for 12 hours at least. And you have to be able to say, oh, well, then I brought my own, you know. And that's -- you can't do that unless you understand why it's so important.

MS. EGGERS: Uh-huh. Thank you, Piper. I

think Rita -- you have a question?

DR. ALLOWAY: I was going to make a comment before. I think that as a pharmacist I can say this. We're kind of obsessive compulsive. And we want -- you know, we're trying to give you all these little details of exactly how to do it perfect. When really and truly, we need to step back and look at the immunosuppressive regimen and ask the patient what about -- what time of the day does an immunosuppression regimen work for you. How do we build it around you. Yes, all of these things that we tell you to do two hours before, one hour later, with food, without food creates the ideal circumstance. But we do, as you said, have ability to adapt that regimen and monitor the drug levels as such that go along with that.

However, it requires consistency on the patient's part as well, so we can adapt and adjust to those particular changes. And I think that when we talk about we really don't know the percentage of which patients need to be compliant, I think that just as you do to yourself we say a hundred percent,

knowing that it's never going to be a hundred percent. You know, and we're hoping that we minimize the lack of -- the nonadherent times that we can. So, you know, we're learning. But -- and we continue to learn.

MS. EGGERS: Okay. Thank you. Any other on the panel, thinking of question one about the whys of nonadherence, that you -- that's a burning question for you or a burning comment you would like to make about that? Go ahead, Mary Amanda.

DR. DEW: I was struck by the comment that Jack had made this morning -- I don't know if Jack is still here -- oh, there you are -- about how if a medication is missed there's nothing that you immediately notice, you know. And it can lull a person into thinking, well, if I'm not going to notice anything it can't be all that important. You know, it's important, sure, but it's not that critical -- like if you had some immediate issue. And so, I think it gives -- sometimes it can give people a false sense of confidence and without having enough understanding of the real consequences that might not be observable

for a while, it becomes a problem.

And then the second thing is I'm concerned about all of the people that are not like you all, that are not here. And how they can be reached, that -- because they don't see this as a critical issue. You're here because it's so important to you, and you thought about it a lot. But what about all of those other people that don't think about it a lot. Like how are they managing? How are they figuring out -- or maybe they're not figuring it out, and they just don't even realize that it's such a big issue.

MS. EGGERS: And Peter?

DR. NICKERSON: So, I think one of the other things that comes into what's been discussed and the point you raised, we don't understand how much nonadherence is acceptable or -- in terms of tolerated, and not have a bad outcome, in part because we're treating everybody as if they're the same. And you made the point earlier, what we really need to get to is personalized immunosuppression. And we honestly don't know how to do that yet. Short of what I showed you with the twin transplants, where you don't need

any drug, there are some people who don't need as much drug.

And we certainly -- I showed you the clinical trial that we did with the NIH, where we withdrew the tacrolimus in a number of patients and we stopped the trial. But we stopped the trial because some people rejected. But there were other people that came off and they were fine coming off, right. So, that's the other problem here, is that there's a biological difference between everybody who is getting their transplant. Some need more drug than others. The problem is I don't have the magic wand that tells me who does and who doesn't. And that was the whole point of the trial, could we predict who could come off one of their drugs and try and get to a personalized immunosuppression regime. And we couldn't do it, because none of the things that we thought were going to predict it predicted it.

So, I think that's the other complexity here, is that nonadherence is probably okay in some people. In other words, it gets to some people need less. But we can't predict who that person is. And I

think that's some of the challenges that we face, and that the drug industry faces -- is how do we actually identify and move to personalized immunosuppression. Because I think that is part of the solution here, is allowing patients to realize how much they really need for the transplant that they have received.

MS. EGGERS: Thank you, Peter. And Robert?

DR. ETTENGER: What you're all hearing when you're hearing that the patient needs to take the medications at 12 hours, on an empty stomach, et cetera, what you're really hearing -- and I see transplant patients sort of every day -- what you're hearing is our insecurity as physicians. Because we don't know how much is enough. We also don't know what the difference is between patients, and data that Peter has generated suggests that depending on some very sophisticated sorts of matching -- that we don't do yet well enough, that's coming -- that some patients may be more privileged than others. So, unfortunately, we do have a one size fits all policy, because that's about the best we can do. So, what you're hearing is the insecurity of the physicians.

Because we know -- we think we know that perfect adherence is the best that we can hope for. So, that's what we tend to shoot for.

The other thing I want to say is that the issue of not having any specific issue when you miss a medicine -- an immunosuppressive medicine -- becomes a major issue in adolescence, to the point where I was thinking of floating to the FDA that we spike all -- because it doesn't hurt when you make the medications. So, I was thinking that we spike all of the tacrolimus with heroin, so that if you miss your medication you go into a bad withdrawal response. You'd be surprised -- everybody is laughing and says, you know, what a good idea. I don't think the FDA will go for it, but they're here. And so we can see. No, I -- I take that back.

MS. EGGERS: All right. So, Robert, what you're bringing up, I think, is going to tie into the next question. And before we do that, let's hear one more from Kevin.

MR. LONGINO: Well, just a general comment. What would it take to start a personalized medicine

initiative for transplantation?

MS. EGGERS: What would it take to start a personalized medicine --

MR. LONGINO: Initiative.

MS. EGGERS: -- initiative. Yeah. I think it's a broader question.

MALE SPEAKER: (Inaudible).

MS. EGGERS: Uh-huh. Okay. So, let's move on and then we can always come back, if we have time. But let's move on to question 2, about the role of health care providers in this. We've talked a lot about health care providers today. But this question, sort of, I think, wraps it up. Are health care providers appropriately involved when it comes to promoting adherence or are they not paying attention, and what improvements would you suggest. And I'm going to start with two of the panel members, and then we'll open it up. So, if we can start with Mary Amanda -- do you have any -- okay, wait --

DR. DEW: My view --

MS. EGGERS: Okay. Let's --

DR. DEW: Start with Peter. Okay.

DR. NICKERSON: So, it really comes back to -- I think there's been a really good discussion this morning about individual autonomy, and what are we trying to create. Are we trying to create a situation where patients are relying upon themselves and developing their own systems and strategies to have autonomy, in essence, versus us trying to assume that autonomy. And I think from one perspective I would say that we try to be too much assuming your autonomy, and we need to elicit you being autonomous and working a solution that would then be something that works for you. And I think that that actually would be a better strategy. So, from one perspective I'd say we're maybe too involved, and that may be leading to problems in and of itself. Although I could argue the other side, and maybe -- Mary Amanda, I'm sure she will.

DR. DEW: I could probably argue both as well. But, I guess I tend to think that the problem is not that anybody wants the health care provider to hold everybody's hand and hand out their pills all the time, and be in their house. It's that they don't ask

enough when patients come back. They don't show enough interest, often. You know, they assume that things are going okay or that there's no issue, if the patient doesn't have any questions. And by not showing interest, I think sometimes patients -- and all of us have been patients -- feel that then the person doesn't care about that issue.

And they are given -- I know in our program they're given logs, they're told they have to record certain things, and then after a while the program staff just never ask about that anymore. And the person says why am I doing this, and the staff's view is, well, they're supposed to be doing it for themselves. But, what's the point of endless little pieces of numbers written on a page, if the provider never looks at that and says anything about if it's okay, if it's not okay, is there something that's not being understood. So, in that sense I think there's need to be more involvement in the sense of being committed to talking with the person about how things are doing. Not holding their hand. Talking with them and coming up with new strategies, as needed.

MS. EGGERS: Can you hear me now? What if I move over here? Can you -- just kidding. So, let's ask a question this way, to get at -- thinking about what you just heard from Mary Amanda and Peter, I'm going to ask first if -- can someone or a few of you think of the best physician you've had, with regard to the helping you in -- as one of your support -- in your support network, addressing the challenges of adherence. Anyone want to talk? We have Dan, over here. And then we'll go to Leilah. And what was it? What did they do, and how did you feel about it? Were they too -- were they really involved? I guess too is not -- if you liked this, but were they involved? Were they laid back about it?

MR. BONNER: So, I actually -- I'm not thrilled with this question, the way it's worded, to be honest.

MS. EGGERS: Okay.

MR. BONNER: Because health care providers is such a general term. Does my dentist really care about my transplant medication adherence? I'm not so sure that he or she is. But -- so, the question to me

is which one of our health care providers are adequately -- are engaged in our medication adherence, and which one of our health care providers -- maybe who should be -- aren't. That's, I think, a more interesting question.

But, I come from a transplant program that's large in nature. And I really need to take a moment to credit the post-transplant liver coordinator nurse that I have, and the nursing team. I can't say enough about what they do, in terms of patient engagement, because they are the lifesavers behind the brains and the technicians of the doctors. It is that liver transplant coordinator, Samantha, who is my advocate, who is my person who is checking to make sure that adherence is done to the best of her ability. And because of her, and because of her sort of follow-up skills for me personally, that's what has a huge influence on my adherence.

So, if you were to sort of take that a step further you then would have to sort of say, okay, so in order for Samantha to be more effective at her job how big is her patient list. And I believe it's

hundreds of patients long. So, how can someone like Samantha be effective across a large pool of people like that? So, what is that right number of patient transplant people that she can engage with? What is that right number to possibly lift adherence to medication and things like that. And then from a suggestion standpoint is, you know, I would say that this here -- the education I got today in adherence and the things that all of you have brought about -- is so eye opening. But, I also think we need to find ways to get that to every transplant patient, in terms of suggestion to improve our overall education of how important adherence is. Because, you know, 11 years out it's still a very important topic to someone who is 11 years out or 11 months out. So, those are just, you know, a couple of quick comments that I wanted to make. So, thank you very much for that.

MS. EGGERS: Okay. We'll go with Leilah.

MS. SAMPSON: Leilah, again. For me, I would say specialty pharmacy at Northwestern Medicine in Chicago. They're on-call, basically 24/7. They call me a week in advance, to make sure I have all my

immunosuppressants and my medicines. And I live in two different places right now, nine months out from transplant, working full-time, and there are days where, you know, I have to split up my medication between two different locations. And they've been very instrumental in just being able to coordinate that with me.

And then also, Robert Ettenger -- Dr. Robert Ettenger, he really supported what I've been feeling, as far as -- I'm now 28. The last time I was healthy I was 19. You may see that as an adult, but at 19 I was an adolescent. And I was very noncompliant. I'm not going to lie -- like, oh, I was so compliant. No. I was dealing with trying to be normal and not wanting to tell my friends and I want to hang out and I'm in college.

And then now, to be healthy again, and the -- I find that issues -- those issues with scheduling and all the things that you deal with as -- at adolescence, because I spent eight years of my life fighting kidney disease -- I haven't fully developed mentally. And now I'm 28, and I'm thrown back into

this real world of being healthy. And I'm like what do I do with this. I don't have these skills. I gained a lot of wisdom and skills on dialysis, but now to, you know, be 28 with basically the mindset of a 19-year-old, is something that I'm kind of struggling with. So, he really supported that for me. And everything that I've learned here today from everyone helps me to move forward and feel more motivated that I am definitely far more adherent.

MS. EGGERS: We're going to take one more here, and then I'll have a show of hands, questions, and then I -- it's important to get a little bit to the last question. So, I'm --

MS. PAM DUQUETTE: Pam. Pam Duquette. I'm Lindsey's mom. And something that struck me was a lot has to do with patients not understanding that they can self-advocate. A lot of people -- and it's been touched on before -- where they just -- okay, I'll do what you tell me to do and that's it. I think a lot has to do with the health care providers or the centers.

At our center -- and it's a very large

center -- every person that we spoke with, and this is over eight years of her course of her disease, and I'm talking from the -- some of the pharmacists I actually would speak with, to the nursing staff, to the prestaff, to the dialysis nurses -- everybody always said are you okay with this, do you understand this, do you have any questions about this, what do you feel -- there was a lot of back and forth, which when I was -- we were both thrown into this, I was petrified. And I just sat there with -- deer in headlights, didn't know what to do.

But, it was the constant prodding in a very gentle way. And the fact that they respected my opinion, when -- in advocating on her behalf. That was really important.

MS. EGGERS: Okay. So, to wrap this up, we'll do a show of hands and on the -- all -- anyone up here can show -- raise their hands, and in the audience. Who -- now, I know you -- I think you guys were assigned those cases, but who -- what type of -- what's the reality for you? Who is making, whether it is the less -- the provider who wants to give you more

autonomy, that you're dealing with, or the one where you wish -- they're too much, they're too much in your face about it, if I can use that term. So, how many think that their -- it's too overbearing? That the health care providers -- and let's -- I think we've learned that we need to think of it broadly, across the spectrum of health -- of providers that you're doing, that -- basically, that you agree with Peter. Okay. What about Mary Amanda?

FEMALE SPEAKER: He's used to that. He's used to that.

MS. EGGERS: Okay.

FEMALE SPEAKER: (Inaudible) too overbearing or too --

MS. EGGERS: Okay. Too overbearing, that the -- that the providers, collectively, are too overbearing about adherence. Okay. Is underbearing a word? Too passive -- not asking you enough questions about adherence. Raise your hand. Okay.

FEMALE SPEAKER: (Inaudible).

MS. EGGERS: Well, it could be that it's just a very hard question. I think what we're hearing

is that most people would have sided with Mary Amanda in the description, and in terms of what you would like to see. So, we'll leave it, we'll leave it with Robert.

DR. ETTENGER: But in the pediatric setting, the adolescents will tell you to a person it's too overbearing. I had a full head of hair before I started taking care of adolescent transplant recipients. And I can tell you that every fellow, every time, every doctor, every nurse makes attempts to make that connection with the adherence, and the kids get tired of hearing it after a while. So, we have to dial exactly how we do it. So, again, it's not one size fits all.

MS. EGGERS: Great. Thank you for that point. Renata.

DR. ALBRECHT: And that's actually a great segue. Let me try to tackle, I guess, Kevin's question, and then perhaps try to touch on Nicole's comments earlier in the morning. You talk about individualized medicine. And I guess I'll take the liberty to follow Bob's comment about our insecurities

-- the clinicians' insecurity knowing the doses. The FDA approved drugs called prograf, cellcept, myfortic, nulojix, et cetera -- they come in certain strength and certain regimens are recommended.

But, if you think about it -- I'll sort of venture to say that that personalized medicine is in its baby steps. Because your physician doesn't prescribe you a fixed dose every day, the same dose, and just lets you go. For certain of them, the calcineurin inhibitors, you're getting your levels measured early on after transplant more frequently, later less frequently.

Rita talked about medical adherence, which is not a passive act. It's a dialogue between the clinician, be it your primary physician, be it your nurse coordinator, be it whoever is taking care of you. And I guess I've heard also people saying I ask. I ask what's my value. You know, the gentleman said I'd like to know what my creatinine is, can we get a device approved for that. So, I think if you think about the drugs, your interactions with the clinicians, asking about your values, and then hearing

how your regimen is getting modified -- we heard -- I don't know if it was James who said, you know, I'm getting belatacept -- doctors are making changes based on the patient's individual course. And I think that in a sort of simplistic way is the beginning of personalized medicine. Hopefully in the future, as we learn more, there will be more of that. But I think the feedback from you in the audience -- the patients who are saying, you know, I want to know more, I want to understand, I want to know why -- someone said I want to know the mechanism of action. Why am I being asked to do this. How does it make a difference to me personally for my organ, for my lung, for my kidney.

And then the FDA approves the drugs that I mentioned, but economics came up. So, as you aware, there is -- there are not present today, otherwise I'd ask them to speak, but there is a whole group called the office of generic drug products, and they're responsible for making available to the public generic versions of the products that are -- that start as innovators. The goal of that group is make those products -- I'll use the phrase carbon copies. They

should have the same effect, the same efficacy and safety profile, as the innovator, because they really are trying to be carbon copies in terms of their therapeutic activity.

Anecdotally, we will hear that patients don't do as well. Can I ask for people who have those experiences -- what Sara said earlier, please share those experiences. Perhaps we can look into that. You know, every so often a drug company will have a problem in the plant -- something goes wrong. The tablet is not full strength. That's a solvable issue. But that's different from, you know, maybe a patient didn't do well because they didn't take it the same way because it didn't taste the same way, or they couldn't swallow it the same way. It's unclear. But the only way we will know is if you find out something or you hear something, you send it to the FDA. And, again, let me make the plea that Sara voiced earlier. Until November 27th, everyone here, everyone on the web, if you have information that you think we would find valuable -- like we have all the discussion that we've had -- please send it in.

MS. EGGERS: Thank you, Renata.

DR. ALBRECHT: And that may be a segue to your last question.

MS. EGGERS: Yeah. At the break, we will put the information on how to get to the docket, which is your way of submitting a comment electronically. So, I think we want to make sure we address the last question quickly. And then we will go into a break. So, we will do it kind of a lightning round. So, first of all, can I have a show of hands how many of you have participated in a clinical trial? Okay. We've had some experience here.

Okay. So, unfortunately, I don't think we get to get into what might make it difficult or hard about measuring adherence in the clinical trial. We can -- you can write that in the docket. But, let's get a -- anyone on the panel who wants to address this question briefly, about how critical it is to collect the adherence data. I think we heard from the panels, but any other thoughts on that or perspectives?

DR. NICKERSON: So, maybe just -- from the concept that if you're trying to qualify a new drug

and you end up showing it doesn't have a benefit, but if the patients weren't taking that drug or adhering to the regime of that new drug, then is it -- you've essentially disqualified a drug. But, it might actually have had an effect, had it been taken appropriately. And that's the risk of a clinical trial, not knowing their adherence activity around that drug. So, you -- ideally, you would know for both arms of the trial what the adherence rates are, and that then you're actually judging the drug on its effects, as opposed to the nonadherence, which may show that it has a negative effect.

MS. EGGERS: Okay. Any other thoughts? Yes, William.

DR. FITZSIMMONS: And the other side of that is if you're performing a study that is a noninferiority study, rather than failing to show the effect of the drug you may make two drugs look very similar, because they're not -- they're muddling the two arms of the trial. So, there are consequences either way, depending on the design. But, I think it's important to keep in mind the clinical trial

setting, particularly in the registration driven trials, is very different than the real world setting. We're already out there having patients sign informed consents, putting them on a specific schedule, counting the medications when they bring them back and when they're dispensed. It's a very different setting. So, we have to be careful in realizing that that's not immediately able to extrapolate that to the on-market real world setting outside of the trial.

MS. EGGERS: Okay. Can I show a hands? So, of the number of you that have participated in a clinical trial, was adherence -- the challenges with adherence easier when you were in the clinical trial? Harder when you were in the clinical trial? Anyone -- we can take probably two comments on anyone's experience having to be adherent while on a clinical trial, and challenges that you faced. Okay. We're putting you on the spot. So, I think we will take that as a sign that -- I'm going to take it as a sign that it's a break time. So, we will take a break and come back at 3:15, and continue with some more enlightening presentations. So, thank you.

(Off the record at 3:03 p.m.)

(On the record at 3:15 p.m.)

DR. BELEN: So, hello everyone. We're going to go ahead and go ahead with this session 2 of afternoon scientific session, interventions to mitigate nonadherence. Our first presenter is Dr. William Fitzsimmons, of Astellas Pharma, and he is going to discuss pharmaceutical dosage forms to improve adherence.

DR. FITZSIMMONS: Good afternoon, and thank you very much. I want to express my appreciation to the FDA for organizing and leading this patient-focused drug development discussion, organ transplantation. I really believe this is a -- is a milestone in our field, an important one. And also, thank all the patients who -- particularly those who have been participating this morning as well as this afternoon. It's really the motivation for people like me, who work in drug development, in this area to hear from you. Because we don't have that opportunity as much our colleagues that are direct health care providers. And it's really motivating to hear that.

My disclaimer is I'm an employee of Astellas Pharma, a pharmaceutical company. I've been working there 26 years, starting on the development of tacrolimus in 1990. But, I'll be expressing opinions today that are my own opinions, even though I've been working at the company for quite a long time. But they shouldn't be considered the opinions of Astellas.

What I'd like to stress, and has been touched on in a number of the themes already, that I think will be great because they tie well into my presentation, is that I'm going to focus on pharmaceutical dosage forms that pharmaceutical companies could work on to help improve adherence. But, I think it's important, as we just discussed, to realize this is a very complex multi-faceted issue of adherence. So, I don't want to fool myself or anyone else to think that dosage form development is the answer. There is no magic bullet here.

What we need to do is try to work together on all the different aspects of this, and one of the things that the pharmaceutical industry can do is help in terms of regimen complexity, as well as

pharmaceutical dosage forms. So, I'll be focusing in there with the big picture that this is one small element of the big -- of trying to address issues in adherence.

So, what can we do from the standpoint of dosage form technology and what have we done in the industry to try to improve this. Probably the most fundamental one for oral drug development has been sustained release technologies. And there are a lot of different sustained release approaches, and with the main goal of trying to decrease the frequency of dosing. I'll talk a little bit about some of these, from the standpoint of transplantation, to give you more specifics there. But, if you think about some of the products that are out there that have made a difference already -- outside of transplant -- in sustained release technology, there might be a couple of approaches.

We were talking about difficulties with adolescents and adherence. So, attention deficit hyperactivity disorder medications used to be all immediately release, multi dose per day. And

sustained release technology came out. It really helped, because those kids then didn't have to try to bring medications to school. Didn't have to go to the nurse or somewhere else to get their ADHD drugs, didn't have to worry about trading those drugs or having someone acquire them while they're at school.

So, we don't really think about those things too much but that's a big improvement in the lifestyle for an adolescent with ADHD, that can be helped a lot just by a reduction in the dosing frequency.

Another example is improving adverse events if they're associated with a high drug level. A very simple one, if you're taking niacin for the treatment of high triglycerides -- if you take immediate release niacin, there's a very dramatic flushing that lots of people get. And if you just put it into a sustained release, you can dramatically reduce that amount of flushing and make it a tolerable medication for hypertriglyceridemia.

The second approach I want to touch on was transdermal patch. We're talked a lot about those in the past. I believe that, honestly, this -- they

aren't applied all that frequently. But, if you think about transdermal patches, what they can do is, one, decrease frequency of dosing, because you can put a patch on for potentially days. You can also avoid the issue of the oral route of administration, for people who have difficulty swallowing. So, the -- probably the most common ones you think about are scopolamine patches for people with motion sickness, nicotine patches that you see over-the-counter now for smoking cessation. Those have been very common.

Within prescription products, probably the ones that have had the biggest breakthrough are things like opioids, using fentanyl patches for chronic pain control. Also, topically, testosterone. Most of testosterone replacement therapy is done topically, not necessarily in a patch but counting on oral absorption. Because one of the advantages is it -- when you put a drug on the skin rather than swallow it, it doesn't go through the liver. Most of the blood flow from the intestines goes initially through the liver. We call it first pass metabolism. And that will greatly affect some drugs, and this is a way

of getting around that.

Third is melting tablets. Some people call these melt dose or WOW tablets -- without water tablets. It's not used too commonly, but it's another approach that oftentimes people have to run around and worry about where -- if they have a source of water, right, to take all their medications. People have difficulty swallowing them. This is a way of pharmaceutical formulation where it will dissolve very rapidly in the mouth, and reduce your need for water.

Long-lasting injections. Most of the time when we have proteins or biologics that can't be absorbed through the GI tract, so they can be put into an injection, hopefully the thing can be dosed at a very infrequent time. But, patients sometimes can do that at home, with self-injections -- particularly subcutaneous injections at home. But, they may need to go to the clinic for their administration. But, hopefully that will be infrequently.

And then chewable tablets. I could probably put also sprinkles and granules and liquids into this group as well. All formulated to help make it easier

to swallow, particularly in the pediatric populations that have difficulty with solid oral dosage forms and the size of them.

And then lastly, fixed dose combinations. The simplest way to think of this is we've taken two drugs and put them into one pill. So, commonly, our -- you might see this in areas like hypertension, diabetes -- I'll show a few of those. It's also used in antiviral therapies. And now you're seeing more and more products come out that combine things like a nonsteroidal anti-inflammatory drug along with a drug to protect the gut, like a proton pump inhibitor or H2 blocker, so that you put them both together -- one drug that protects against the side effects and one drug that causes that side effect, all in the same tablet or capsule. Another way of -- and I'll show some of the data on how that effects adherence.

So, if we think about overall regimen complexity, one of the -- there's a number of factors to consider. One is simply the number of doses and dose frequency per day. And I'll show data on once, twice, three times, four times a day dosing. But,

also, just the total number of pills. It struck me this morning, people were talking about 20, 30 pills a day -- the more the pills, the more complex. Even if they're once or twice a day, simply the number makes a difference. The third is liquids versus solids. Liquids are harder. They're harder for people to carry around, for people to take. So, we want to shoot for solid dosage forms if we can.

One thing that was talked about a moment ago was the issue of taking products with food restrictions. So, you go to the pharmacy and you get the little label on the side of your bottle that says take this on an empty stomach, one hour before or two to three hours after a meal. That is actually the most complex. People have the hardest time trying to space drugs with that instruction. That's worse than saying take it with food -- that's easier. And then the easiest, of course, is it doesn't matter whether it's on an empty stomach or with food. So, we have to keep that in mind for the complexity of the regimen.

Other things to think about -- refrigeration. Patients don't have the ability to

keep something on ice and at a low temperature, even though stability for some products is an issue. And then, as I -- with the liquids, the issue of whether you have to reconstitute it. Is it a powder that you then you have to add a liquid to? Again, that step adds to the complexity of the regimen.

So, these are all things that we have to consider. A lot of the work on this, actually, came out after the treatments -- the antiretroviral treatments for HIV/AIDS, because they were concerned about all the multidrug regimens and trying to maintain adherence in that setting.

So, what's the best? The best situation, when -- and the patients described it this morning, was if you could take one tablet or capsule once a day, regardless of food, and take it in the morning. Right. That's the ideal scenario, if we could accomplish that. That's the rarity, but that should be our goal for oral therapy if we can do that.

I'm going to look at some of the data both in and outside of transplant, in regards to adherence, but I want to put forward a couple of assumptions that

I'm making. And one is that simplifying the dosing and reducing the complexity of the dosing should improve adherence, even when there are very few studies to show that. It's not -- there's a lot of studies on adherence that you heard about earlier this afternoon. But not so many that really show the impact of just changing the dosage form. But, I believe we have to go through the premise that simplification and reduction in complexity is good, and we should strive for that.

The other thing is that we tend to get hung up, sometimes, in our field on saying but has it been studied in transplantations. And so what I'd like to say is that we can extrapolate from other chronic diseases to transplantation. For instance, we know that diabetes, hypertension are very common amongst transplant patients. We've heard about that today. Hypertension is a good example of a fairly silent disease, like preventing rejection, right. Normally, everything is going fine until something big happens. So, I think that these are valid areas to extrapolate to transplantation.

So, what do we have in terms of examples of dosage form technology for transplant immunosuppression -- actually, very few, if we focus just on immunosuppression. One that was talked about -- introduced by Jack this morning is nulojix, or belatacept. A once monthly -- when it's in the maintenance phase -- intravenous injection. So, that's an area where if you are able to get to a clinic that can provide that once a month injection, it's a way of ensuring that patients have exposure over a full month with just that one hour injection.

Now, you do take other oral immunosuppressants along with it in the regimen. But, it's sort of an all or none, right. If you get your injection, you've got a month's worth of immunosuppression, at least from that agent. So, that's one approach. The other approach that has been used in transplantation is -- with tacrolimus, going from the immediate release twice daily formulation, which is how we originally launched it, to once a day formulations. There's two that are on the market in the U.S., Astagraf XO and Envarsus XR.

So, let me start out first to say if you're looking at once a day, does once a day versus multiple doses help. Now, I think it's fairly clear. We already have heard from patients that that's desired. So, I think all this does is validate the opinion that you have. But, it's important to also look at that data.

So, this is a group of -- a systematic assessment of studies that used electronic monitoring. Rita talked about different monitoring methods for adherence. This is with electronic monitoring across numerous disease states, starting at the left side with once a day dosing all the way to four times a day dosing at the right. And somewhat intuitive to you, but shown by these studies, you can see that the average adherence rate drops as you go to increased number of doses per day, with four times being much worse than once a day and once a day being the best. Fairly intuitive. You might say does that hold up for a disease like hypertension, where you're not symptomatic. And the answer is yes, it does. It's not as striking the numbers, but once a day in

hypertension is definitely better than twice a day and three times a day, in this situation. And this was looking at if you took at least 80 percent of your prescribed meds. If you cut this at 90 percent -- if that's your criteria -- these differences actually even get bigger.

The other thing is what about a nonlife-threatening but symptomatic disease, like overactive bladder. Does it hold up there. This is oxybutynin, one of the most commonly used drugs in the U.S. for treating overactive bladder. And once a day ER on the top line, you can see that -- has a much higher percentage of patients staying on therapy than when you go to multiple doses in an immediate release. And you see very low rates of one year persistence. Less than 10 percent of patients stay on twice a day oxybutynin for a year. It's remarkable how long the adherence rate is.

Now, I just want to touch on what do we know about transplantation for once a day. There has been some studies done. One of the studies is of 219 patients, where they were randomized to once a day

versus twice a day tac after kidney transplant, and then followed for six months. And what they found in this study was after a three month running period -- and then there's that vertical line through the slide at the point of randomization -- the top line is the once a day group, the bottom line is the twice a day group. And this was looking at the percentage of patients with correct dosing. And they used an electronic system, so every day they could check on the dose. So, that's what -- that's every day you're looking at the compliance. And you see that they separate out. So, once a day in transplant patients you see higher percentage with correct dosing relative to twice a day.

The other thing that was interesting about this study, that taught us a little about human nature, was they looked at the day of the week -- because they did this every day. And what you can see at each day of the week is that the evening doses there's a higher rate of missed doses -- that's the top line -- than the morning doses. The other thing is the worst time is Saturday night. So, Saturday

night -- I guess that's intuitive too -- is the worst time in terms of compliance. Okay.

The last thing I wanted to touch on was this idea of fixed dose combination. Fixed dose combination, where you put two drugs into one dosage form, compared to having to take two pills, has been studied in diabetes and shown enhanced adherence rates. It's also been studied in hypertension with ACE inhibitors, along with diuretics. These are the data on lisinopril in single pill versus two, as well as the data on enalapril, along with hydrochlorothiazide. So, there is no doubt that combining, in certain situations, you know, into one dosage form helps over two. There are -- you could extrapolate this, and there's data to say, that even if you package it together in a unit dose package, so that patients get them both together, does help. It's the best to put it in the same pill.

So, let me end by saying I think that there is a number of pieces of data -- there is a number of innovations that pharmaceutical companies can help with, in terms of enhancing adherence through dosage

form development. But there are some limitations. And as we heard well today, transplant patients are on multidrug regimens just for the immunosuppression, let alone all of the other indications they're taking. So, just going from twice a day to once a day tacrolimus -- but then you have to take twice a day mycophenolate and you have to take all your other medications -- doesn't mean we've solved the issue.

Secondly, that when you looked at that list of possibilities a lot of people say, well, you should do all of those things with your drugs. Why aren't you making all those different dosage forms. The reality is we're limited by the science of the chemistry, as well as the pharmacokinetic, or how a drug moves through the body. Those molecules that sometimes make it impossible -- sometimes we can't get it to go into a solution to make a liquid, we can't it go through the skin -- so, we do what we can but it's not -- we don't have the ability to apply it in all circumstances.

And lastly, that what we try to do is speed drugs to market, particularly to get it to patients in

need, and almost always we don't know everything there is to know about the dosage regimen, nor have the best formulation. We have a good formulation. We know as much as we can to get the drug out on the market.

But, there's a lot of work that needs to be done. And so, once the drugs are generic, that some of the -- there's some disincentive for doing some of the work to enhance these formulations. So, we need to work on, together, to make this practical, to do it quicker, less expensive and with less complexity, so that we can get some of these innovations out in terms of new formulations to enhance adherence.

Thank you very much. And our next speaker is -- Dr. Dew is coming back, from the University of Pittsburgh.

(Applause).

DR. DEW: Okay. I'm going to briefly review the evidence that we have about adherence in heart, lung and liver transplant in adults, and then Dr. Chisholm-Burns will cover kidney transplant intervention studies. There are a number of challenges, if you think about what can transplant

programs do in order to help their patients maintain adherence or improve adherence to their regimen after a transplant. People go to big centers. They often -- they may live thousands of miles away from the center where they got their transplant. Transplant teams have limited resources, that they're constantly having to justify to their institutions. We've already talked about how adherence to their regimen is really composed of a number of different elements. There haven't been many interventions tested directly in transplantation, and we really don't have powerful interventions from other chronic disease populations. We have some, but they are only modestly effective. So, the key issues are when, where and how to intervene with transplant recipients.

This is adapted from a review that was focused on hypertension, and in this review they pointed out that adherence problems can develop anywhere from shortly after the onset of treatment or care all the way through the very long term. And that's come up in some of the comments today as well. So, over on the left side, if you think about in the

transplant case when you have the surgery as the beginning point, then you can think about the period after transplantation as first -- in the first year, dealing with things like maybe trouble initially getting into the routine, low motivation to get into the routine, the onset of intolerable side effects that inhibit adherence, confusion about the regimen.

Then, as time goes on and you move over towards the right-hand side here, there may be delayed toxicity that creeps up over time. It may be hard for the person to sustain their motivation to adhere to the regimen. And so, those kinds of problems can develop in the long-term.

In terms of where and how to intervene, if you look at the chronic disease literature in general we only have a fixed number of possibilities concerning the mode of offering the intervention. We might do it face to face, at discharge or at clinic visits. It could be done on the telephone, through smart phone apps or through other kinds of internet or web-based applications. And then in terms of what the interventions could be composed of, these are sort of

the fixed set of elements that people usually begin with when they try to put together an intervention. Some educational component, or maybe solely education, behavioral aspects, problem solving therapy, for example -- teaching people how to use certain techniques to deal with new problems, focusing on psychological aspects, using motivational interviewing -- which is not interviewing, but trying to bring out the person's motivation -- their own motivation -- for doing something. Technology-based approaches, and then multicomponent strategies that put these things together in novel packages.

In chronic disease, we know that the types of interventions that have been used across studies are very heterogeneous. People have tried a lot of different approaches, but in looking across the literature it's the things that are multicomponent that seem to be the most effective. So, you don't just offer education. You offer education plus some kind of problem solving or education plus some psychoeffective kind of element. It can be difficult, then, to say what element of this multicomponent

intervention is the thing that's really potent. But, the fact remains that it seems to be the synergy of different elements that matters.

We know that effectiveness is increased by tailoring it to the patient needs. So, you don't just use a one size fits all intervention strategy. And also, tailoring it to incorporate dynamic information. Meaning that if you used one of the medication monitoring systems and you got feedback on the times that you were most likely to miss doses, that kind of dynamic information on how you've been doing lately could be really useful for how to improve in the future.

We know also from this literature that the degree of impact is variable, but it tends to be small to moderate at best. So, no intervention is hugely effective, but it has resulted in measurable improvements. And whether interventions improve clinical outcomes is a whole other issue. Many intervention studies don't address that issue. Finally, new mobile health strategies appearing promising and are really increasing in terms of

visibility in the literature.

So, then, what do we know directly in transplant? Well, I'm going to focus on the extrarenal studies, the heart liver and lung studies. There have been descriptive reports with no evaluation. So, we really can't say anything about whether they're helpful or not, except anecdotally sometimes they seem to be helpful. There have only been six trials to date that have actually looked at interventions in heart, liver and lung recipients. Two of them I'm not going to talk about. They were just education and they showed that education alone doesn't work.

There have been two others that used electronic platforms, and those were done by our group in Pittsburgh. And then two others that used face to face multicomponent interventions, and both of them were done in Europe. So, these four studies I'm going to talk about, because they did show some evidence of effectiveness.

About 10, 12 years ago we did a study focused on heart recipients, and we developed a

website that was multicomponent. It had education. It had a question and answer library. It had discussion groups. And it had coping skills workshops that, as you can see here, one focused on managing stress and the other focused on managing the medical regimen. So, it was a short trial and we compared people who used the intervention to historical controls who were the same amount of time post-transplant. And what we found was that their mental health, even in this short four month trial period, improved relative to the controls. Recipient adherence improved in some areas, but it was only among the people that actually used that component of the website. Recipients social functioning and their quality of life in that area improved, and we found a dose response relationship between the frequency of the website use, no matter what component they used, and intervention effects.

But the issue is that the sample was small. It wasn't randomized, even though it was a prospective study and it had a short study period. More recently, we focused on a large randomized trial in lung

recipients. And we were testing a smart phone app called Pocket PATH. And Pocket PATH gave the user a variety of tools that they could use on their phone to monitor what they were recording. So, rather than using paper and pencil logs, they could record information about their spirometry, their temperature, their blood pressure and so on directly into this app. And they could see both a listing of what they had recorded, but over on the right there at the bottom the most important thing was they could see graphs. They could see how their numbers were trending over time, and it had critical values so that they got an alert if they were going outside of their critical range, or if they were showing good improvements or whatever. And that kind of feedback seemed really important.

So, in this trial we randomized patients at discharge and we compared them to a usual care group and we found that those that had the app were more frequent in their self-monitoring, had higher regimen adherence across the board, to all of the elements. They were more likely to report abnormal indicators to

the team. We didn't find effects on rehospitalization or first year mortality. So, this just shows graphically the self-monitoring difference for Pocket PATH versus usual care. The higher bars -- the green bars -- for Pocket PATH showed that self-monitoring was higher and adherence was higher, but you can see that for everybody adherence declined over the first year. So, Pocket PATH helped but it didn't prevent what we always see, which is that adherence generally does worsen over time in almost everybody, transplant or not.

This study didn't follow people past their first year post-transplant. However, a follow-up report that's just going to come out now -- it was under review when I did these slides, but now it's going to be published -- looked at subsequent years and did find that the people who benefited from Pocket PATH in the first year did show a lower mortality risk in subsequent years, up to about six years post-transplant.

And then, we've more recently been testing a version of this for adolescents, called Teen Pocket

PATH, which focuses only on medication use. And again, as a smart phone app that helps them to monitor that, to see their trends in taking it and to contact the team as appropriate.

The third intervention out of the four that I'll discuss is a face to face pharmacist-led educational and monitoring intervention. It was done in Germany, and involved a very small group of 41 liver recipients. But they were randomized, so that was a great strength of the study. It used education as well as quarterly meetings with the pharmacist to review their medications, their lab values, any problems they were having and so on. And this slide, it shows box plots. The point of the slide is that the higher box on the left is showing better dosing compliance. They were more likely to open this electronic pill bottle, with the correct number of openings per day, than the control group, which has a lower box, which was not as good at doing that. So, the intervention was effective from that standpoint.

They also found higher target serum levels. They didn't find effects in every area. For example,

self-reported adherence didn't change and graft rejections didn't change either. But, the issue, again, is that the follow-up period was short and the sample was small.

Lastly, the MAESTRO study, which has just been completed recently in Belgium and is almost accepted as a publication -- it was present at an international meeting in the spring -- is a really nice example that involved heart, lung or liver patients. It had a long follow-up period. All the patients were beyond the first year of post-transplant when they were randomized, and this intervention focused on giving them feedback using electric monitoring. So, it was dynamic information that I mentioned earlier. It helped them with goal-setting and action plans. They had social support and education, and it used motivational interviewing to draw out the motivations for people to want to adhere closely to their regimen. It was also tailored, based on their initial level of difficulty.

They looked at adherence outcomes, up to 12 months after the baseline, and then they looked at

clinical event-free survival over five years. So, they found that they did have an effect on adherence. They had only a marginal effect on clinical event-free survival. So, this is a graph of the adherence effect. You can see the green bar is the intervention group. They had better dosing adherence. It was about the same at baseline, by intervention, and it was clearly better. And notably, they maintained that over the subsequent 12 months, even though they were no longer getting components of the intervention. So, it went beyond Pocket PATH and showed durability.

The problem is that it may not be feasible in a given transplant program's practice, because it's a relatively complex labor-intensive intervention, and you might have to have somebody that was dedicated to offering that intervention.

So, to conclude, there are very few studies in heart, liver or lung recipients relative to about three or four times as many in kidney recipients. Education alone does not work, even though clinicians, if you ask them what works, they say education, that's what going to work. It doesn't work. Multicomponent

strategies can improve adherence, but tailoring is needed, I think, to make them maximally effective. And most studies to date have just short follow-up periods. So, the durability and impact remains not as well understood. Thank you.

(Applause).

DR. DEW: So, Dr. Chisholm-Burns, who hasn't been introduced before, is the dean and professor, college of pharmacy, professor of surgery, college of medicine, at the University of Tennessee.

DR. CHISHOLM-BURNS: Thank you, Mary Amanda. I also want to thank you for inviting me here today. I'm humbled by the experience. I always like to see my fellow colleagues and present with them. We've been presenting over the years on different issues. So, again, thank you for inviting me.

I also want to thank you guys out there for reminding me of why we do what we do. And it's because of you. So, again, thanks for allowing me to share this time with you.

I'm going to talk to you a little bit about interventions to improve adherence among the adult

renal transplant population. And as you recap and think about today, you learned -- or, we talked about many things, all the way from organ donation to polypharmacy therapy to adverse drug events, cost, rejection, whose responsibility is it anyway, in terms of adherence and -- side with Peter on that one. I know it was a hard call. Are we too passive about adherence. We also talked about -- you reminded us about engaging patients, empowering you guys -- what I call self-efficacy. And so what I'm going to try to do is kind of tie all of this together using two studies to do that -- two studies that I have been involved in over my career, looking at adherence. And among the six or seven that I've done that looked at intervention groups, I think these two are the ones that could tie this together the best.

The first one was published in The American Journal of Transplantation a couple of years ago. And it looked at improving outcomes of renal transplant recipients with behavioral contracts. You might be thinking, oh, now that's really heavy -- a contract, right. This is like closing on a house or going to

make me sign something, now I'm liable and responsible. But, I don't want you to get caught up in that. This is just a mechanism -- a medium, if you will, that we use to make the health care professional and the patient pause to talk about adherence. And you talked about that. Let's pause. Let's make them do it, and talk about adherence.

So, let me give you a little bit of background about behavioral contracting. I know this came up in Mary Amanda's talk. All it really is is a behavior modification technique, which is grounded in social cognitive theory in which there is patient-specific written agreements, or contract, if you will, that's developed between an individual, patient and a health care professional. So, it's not a legally binding contract. Okay. It's just a way to pause, to get some thoughts written down on paper, and I have a copy of the contract. It's a one page sort of deal. And what this contract does is identifies a target behavior. In this case, the target behavior is medication adherence, specifically immunosuppressive therapy adherence, and it looks at those factors that

influence that behavior, okay. And we talked about a lot of those factors here today -- cost, and I know that's probably the elephant in the room. I had a discussion earlier today with an individual that is pretty high up in one of the pharmacy chains, and I know the question was put forth to the group about changing drug vendors. And a lot of that sometimes is controlled by a lot of other factors, including PBMs and things of that nature.

But anyway, it was looking at factors that control that behavior, and proposes strategies to modify the target behavior to achieve a desired outcome. So, all the factors that you talked about, all the factors that we didn't talk about -- because it's very individualized. And so, in this study, again, we looked at adults. So, the study included renal transplant recipients who were 21 years of age or older, who were at least one year post-transplant. So, these were people that -- probably for the most part they were established on a drug therapy. They were prescribed tacrolimus or cyclosporine. They obtained their immunosuppressive therapy from a

specialty pharmacy. And I know someone made a comment about that earlier. And they had to be enrolled in a specialty pharmacy for at least one year prior to study enrollment and during the entire study period.

Now, participants in the intervention group met with the study pharmacists at baseline to negotiate the behavioral contract, then again at months three, six, nine to review the contract, to discuss progress toward the goal -- which, again, is to achieve the highest possible adherence that we could, to update the contract, and to resign the contract for the next quarterly period. And they met the last time at the 12 months, to terminate the contract.

Now, what did the behavioral contract address? Well, it addressed several factors, including the motivations for achieving immunosuppressant therapy adherence. Today I've heard people talk about they want to be adherent because they want to be around for their loved ones, or they want to participate in a particular activity. So, the motivations. Again, done on a very individualized

scale. They addressed barriers that interfered with adherence for that particular person. And solutions to these barriers, which could include social support.

We also looked at other tools and strategies to help remind the renal transplant recipient of the dosing schedule, and possible consequences of nonadherence. So, tying the whole picture together. Now, participants in the control group received standard or usual care. So, once we applied our criteria to the patients -- we had 286 patients in this particular pharmaceutical pharmacy, that actually met the criteria. I need to tell you that it was a multisite intervention, and it was spread over several states. Most of the states were in the southwestern part of the United States. So, I didn't live all my life in the state of Tennessee. So, I was out in the southwestern part for a little while.

And 286 people met the study criteria. 150 people were accepted into this study. And at the end, we had 67 individuals in the intervention group and 68 individuals in the control group.

In terms of results, there were no

significant differences between the intervention and the control groups based on patient characteristics. So, for the most part, the patient characteristics -- the big global ones -- were the same. I have to tell you, we've seen this throughout many of the talks today -- I know Mary Amanda mentioned it and Peter mentioned it when he looked at Nevins' study of 2014 -- that baseline adherence was associated with months post-transplants. Meaning, the further you were out from transplant the lower your adherence rate became in most cases. But no other factors or characteristics were associated with adherence at baseline.

Now, the intervention group had significantly greater adherence compared to the control group at months 6, 9 and 12 months, and over the entire study period. And that's what's really depicted in this graph. So, you have a line graph here. On the Y axis, you have the month post-study enrollment. On the Y axis, you have the compliance rate -- if you multiple that by 100 you get the compliance rate or the percentage. The solid line

represents the intervention group. The dotted line represents the control group. And you clearly could see that the lines diverge. However, just like Nevins' study in 2014, you didn't really see this line diverging until after the third month post-study enrollment. And you could see clearly that the intervention group, as I said earlier, had better adherence.

Now, I will tell you that we did follow these people after the 12 month study period. We actually followed them out three months after post that period -- so, a total of 15 months. And this study did hold. The intervention still had higher compliance rates or adherence rates, compared to the control group. In terms of cost -- I mean, in terms of cost as we look at health care utilizations, and in particular hospitalizations -- 40 percent of the patients reported hospitalizations during the study. And if you look at the two groups, 57 percent of the control group was hospitalized during that 12 month study period, compared to only 24 percent in the intervention group. And this really boiled down -- if

you want to look at the cost again, not to mention all the other things that associated with hospitalizations, like quality of life -- but just looking at the cost alone, the intervention group was 78 percent more likely not to be hospitalized, saving $28,000 a month in health care costs.

So, what did we conclude at the end of this study? For us, having multiple sites out there around the country, we concluded that behavioral contracting is a practical and easy to employ adherence strategy that resulted in several significant improvements, one in adherence and the other in decreased health care costs.

So, just to recap this study, it was done, again, in multiple sites. So, you, I believe, talked about scalability. This has the scalability potential. Again, you have to stop and pause and engage in the discussion.

I want to present to you another study, which was a study that was done at one site. It was in a renal transplant clinic at the Medical College of Georgia. Now that institution has been renamed to

Augusta University. But, we looked at the impact of clinical pharmacy services on renal transplant patients compliance with immunosuppressive medications, and again a multicomponent study where we did lots of things to help with adherence. Very individualized, similar to what you saw in the first study.

Again, this study involved adult renal transplant recipients. And since it was done in the center, we had some clinic data that we could go to as well. So, everyone who received a renal transplant at the Medical College of Georgia, over a two year time period, was evaluated to see if they met the study criteria. The study criteria included they had to be at least 18 years of age, this had to be their primary transplant -- meaning that they couldn't have any graft loss prior to this -- and they had to receive follow-up care at our institution, and receive their medications from our institution's pharmacy.

After receiving informed consent, patients were randomized, just like the other study, into one of two groups -- an intervention or a control group.

Patients in the control group received traditional services, which meant no clinical pharmacist interventions, while patients in the intervention group were seen by the clinical pharmacist at each clinic visit, and they interacted with the clinical pharmacist at least on a monthly basis.

Now, what were the clinical pharmacies' duties? Well, they included performing medication reviews with an emphasis on preventing or resolving medication-related problems, monitoring therapy, providing medication recommendations and drug information, increasing patient access to medication -- and I note that was one of the things that you guys talked about earlier, the access -- and encouraging patient compliance to medications.

This study was a small study. It involved 24 patients, 12 in each group. You could see that there were no differences between the two groups in terms of gender, age, whether they received a living related donor kidney transplant or a deceased donor, as well as no differences between race or ethnicity. This graph -- you've seen something similar to it

before, but I do want to remind you this study differs from the first study in that the month post-study enrollment is also the month post-transplant. So, these are freshly or new transplants. The other one was out a year. So, they kind of developed some patterns before we got to them.

Again, reemphasizing the point that many of my colleagues made, the point that Dr. Nickerson talked about in Dr. Nevins' study, is that you really didn't see a big divergence in adherence until after the fourth month. And then you could see that yellow line which was the intervention group, and that control group, that red line, where you see the decrease in adherence. So, it does happen early on in the post-transplant time period.

So, the message here is that the intervention group had a statistically higher intervention -- had a statistically higher compliance rate compared to the control group. Now, since we had clinic data we could triangulate the compliance rate. And so in both of these studies, we looked at refill records. However, with this study we were also able

to look at immunosuppressive drug concentrations, and we found that more people in the intervention group were in the desired therapeutic range with their drug concentrations, compared to those individuals in the control group. And that was statistically significant as well.

Now, the study wasn't powered to look at graft rejections, but I will tell you that two people in the control group had graft rejections compared to zero people in the intervention group, leading to some of the other things that you guys talked about.

In terms of the economics, we didn't see any differences in hospital costs, as well as clinic visits, emergency room visits, or total costs between the intervention and the control group. But, we did see a statistical difference in the cost of the medications, with the intervention group having a lower cost of medications compared to the control group. And that's really, really important. What we found is when we looked back at the interventions that the clinical pharmacist was making, many of them involved discontinuing medications that the patient

didn't need to be on. There was a lot of duplications of medications. There was a lot of doses that could be decreased. So, that was something that we keyed in to. And as we looked at -- more and more into the cost of the medications, we found that patients in the intervention group had a mean total cost charge of about $2,600 less per patient than patients in the control group, and that equaled to about $68,000 just for the intervention group alone.

So, looking at both of these studies we came up with some conclusions in summary. The interventions have been developed that successfully improve IST adherence in transplant recipients. Again, as my colleagues have said, most of these are multicomponent interventions, and they're very individualized interventions. And I believe, as well as my colleagues, that resources should be devoted to implementation of evidence-based interventions on a very scalable or large scale medium. So, with that, I want to thank my funding sources, that include NIH as well as the Carlos and Marguerite Mason Trust Fund. I want to thank all of you here today, and I want to

thank you guys for inviting me.

With that said, I want to introduce the man who reminded me that my child is in adolescence ever since I met him. And so, if you could come up here -- and that's Dr. Robert Ettenger. We know that he's distinguished research professor, emeritus, with the department of pediatrics, division of nephrology, at Mattel Children's Hospital, as well as the school of medicine at UCLA. So, thank you very much. (Applause).

DR. ETTENGER: So, I have -- excuse me, but I have only one thing to say to you, and that is Mom. Okay.

So, quickly, let's talk about what interventions can improve medication adolescence and outcomes. And I think this is very much of an open question. The first question, of course, is what is a successful intervention. And as I mentioned, we tend to talk about taking adherence, because that's what we know, but what we really want to be able to measure is the absence of adverse biological outcomes, and that's a much more difficult situation because of the human

condition and different immune responses and metabolisms, et cetera. In addition, different developmental stages, different barriers and different emotional problems require different approaches. And so, as has been said, one size does not fit all and nothing is really more characteristic in adolescent outcomes than one size does not fit all. We can't have just one intervention, unfortunately. We have to tailor the intervention to the family and to the patient.

The inherent problems with adherence in adolescents really revolve around the adolescents being concerned with the here and now. As we talked about, there is no pain due to missed medications. In addition, and something that is very, very important and something that adult centers that are trying to take care of adolescent patients will tend not to pick up on is that adolescents benefit from immediate feedback and from incentives. And I'm going to be coming back to immediate feedback and incentives again and again.

So, from my standpoint having done this --

and I will say, not immodestly, I have taken -- we've just counted up all the transplants that have been taken care of at UCLA since I got there, and we just passed a thousand. So, I know I look like I'm only 35 years old, but that's not quite the case. What are the minimal practical guidelines to which to build a successful adherence in adolescent medicine transplantation?

Number one, and quite important, is the medical team's communication with the family. We need an interactional model rather than we and they. The approach needs to be non-judgmental, and we need to avoid selective attribution. I always start when I'm asking about issues with my adolescents, and I'm talking one on one with them -- I'll always say I know it's hard to take the medications routinely every single time. Let's, you know, let's talk about this. You really want to stress a team approach. Kids respond well to teams. So, patient, parents, health care providers represent the team. And in fact, personal chemistry develops better with a nurse coordinator, sometimes, as we've heard before, than

with the doctor, so that we utilize different individuals to ferret out the presence or absence of medication nonadherence.

What sort of post-transplant interventions do we need to put in routinely, even before we start to do any research in one versus another? What do we need to be doing routinely to intervene and improve adherence?

Number one, we need to continually educate with every visit. On an individual basis, medication nonadherent behavior can fluctuate dramatically over time. So, what was right this month is not going to be right six months from now. And so these kids, therefore, need to be seen more frequently to provide continual reinforcement, even years after transplant. That is sometimes a difficult pill, and -- you know, I was really interested in talking about not intrusive versus too intrusive. We are most certainly, in the pediatric transplant arena, regarded as too intrusive. Because we'll bring these kids back every six weeks, two months, if we think that there are any issues at all.

What happens all too often, and I just -- I was on call Sunday night, and what happened Sunday night, a kid who was taken care of at another center hadn't been seen in four months, came into UCLA because they weren't feeling very well, and the creatinine, which had been 2.0, was 11. And the kid had not been seen for four months, because he didn't need -- you know, he was long out. He was four years out afterwards and didn't need to be seen, and he had stopped his meds. So, we -- unfortunately, we need to see these kids more frequently.

Finally, we need to address parent and patient psychological and social problems promptly, and that goes along with seeing these kids frequently. Now, I'm not going to cover each of these areas because Mary Amanda sort of -- this I took from some of her writing about the different sorts of interventions.

But, it's important to highlight a few things. With regard to counseling and behavioral interventions, we want to try to change behavior to empower adolescents to participate in their own care,

and to develop new skill sets. And you'll see how at least one controlled trial is doing that. We want to try to be alert the psychological and effective issues of the kids addressing their feelings, emotions, and their social relationships. We tend to perform mixed interventions, because one size does not fit all, and almost everything in the literature now is multicomponent interventions.

But again, I want to come to a few issues with the immunobiological. Number one, tolerance induction is something that really needs to be considered, not only in the adults, where it's being tried in some centers, but it needs to be really conceptualized in adolescents, because these are the poster children for nonadherence. And yet, they want to show it in adults first. Well, the big risk in situations is not with the adults not taking their medicines near as much as with the adolescents not taking their medicines.

Peter has written about improved matching, so I'm not going to be discussing that too much.

But I do want to say something about the

last point here, and that's the simplifying the drug regimen or reducing the drug burden. All -- a number of the -- and I'm addressing this to my colleagues and friends on the left. I don't mean the left political spectrum, I mean the left -- my left hand. But, those interventions, like one a day tacro, like belatacept, is available to adult patients. They are not available to my adolescents, because we don't know the pharmacokinetics of the once daily drugs. They haven't been adequately reported, that they're not approved in pediatrics. Belatacept, we don't know the pharmacokinetics because the study is just now being completed, and we're not going to have a control trial to meet FDA requirements until, at the very least, 2018. We need to get these drugs into the hands of pediatric nephrologists to help manage these things to help ameliorate the issues of medication nonadherence.

I will go -- only briefly mention with regard to the cognitive and educational interventions, is that while educational interventions are important educational interventions alone are insufficient by themselves to improve adherence. However, an area

that needs to be targeted if we are going to target adherence improvement in pediatrics is in that middle bar that I showed you -- that I'm showing you -- useful intervention have to be targeted during the period of time when patients and families are transferring responsibility from parent-directed care to self-adolescent care.

General considerations with regard to intervention adherence, multicomponent adherence probably have the highest effectiveness. But treatment effects are strongest immediately after intervention and dissipate over time. Just as we have heard, and it's very true in adolescents, that late out you see this nonadherence. In fact, in addition, we can put in interventions. They may work for the 12 months that we're putting them in, but if we don't follow them up and continue to follow these closely, then all that work that has been done in that year is just not going to be useful. So, interventions that study a specific area of time have to be generalizable for longer periods of time.

Finally, and something, again, to remember

-- there are few randomized control trials in pediatrics. One randomized control trial, the results of which have not been reported, are the take-it study done by Beth Foster up in Canada, and Mary Amanda has been participating, and they utilize a multi-dose pillbox. They use therapeutic drug level variability monitoring, and they're looking at biological outcomes. And they're identifying the patients by the barriers that I mentioned in my first talk, and trying to develop problem-solving skills and developing concrete contingency plans for specific occasions to develop appropriate strategies, if the kids are in situations where they're not able to take them -- so, to develop the best habits for medication adherence.

PTSD -- something that I think may resonate with some of you out there, has been studied by Al Shemesh, and reported back in 2000. PTSD is characterized by reexperiencing of emotions, avoidance and hyper arousal responses from previous trauma. So, they did a PTSD response index in 19 liver transplant kids, and 6 of the 19 had positive scores in all three components of the PTS responsive index. Three of the

six patients had documented nonadherence, and the PTSD was treated in these three patients with good subsequent adherence. So, the PTSD that somebody mentioned this morning is in fact maybe an important component of adherence, and has not been addressed in a study since the year 2000. So, this is clearly an area that we need more work on.

It's also important -- and I don't know if the mother of the pediatric recipient is here -- but PTSD has also been reported in the parents of pediatric recipients.

A word about simplifying the drug regimen. It's been recently reported by an ex-trainee and a colleague of Dr. Nickerson's, Tom Blytd-Hansen, that poor adherence is significantly associated with increased medication frequency in pediatric CKD patients. So, this is true with peds as well as adults.

So, one should consider and study forgiving medication regimens, and one hypothesis that I have liked is that a once daily regimen of sirolimus and low-dose tac -- with once daily tac or monthly

belatacept -- can be a regimen best suited for adolescents. The problem is, as I said, neither of these are available to me to try right now. One danger, of course, with once a day dosing is missing one dose really means missing two doses, because patients are missing morning and evening because they're missing a whole day of dose. Does this put the patient at some increased risk? In any situation where we're studying adolescents, to look at once daily dosing should probably be answering this question. Nonetheless, the table that -- or, the graph that was shown by Bill Fitzsimmons shows that the evening doses are clearly the problems and we know our kids -- our adolescents like to be out in the evening.

A word, very quickly, about transition from pediatric-centered care to adult-centered care. We tend to transfer our kids when we have to, which means transferring them when the law says we have to rather than when they're developmentally able to be transferred, and care in a pediatric center is different than care in an adult center. And we see,

as I show in the first bar, transfer to adult center care is associated with worsening clinical outcomes. Single transition clinics may work, and may be helpful, but they are resource heavy and we don't have a lot of them right now. But, this is another area that we really need to aim at.

Text messaging -- the last two slides are going to be about new developments, mobile health, et cetera. So, what about text messaging and adolescent adherence? With regard to text messaging, the pros are convenience, it addresses forgetfulness and the possibility of instant feedback. The cons, unfortunately, are costs. There is cell service that has to be maintained by the patient, and can be intermittent at times -- so, the texts may not get through. And the patients may get burned out. And there are actually focus groups asking adolescent groups who have been participating in this why don't they acknowledge the text messages anymore, because, as we know, adolescents will sometimes turn us off. Text messaging has been utilized successfully in liver transplants, when you're transferring care from

parent-directed care to adolescent self-care. But, there's likely interventions -- additional interventions are going to be needed, in addition to just the text messaging.

Finally, two new provocative developments -- and this, literally, I found this headline shown on the left, the Proteus's ingestible sensor system is now being used in pediatric organ transplant patients. I'm not sure how well adolescents are going to adjust -- the way this ingestible sensor works is you take a pill where the -- a small wafer -- a vegetable wafer that sends a very weak cell signal is swallowed, goes to the stomach, goes to the -- the pill goes to the stomach. The sensor sends a message to an abdominal or arm patch, which goes to a phone which sends a message to the doctor you took your medicine. This is -- has been tested in adults, has been -- is being betaed in pediatrics. It's an interesting system. It does have some technical issues, and I don't know how many kids are going to go around wearing a bandage on their arm. But it's one other issue.

Directly observed therapy is the best way

for us to see the kids have taken medications. It has been tried in front of computer screens with adolescents with sickle cell anemia, using a computer platform, and has been found to be successful in getting kids to take their medications. There's a new platform called AI Cure, which uses facial recognition with a smart phone. Kids take the medications as they're -- or, not kids at this point, but only adults -- are taking their medications. It's used in certain clinical trials. I happened to ask one of our audience and one of the previous panelists would you do this if you were an adolescent, and she no, it's too intrusive. But then I said, well, what if we made it worth your while and gave you some extra message units, you know, and bought you a message plan. She goes I'd have to think about that.

So, adolescents are quite a challenging area. We can use new technology, but we're going to have to work with what we've been -- the hands we've been dealt, and the hands we've been dealt with adolescents sometimes require some extra work. Anyway, I want to thank you very much for your

attention. I turn it back over to the crew. (Applause).

MS. EGGERS: Thank you to all the panelists. As a nonexpert in organ transplant, I can speak that it's very appreciative that you're -- all of the panel presentations were very much -- you could tell that you were keeping the nonexperts in mind when you prepared those, and I found them to be -- and I'm seeing head nods, that it's very much appreciated. So, thank you.

We have a lot of question in this session. I think we get to dip into a little time. We're actually going to -- there are a couple open public comment, and we're just going to wrap that up at the end of this session. So, we can go for about a half hour with this conversation. And in looking at the questions, they really boil down to three main topics. One is, of all the things we've heard about to help and promote adherence, what resonates. That's questions 1, 2 and -- I'm sorry, 1, 3 and 4. And then there are some questions about resources and can we develop drugs that can solve some of these problems.

So, let's focus first on what has resonated about the efforts to promote adherence. I'm going to first ask -- I'm going to call in Kevin, with your advocate hat on and thinking globally, what of the strategies that you hear speaking -- what resonated with you? What kind of thoughts came through your mind?

MR. LONGINO: Well, I think most of it's -- to use computer terminology, ease of use. You know, the easier the regimen is -- and we're already talked about it. One pill a day, with or without food, is ideal. And if we -- the closer we move to that, I think the more compliant everyone is going to be.

MS. EGGERS: Okay. Okay. In the participants here, anything that really resonated with you about strategies that could help address adherence. Kevin, wait -- with the mic.

MR. FOWLER: I think just going back to Dr. Dew, your presentation -- you know, just the whole part, your message is understand your population. You know, develop a strategy that's specific to those people. I don't think there's one size fits all. I

think the work you have there proves what my intuition has said. So, I would support that.

MS. EGGERS: Okay. Anyone else? Right here.

MALE SPEAKER: I was dreaming a little bit when the Astellas representative said something about combining the drugs, right. I mean, then I had this magical -- like, I felt like I just woke up, and I said oh, my God, my prograf and cellcept and everything is combined in one pill, and it's going to be so easy. Right. And I doubt that you'll ever get to genetech and, you know, try to combine a pill and -- because there's so many different doses and there's so many different ways to take it. But, that would be huge. Right. I mean, I'm a chronic patient. But I know everyone here is a chronic patient too. And I am on name -- I am on prograf, by the way. And, I mean, I'm not on generic. So, yeah, if they could do that that would be huge.

MS. EGGERS: Okay. Right here.

MR. RUSHACK: You use patient established support groups.

MS. EGGERS: I'm sorry, use?

MR. RUSHACK: Patient established support groups. Again, I can give you examples. At HUP there is a website established -- it's a Facebook. Actually, it's a private Facebook on the internet, established by one patient several years ago. And now there are about 130 members.

MS. EGGERS: Okay.

MR. RUSHACK: And these members interact. Not even daily -- like hourly, with each other. And lots of topics being discussed, and the members provide support for each other and lots of information exchanged. And I think, especially for adolescents, if somehow a -- like providers could find a couple of young patients who could -- would start a group.

MS. EGGERS: Okay.

MR. RUSHACK: They may be able to influence their peers, better than the -- in formal settings.

MS. EGGERS: Great. So, in case you couldn't hear Mikolos, what he was saying was the patient-directed support groups, and he gave Facebook as an example. Has anyone -- or, is anyone currently

or have been a part of those support groups? Okay. Anyone else want to talk about the positive or negative effect that it's had? Heather? And speaking of adherent -- like, adherence.

FEMALE SPEAKER HEATHER: Adhering, right. Yeah. I think in a way there's a little more -- I guess you have people discussing how long they've been out and the positive -- you know, and you can ask, you know, well, how did you do that, you know. I mean -- in fact, that was one of the things I did. I was like, oh, you know, I need all of the information I can. You know, was it exercise, was it, you know, the -- I mean, I never even assumed people stopped taking their medications, like for good.

You know, that never occurred to me. I mean, but that is one of the things you hear, you know. This is -- it's like oh, this medication is causing me so many problems, what have you done. And you'll get 15 replies that are really useful. Others are just I'm praying for you. You know, there's all that. But, it's so informative, because you can at least feel like, oh, I'm not the only one with nausea.

And this person took, you know, something to help it or that doctor said this -- so, at least it gives you something to ask your doctor. It gives you more pointed questions. So, I find it's been helpful. But can I mention something? I did have a reply for that one thing --

MS. EGGERS: Sure.

FEMALE SPEAKER HEATHER: -- because I thought when we were talking -- the interventional studies that you were talking about, if that could become -- if, you know, we can convince our groups that that is something -- because we were talking about the psychological issues and the posttraumatic stress and all that, and I'm wondering, now that you do have some studies out there, where this intervention is so -- is useful, is cost-effective, if that couldn't be a -- something that could be part of the overall care across the board. That just -- it just seems right.

MS. EGGERS: Okay. We'll go back here.

MR. LENNON: So, regarding your -- the discussion on support groups and how it affects

adherence and -- one of the things I'm known at -- known as at Cincinnati Children's, among patients and families, is Uncle Jack. We need to bring Uncle Jack in to have a conversation with one of the patients. Right.

Because being able to relate to somebody who has been through it before and isn't going to necessarily have that position of authority, right, as the doctor or as a parent, and what are the consequences, right. There's no consequences by talking to somebody who has already been through it and, you know, made mistakes in managing the care for themselves previously. And really sharing that, you know, so that they're not able to -- you know, they don't make those same types of mistakes.

MS. EGGERS: Uh-huh. We'll go here with Piper and then Kevin, and then --

MALE SPEAKER: You know --

MS. EGGERS: We're getting good stuff here, and we're going to keep going, I guess.

MALE SPEAKER: Following from Uncle Jack over here -- but I think, and I've had conversations

with Dr. Nickerson about this too, but I think the one thing to look at this, too, is that you have an untapped resource with patients. So, when I had my transplant my level of wanting to help that first year was so high, but when I wanted to go reach out to the center and support groups to help, the reception wasn't positive. So, I think that, you know, there's a lot of people that really want to help. It doesn't have to be that difficult. You know, you find some trusted people that you can do, and you've got people who are going to be the ambassadors and get that message, and reinforce right behaviors.

MS. EGGERS: Okay.

MALE SPEAKER: It's not that hard.

MS. EGGERS: With Piper.

MS. BEATTY WELSH: Okay. I hope I don't get too much backlash for this one, from other patients. But I do want to say that there's -- there is a little bit of a problem, particularly in lung transplant. There's not a lot of standardization of care across centers. And I think some of the support groups can actually cause difficulties for people, because they

hear, for example, oh, my center says it's fine to eat sushi. I mean, I've actually heard that. And then, you know, for most lung transplant centers they'll say no, you can't do that. And it becomes a little difficult, because there might be reasons that doctors are telling one particular patient that they can't do X or Y or Z, whereas other patients can.

And I think that sometimes a little bit of defiance against the centers -- for example, my lung transplant center does not allow the use of alcohol at all. Some centers seem to allow that. And then -- so, patients sort of see it and they think, oh, well, maybe I can use it sometimes. But then they might not be honest with their doctors, because they know that their doctors don't want them using it. And it just -- it sort of creates this instability, I think, of communication. So, I think working on standardizing -- or, at least getting some consensus on the proper way to care for patients is something that could really help maybe make the benefit of those support groups a little more tangible.

MS. EGGERS: Great. Thank you, Piper.

Comer here with Leilah.

MS. SAMPSON: Yeah. Is the mic on? Okay. I feel as though social media and support groups have really held me to a certain level of accountability, because as I've talked to other patients are coming up behind me or who are dealing with transplants and who are on dialysis, I find myself feeling like, okay, I have to take my medicine now because these people are watching me. And if I'm -- you know, if I've already self-appointed myself as support for them, I do also share the good and the bad. You know, I discuss my process and just certain days where I'm not feeling so happy-go-lucky as I'm supposed to feel, post-transplant. And I think they really value that authenticity.

And also working with the peers program, with the National Kidney Foundation, as I talk to my mentees and they have questions about post-transplant or things I went through on dialysis, I can go home and I reflect. And I'm like, okay -- it's humbling for me. I used to be on dialysis. I could be back there. So, let me pull it together. Whatever it is

I'm dealing with right now, whatever issues I'm having with this medication, just reaching out to people who are coming up on transplant or in transplant help me to hold myself accountable.

MS. EGGERS: I think we're hearing about the power, and maybe some limitations of the support groups. I want to make sure we also touch upon the monitoring -- the reminders and the automatic things that we're also touching on today. Any -- from what you heard, about those types of -- any thoughts that resonate? Yeah, that would be great for me -- no, I don't -- I -- for me, anything of that sort.

MR. LENNON: I think it sort of maybe goes without saying for some of us, I think most of -- and we've made this observation before, the reason that we're all here is because we own our disease and we're invested in making something work. That said, I also think that most of us in the room and probably those online and those who didn't know about this meeting, et cetera, don't want to be reminded we're sick. I mean, we're patients, right. We have our own classification, right. There's a reason that you guys

are holding this meeting for transplant patients, right. No one really wants to be reminded through whatever system -- and by taking their medications, I'm sick, I'm not normal. Right. And so the more and the faster we can get to some of those transformational changes, I hope, you know, that adherence eventually -- the goal of adherence goes away. We don't need adherence, right, because the need to take a medication isn't there at all. So --

MS. EGGERS: And that's what -- and so, that's with all -- that's -- you're talking about reminders sort of globally, no matter how they come at you. Okay.

MALE SPEAKER: You know, Doctor, what you were talking about earlier about the incentives for adolescents, I was thinking about my son -- 16 years old. He would respond to that. So -- but I think that, you know, to -- I think, again, when you're looking at incentives to promote an adherence, I think they're not sustainable. I think it goes back to the fact that the transplant population as a whole is not really well understood. And where the -- my

recommendation is is that's where the time should be spent, to understand your patients. I don't need to be told what to do. Many times I'll tell my doctor what needs to be done. So, I think that's where the shift needs to go. We're not a monolithic group. There's segments, and if you get to understand that segment of patients and implement strategies accordingly.

MS. EGGERS: Okay.

MALE SPEAKER: Yes. I work in a community in Alpha-1 antitrypsin deficiency, and many of our -- many of the people in the community -- not a great percentage, but there are several that have had either lung and/or liver transplant due to their condition. And the nonprofit organization that I work for is called Alpha Net, which is -- everybody that works for Alpha Net is somebody with Alpha-1 antitrypsin deficiency. And it was really refreshing today to hear all of these different adherence -- you know, different angles to get people to adhere more to their medication regimens and to manage their care well.

It was very validating for me, because

that's exactly the model that we use. We telephone alphas ever month. We talk to them about are you taking your medications, have you been to your doctor, have you kept your appointments, are you exercising. So, all of the critical components of compliance we cover.

And it seems to have great outcomes, with some preliminary in-house studies that we've done in promoting, you know, better quality of life for these people as well as, you know, increasing their quality of life as well as their longevity. And I know our medical director, Dr. Sandy Samhouse -- I don't know if any of you know him, but his most recent studies have shown that together with that personal touch, with checking in on compliance items with people that have a specific condition, as well as -- even for those that have been transplanted, those same kinds of questions -- has really made a difference in their lives. So, again, all of the things that you're doing and the presentations that you've made have really validate for me personally that we're on the right track.

MS. EGGERS: All right. Jim, I'm going to tie in to Jack's comment. I'm going to put the spot -- this is the second time now I'm putting the spotlight back on you. Sorry. But what Jim's talking about is a type of reminder I think of as the mixed intervention approach. You have reminders and support coupled in one, because you're calling every time.

Take it to what you were talking about, about monitors or reminders that are coming at you. How would you respond to Jim? With the support aspect of it, does it remind you that you're sick or does it help you in any way? Do you have any thoughts following up on that?

MR. LENNON: Yeah. So, I'm going to, I'm going to seem like a hypocrite, but I have an alarm on my phone to help me take my meds, right. But every time that goes off, I'm like, oh, yeah, no -- you know, most of the population doesn't have to do this. My brother doesn't have to do this, et cetera. And they're not -- it's not that they're not good interventions, right. But -- and it's not that I haven't recommended them to other patients, techniques

that have either worked or not worked for me. But, really -- I don't know, I sort of want to -- I mean, well, just to take it a step forward and think about, you know, how do you minimize the impact on the psyche of the patients. And those reminders and that -- you know, it's just more concentration that you have a disease. And if you can have it minimally invasive within the patient's sort of, you know, routine, those are going to be sort of the best interventions. And obviously, those are going to be individual -- you know, individualized. We talk about individualized medicine. So -- yeah.

MS. EGGERS: Uh-huh. Thank you.

MR. LENNON: So, not that the techniques or reminders aren't good. It's just --

MS. EGGERS: But coupled with something else. Something -- a support or just part of your daily life.

MR. LENNON: Right. And mom nagging me.

MS. EGGERS: Yeah. We'll go right here, and then I -- we'll go over to you.

MALE SPEAKER: I think I was just taking

everything in, that you were saying. But I also think it's very individual, you know what I mean. To be quite frank with you, I have a reminder too. I don't listen to my reminders anymore, right. Because it just goes off. But I don't think I'm sick if my reminder goes off, right. I mean, right.

I mean, I used to think I was sick because I had so many doctor's appointments. That was my big thing. But that's all individual, right. So, for you it may be something else. For me, it's a different issue. But, I really hope technology -- and I think that some of the presenters were going there. We're not there yet, right.

This electronic pillbox, I don't think it's perfected yet, quite -- you know. But we hope that Apple or someone else comes out with a really, really cool thing, right, where it's so easy that you do it. And -- but, I just don't think we're there yet. That's all.

MS. EGGERS: Okay. Thanks. Let me turn -- okay, I was -- Kevin, please.

MR. LONGINO: Well, I had a question. If we

had the transplant programs represented here, I wonder if we could ask them the same question. Do they have the right incentives to promote adherence. Do they have the right metrics. I know they have a disincentive. If a graft fails, it impacts their score on their quality measures. But, that's driving some behavior. But, do they have the right metrics or incentives to promote adherence to put these kinds of programs in place that we heard about, where people are doing essentially reviews every 3, 6, 9, 12 months.

MS. EGGERS: All right. Well, then, is this an answer to the question?

MALE SPEAKER: It is exactly an answer to the question. There is a disincentive, frankly, in practice to be dealing with adherence, for the following reasons. Number one, usually if you're going to address it you want to be able to do something about it at that time. That means more personnel. The transplant administration is not going to give you that additional personnel. We used to have a psychologist in our clinic. We don't anymore,

because of budget cutbacks.

Number two, there's an issue of time. Given the large volume in a lot of the adult transplant centers, there's not sufficient time for them to be dealing in-depth with that. If you have a liver -- somebody was mentioning this morning, the liver -- and the transplant nurse coordinators are the best invention ever. But, the fact of the matter is that they -- if they have caseloads of 150, 200 patients, they're not going to be able to spend time or call the patients or whatever. So, in fact, adherence monitoring and everything is disincentivized for those reasons.

MS. EGGERS: So, in the interest of time, we'll go -- yes, please. Please, go ahead. And then we'll go with Kevin. And then we'll wrap up the --

DR. MANNON: So, I've been keeping my mouth shut because I'm a transplant physician. I'm Ros Mannon, and I'm a transplant nephrologist and clinical investigator at University of Alabama, Birmingham. And appreciate the opportunity to be here. I just wanted to address the question about adherence,

because I'm in one of those large adult programs. And I think that we have a limited budget, and we do a lot of transplant and you think we're making money but we're a not-for-profit state hospital.

And so, the issues of immune monitoring are very expensive now. And we have pharmacists as outpatients, but recently our budget was cut and junior pharmacists on the inpatient squad quit and we had no inpatient pharmacist, so teaching the predischarge all went to nursing staff, who are already overburdened. I think we want to do it.

What our program has tried to do is focus on high-risk groups. I'm in a pretty diverse socioeconomic -- I'm in the Deep South, so we have to focus in the first year and we have weekly calls with the coordinators. And we try to look at levels. And that's what we use. So, it's not that we don't care. I think we are just pushed. And our administrative keeps -- the slot to see patients is like ten minutes. And dude, that is not going to make -- you know, I ask, like, how are you feeling. And you -- that's an open-ended question that may take 15 minutes.

I do see the psychosocial stress. I see it in particular in the long-term dialysis patient, who has had a routine for ten years, the same people, the same nurses, and they lose that. All the sudden they have this transplant, and a lot of what they did is gone. They can't get back to work.

So, there are, I think, a lot of issues. I think that the centers are trying to work on adherence. I don't think most of them do a good job. I don't think we do. And we do look at once a day medications and alterations. But, I think it also goes back to another unmet need is understanding the sufficiency of immunosuppression, because it's different from organ to organ and it's very different from patient to patient.

MS. EGGERS: Thank you. We'll have one more -- Kevin, one more comment. And then we'll wrap up.

MR. LONGINO: I think just to support, like, what Dr. Mannon said and Dr. Ettenger, is that I don't think it's like -- no one is operating with any bad intentions at all. But I think the truth -- and this is beyond the scope of this conversation, is the way

that transplant is set up right now the quality incentives are one year. And until that changes to three years, you're going to keep having these conversations over and over. So, strategically, that needs to be a bigger conversation, to change that.

And then you talk about incentives. Then you'll see adherence education rising. But frankly, until that happens you're going to have a lot of just symptomatic responses. So, my two cents.

MS. EGGERS: All right. So, we are -- we've had a long day. We didn't get to the issue of forgiving drugs, but I think that hopefully if you're on the expert panel and have perspective that you can give to the docket that would be great. Or, if you're an expert out there or have thoughts on this, do it as well. But, I think it is -- I think that we are -- that we have done all we can do in this amount of time.

We have two open public comment -- people who signed up for open public comment, and in fairness we do this all -- we do this for every meeting, a chance to give people a floor to talk about something

that may be a little bit off topic. And so, I'm going to -- usually we have this script we read. But I'm just going to say the big things. Please keep your comment brief. And if you have anything to disclose -- a financial affiliation or relationship, that would be useful for us to know. We encourage you to disclose it. You don't have to disclose anything. And we'll just bring the mic to you. So, we have two people. Debbie Drew -- do I have that right? And I'll ask you to keep your comment to two minutes or less. Is Debbie here? What? She -- okay. All right. And how about Mary Pierce? Okay.

MS. PIERCE: I'll try not to take all four. We started this program by talking about the benefits and the risks of transplant, and I just want to say that with lung transplants the risk is that we'll only live -- 54 percent chance that we'll live for five years. The benefit is that we have a 54 percent chance of living for five years. So, I work with lung disease. I am an Alpha-1 patient. Alpha-1 antitrypsin is a genetic disorder that can cause live and/or lung disease in adults, and liver disease in

children. In disclosure, I work currently as an advocate for Doman Life Science Services. We're a specialty pharmacy. But I'm here at the request of the Alpha-1 foundation, and basically to summarize the results of a survey that they did recently. And frankly, most of the results have been covered today, with wonderful correlation with what we discovered.

We surveyed 81 patients that were a variety, 58 with double lungs, 3 single lungs, 37 liver, and a couple of other various patients. And there were just a few things that we didn't really bring up, that were discovered. The question -- most significant disadvantages or complications of your current treatments. Of the group, 74 percent responded that it was about cost and access. And when I was looking at that, I thought oh, my gosh, I don't even know how much my drugs cost. I'm eligible for Medicare. I'm scared of going on Medicare. I'm under a company plan. I added up the cost of my medications for one month, and they're about $1,500, with the addition of augmentation therapy -- which for Alpha-1 patients we take it before transplant, and it's a bit

controversial whether we do it post-transplant. But, 43 percent of our people are using it post-transplant. The cost of that drug is 8 to $12,000 a month. So, we are a little afraid of what's going on with costs and access.

We talked about support groups. 96 percent of our respondents are in a support group, either an Alpha-1 or a transplant support group. And I am going to skip over a lot of this.

MS. EGGERS: And I hope, Mary, you submit it -- submit the full thing to our docket. So, we'll have it as well.

MS. PIERCE: Okay.

MS. EGGERS: So, submit all of your results.

MS. PIERCE: Good. And then one other question. What's the ideal treatment going to -- what would you consider the ideal treatment for transplant. And again, make it less expensive. 71 percent of the people said that it needs to be less expensive.

And then the positive part. How has your condition changed post-transplant -- 69 percent said their condition is better, and 17 percent there was no

change. So, those are both positives. 69 percent had depression.

And then finally, we asked whether they would be willing to join a working group to work out the next steps, and 88 percent of them said yes, they would volunteer. And I guess I'd pose that to the rest of the transplant patients still in here, how willing would we be to participate in a working group from here on forward. And from what we heard recently, it sounds like it's up to us as patient groups to begin to take over some of these issues that providers don't have funding or time to do. So, I'll leave you all with that question.

MS. EGGERS: Thank you very much, Mary. I suppose if you reflect on Mary's question, you can contact though the docket or through those mechanisms -- through PACE. The slides -- by the way, the slides will all be online in a few days, and you will see in there the contact to our professional affairs and stakeholder engagement staff, who can address that. Or, you can come to our team as well. If an organization is interested we'll connect you with that

as well.

One other thing that came up -- both Michelle and I were going to mention this, which -- there was an issue about CMS and their role in here. And we just wanted to acknowledge that that came up.

MS. CAMPBELL: And a similar issue, that Debbie was going to bring up, who is our heart transplant patient, was -- her thinking is that maybe some reasons for adherence concerns and issues is related to access, in terms of refills with specialty pharmacies, and really that frontline staff dealing with trying to get your refills and all the other comorbidities you're dealing with, from your transplant and other diseases, the impact of just dealing with sometimes staff and the turnover or the merging and -- or dismerging of pharmacies. So, access level of drugs. And that was her comment.

MS. EGGERS: Okay. And another one that I heard about was the strict timelines of the 30 day supply, and the issues that that can raise about that. So, I'm -- that was Ellen's comment. We don't have -- Ellen, do you want to say one --

MS. COHEN: Only one more moment, please.

MS. EGGERS: Okay. We're going to let Ellen do this, because she came up to me so nicely.

MS. COHEN: Well, the -- first of all, I love what the FDA is doing in terms of engaging patients. Let me start with that. The other players in this -- one is CMS, and -- one is CMS. The other is Congress. The whole game at the political end is cutting Medicare spending, and that is one of the stresses that CMS works under all the time. But it means, for instance, when you talk about a one a day pill, or combination pill, anything having to do with making it easier for patients to comply is also going to raise cost questions. And you will get a -- patients need to engage with CMS in understanding that this isn't just a matter of convenience. That some of these drugs -- the fact that you have an easier way for patients to manage their care, it's not just convenience. It is really a matter of improved outcomes.

MS. EGGERS: Great. So, lots, lots of topics were discussed today. Again, go to the docket.

We really do read all those comments. And we appreciate them.

Evaluation forms -- please fill them out. There should be some at your table. Please leave the clickers here. They're really not useful outside of this room -- and they're not decorative either, so -- and with that -- am I missing anything I need to say? Okay. Then, thank you so much to the panelists. We're going to let Renata give some closing remarks. But, I want to thank the panelists and the audience participants for a very engaging discussion. Thank you.

DR. ALBRECHT: So, thank you, Sara. Actually, I think there are a lot of groups here today that deserve a round of applause. Several years ago, Theresa Mullin, who did an introduction this morning, met with our division and she said there's this new initiative about involving patients, and we immediately said oh, we've got a topic, we've got a topic. We'd like patients who have solid organ transplant. And she said, well, we can only do 20 topics. And every year when they met I said we really

want to have a meeting to talk to patients with solid organ transplants. Because in the transplant field, as you heard from our colleagues here on the right with the scientific perspective, and from industry and from physicians and nurses and doctors, we know about their involvement. But we said we really want to hear from patients.

So, it is so gratifying to see that today, on the 27th of September, we actually had this patient-focused drug development meeting on -- with patients who have received a solid organ transplant. So, I need to say that to everybody that I spoke during the course of the day, they are just so happy and so excited and so grateful for this opportunity.

And I just want to say that we are all so grateful for you taking the time out of your schedules, making the effort to drive -- not just locally, but from far -- Beltway notwithstanding, and I apologize, you're probably going to run into Beltway traffic -- but, it has just been such a wonderful day and we have just heard so much from you, and really benefited from it. So, I want to thank the patients

who spoke in the morning. I want to thank Jim, Jeff, Leilah, Michael and Lindsey for the first panel. Piper, Dan, Debbie, Jack and Roberta for the second panel. And all of you that have just voiced your opinion, shared your comment, shared your perspectives and really told us some really important life stories.

I think you've identified a lot of issues. FDA is not going to be able to tackle all of them, but I think there are many people in the audience, and there are people who are on the web, and there are people that the transplant community interacts with. And I think many of the messages that you've shared today are going to get repeated to people outside this room. Because I think we really, in the area of transplant, have had a lot of stakeholders and now we also have the patients as part of the dialogue. So, this has been very important. Again, thank you very much. And in the interest of not prolonging the day, thank you and we really appreciate your input today.

CERTIFICATE OF NOTARY PUBLIC

I, ERICK McNAIR, the officer before whom the foregoing proceeding was taken, do hereby certify that the proceedings were recorded by me and thereafter reduced to typewriting under my direction; that said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

ERICK McNAIR

Notary Public in and for the

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I, JANE W. GILLIAM, do hereby certify that this transcript was prepared from audio to the best of my ability.

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October 10, 2016

<DATE>

JANE W. GILLIAM